Safe and Effective Use of Medicines in Paediatric Intensive Care

Tesis Doctoral

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PRESENTACIÓN

Uso Seguro y Eficaz de Medicamentos en la Unidad de Cuidados Intensivos Pediátricos

Memoria que presenta la Licenciada Dña Sara Arenas López para aspirar al Grado de Doctor.

Esta Tesis Doctoral ha sido realizada bajo la dirección de los Doctores
Dr. Miguel Ángel Calleja Hernández y el Dr Shane M. Tibby

FOREWORD

Safe and Effective Use of Medicines in Paediatric Intensive Care

Thesis submitted by Sara Arenas López, Pharmacy Graduate as a project in part fulfilment of requirements for the degree of Doctor of Philosophy (PhD) from the University of Granada

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Como Directores de la Tesis y hasta donde nuestro conocimiento alcanza el trabajo titulado

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Y para que así conste, se expide en Granada y Londres a 15 de noviembre 2016.

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FOREWORD

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CERTIFY That

As Thesis Supervisors, to the best of our knowledge the work titled

"Safe and Effective Use of Medicines in Paediatric Intensive Care"

has been undertaken by the doctoral candidate, under our directorship, and authors' citation rights have been duly respected when referring to others' results or publications. The work fulfils all of the requirements necessary, in terms of theoretical and methodological content, for its submission and public defence, with a view to obtaining the Title of Doctor in Philosophy. We therefore AUTHORIZE the presentation of the aforementioned Thesis, to be defended and upheld in accordance with the Royal Decree 99/2011 of 28th January,

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La doctorando **Dña Sara Arenas-López** y los directores de la tesis **D. Miguel Ángel Calleja Hernández y D. Shane M. Tibby.** Garantizamos, al firmar esta tesis doctoral, que el trabajo ha sido realizado por la doctorando bajo la dirección de los directores de la tesis y hasta donde nuestro conocimiento alcanza, en la realización del trabajo, se han respetado los derechos de otros autores a ser citados, cuando se han utilizado sus resultados o publicaciones.

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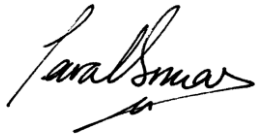
Fdo.: 

Dña Sara Arenas-López

A mis padres que con mucho amor, gran generosidad y tremendo sacrificio me animaron y animan a “vivir” esta aventura, a perseguir mis sueños de farmacéutica clínica con los más pequeños y a conocer el mundo y sus gentes.
Siempre os llevo en el corazón.

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CHAPTER 1: GENERAL INTRODUCTION

1.1 BACKGROUND

PAEDIATRIC INTENSIVE CARE

The Paediatric Intensive Care Society (PICS) in the United Kingdom describes the discipline of Paediatric Intensive Care in the following manner:

Paediatric Intensive Care is a service delivered in the Paediatric Intensive Care Unit (PICU) from birth through adolescence (usually up to 18 years of age) for children with potentially recoverable diseases who can benefit from more detailed observation, treatment and technological support than it is available in standard wards and departments. Intensive care of the newborn (particularly the premature) should routinely be delivered by neonatologists in a neonatal intensive care unit (NICU) [1].

Between 2012 and 2014, there were 59,642 admissions for children In the United Kingdom recorded in the PICANet dataset, (19,760 were admitted in 2014). Of those, 47% (27,949) were under one year of age and a third of those children less than one month old at admission (34%, 9,382) The majority of cases seen in PICU are unplanned emergencies (59.1%) occurring at all times of the day and night and to some extent the causes of admission reflect the different patterns of mortality in childhood [2].

Typically just under 30% of admissions occur in the context of congenital heart disease and 26% occur in the context of respiratory disease although seasonal and geographical variations do apply. Major trauma accounts for about 15% and neurological problems (other than trauma) make up 11%. The composition of the remainder is more varied, depending upon the allocation of neonatal surgical patients and other services. From all admissions 65.7% require invasive mechanical ventilation during their stay and 14.9% will require non-invasive ventilation.

The main seasonal variation is respiratory disease, which is more common in the winter months both as a primary cause of admission and as a complication of admissions for other reasons. This leads to a seasonal increase in bed occupancy during the winter months. It should be emphasised that many children who require prolonged intensive care for respiratory diseases have a predisposing history, for example chronic respiratory disease, a history of prematurity, bronchopulmonary dysplasia, asthma or a background of congenital heart disease. More children with comorbidities are admitted to PICU's in recent years; this may be for a variety of reasons including: advances in neonatal care, better antenatal screening for congenital conditions, increased survival following complex cardiac surgery, more comprehensive vaccination programmes (decreasing the proportion of previously well children

admitted with sepsis), advances in long term ventilation provision and changes in societal expectations for chronic illness. Children with multiple comorbidities typically receive several medicines chronically, which potentiates the risk of drug interactions during their PICU admission.

Despite the fact that the majority of admissions are unplanned emergencies, the median length of stay can be as low as 24 hours. In contrast to adults requiring intensive care, crude mortality rates are low (4-8%) and the quality of survival is normally high[1].

The PICU at Evelina London Children's Hospital is a 20 bed, tertiary referral unit, providing intensive care facilities for the paediatric population of South East England, with a catchment population of approximately 1.8 million children. This unit accepts around 1300 admissions per year suffering from typical general PICU conditions including respiratory; neurology; metabolic; ear-nose and throat; renal; oncology; trauma; sepsis; cardiac and multi system failure.

Approximately one third of the workload is cardiac in nature, many of these patients are first referred in the newborn period having been diagnosed in the large foetal cardiology department also based at Evelina London Children's Hospital. The cardiac surgery program deals with all types of complex congenital heart disease and has one of the largest hypoplastic left heart services in the country.

The majority of the remaining workload (approximately 400-500 cases/year) is retrieved acutely from district general hospitals in South East England. The PICU encompasses the South Thames retrieval service[3] which also provides a service for two of other South London PICU's: King's and St George's Hospitals.

The Paediatric Intensive Care specialty is relatively new, having been recognised as a medical specialty in the 1990s and formal training for doctors established in the late 1990s. The UK Paediatric Intensive Care Society (PICS) sets the curriculae for the training of medical staff but also establishes the guidelines on how units should run, infrastructure required and workforce depending on the nature of the unit (from local hospitals to tertiary referral centres). Among those guidelines in the 2010 document (Appendix 16), a description of the pharmacy service required per type of unit was also included[4].

MEDICINES USE IN PICU

PICU is a medicines high-risk area due to the complexity of paediatric patients, many of them presenting or developing multi-organ failure. In addition to this, there are inherent risks in paediatrics due to the heterogeneity of the paediatric population.

Medication therapy, in children generally and in critically ill patients in particular, is affected by a shortage of age appropriate licensed formulations[5], necessitating the clinical teams to use unlicensed or off label drugs with the potential for adverse reactions, lack of desired therapeutic effect or medication errors[6,7] .

The use of unlicensed drugs in children, especially critically ill neonates and infants ranges from 50% to 90% and this has been extensively reported in the past two decades [5,8-10].

Neonates and infants are commonly exposed to polypharmacy, typically involving formulations that were not developed for this patient group. Examples include age-inappropriate excipients, and use of dilution and manipulation procedures to enable the administration of the adult designed drug to the neonate or infant [11,12]. There are studies showing that the incidence and severity of adverse drug reactions (ADR's) is higher in neonates and infants [7,13] and that the mortality is 40% higher (100 of 243 cases) in the first month of life [14]. Furthermore, children are more likely to suffer harm from a medication error than adults. This occurs particularly at extremes of age, with neonates, adolescents and adults cared for in PICU settings being at particular risk, possibly due to weight based dosing of high-risk medication [15,16]. Therefore, this adds to the challenges faced by clinicians trying to ensure safe and effective drug prescribing in critically ill children.

On the 26th of January 2007 the European Union implemented the Paediatric Regulation, which is an important piece of legislation (Regulation (EC) No 1901/2006). This regulation aims to improve health amongst children in Europe through measures designed to stimulate the development of new medicines for use in the paediatric population, including areas –such as Infectious Diseases, Anaesthesiology and Paediatric Intensive Care, to ensure that they are appropriately tested and authorised, and to improve the availability and clarity of information about the use of these medicines in children. A new committee of scientific experts, the Paediatric Committee (PDCO), was established within the European Medicines Agency (EMA). The PDCO is responsible for the assessment and agreement of paediatric investigational plans (PIP) in line with ICH-11 and Paediatric Regulation, to establish an

inventory of the therapeutic needs of children and to develop a European Network for clinical trials in children [17-19].

Safe and effective paediatric medication therapy requires an understanding of the wide variability and constant changes in pharmacokinetic (PK) handling and pharmacodynamic (PD) response to drugs that occur during the time from birth to adulthood as well as challenges of drug prescribing and administration during childhood[20].

In the paediatric and neonatal intensive care units, the age range is from 24-week gestation to 18 years old. Pharmacists providing a clinical service to PICU's and NICU's need to have an understanding on the PK and PD of the drugs as well as the pharmaceutical aspects across this wide population range that could have an impact on concordance and therefore administration of medicines to paediatric patients. Most of this knowledge and practical skills is achieved by direct patient care over a period of time. In the U.K. for the past 10-15 years all PICU's have a dedicated pharmacist that provides a comprehensive clinical pharmacy service to the patients integrated within multidisciplinary teams addressing issues discussed above. This differs with practice in other European countries where this clinical figure is not yet fully established.

SEDATION

Most of the critically ill children admitted to PICU will require potent analgesic and sedative drugs to facilitate diagnostic and therapeutic procedures, assist mechanical ventilation, avoid inadvertent self-extubation, reduce metabolic rate and oxygen demand, and enhance analgesia and less disrupted sleep[21]. Sedation is also needed to reduce anxiety and distress from the presence of unfamiliar personnel, separation from parents and from the high level of background noise, which can disturb natural sleeping patterns[22]. In the critically ill child, sedative and analgesic drugs are usually given during the acute phase of the illness by intravenous infusions on a standardised dose per bodyweight basis, which are then adjusted according to observation of physiological and behavioural criteria.

Under-sedation and over-sedation are both harmful. Inadequate sedation is unacceptable in a vulnerable child that may be unable to move or communicate its distress due to the use of muscle relaxants, while those not receiving neuromuscular blockade may 'fight' the ventilator leading to ineffective ventilation, accidental extubation or the loss of the invasive access or monitors. In intensive care, inadequate sedation has been correlated with adverse short term

and longer term outcomes; problems include increased stress symptoms such as hypermetabolism, sodium and water retention, substrate mobilization from energy stores and lipolysis; cardiovascular symptoms including tachycardia, increased blood pressure, increased oxygen consumption, altered respiratory rates, altered gastrointestinal motility as well as changes in coagulability, such as clotting time and platelet aggregation, and wound healing[23]. In children the risk of developing Post Traumatic Stress Disorder following admission to Paediatric Intensive Care is higher than in adults [22,24].

Conversely, oversedation also carries risks such as ileus, venous thrombosis and reduced blood pressure. It can also delay recovery (prolonging ICU and hospital stay), promote tolerance to the drugs and lead to distressing symptoms on withdrawal of the drugs (agitation, seizures, hallucinations, psychosis, fever and tachycardia)[23-25].

A systematic review of 25 publications studying sedation outcomes in PICU patients (total of 1,163 children combining all studies) found that children received many different sedative agents and sedation level was evaluated using 12 different sedation scales. Only 4 scales were validated in this setting including the COMFORT Score. Results indicated that oversedation is more common than undersedation (31.8% vs 10.6%) concluding that this may lead to tolerance, withdrawal and overall longer hospitalisation [26].

The ideal level of sedation varies from child to child and for the different clinical situations encountered, however most intensivists seek to maintain a mechanically ventilated child during the acute phase of the illness in a sleepy but rouseable state. Deeper sedation is usually reserved for selected patients such as those receiving muscle relaxants or those with inadequate tissue oxygen delivery.

SEDATIVE AGENTS COMMONLY USED IN PICU

Ideally, the choice of sedative should be based on its pharmacokinetic and pharmacodynamic characteristics that allow safe, efficacious and titratable use in PICU as well as being affordable. These include the cost of the drug itself, its administration, as well as the expense associated with treating any side effects (including tolerance, physical dependency and withdrawal) [27,28].

In recent years a better understanding of the benefits offered by a combination of drugs, acting at different receptor sites, has improved the quality of analgesia or sedation provided when compared to drugs acting alone. The combined action of the different drugs often allows a reduction in the doses used of each individual drug, thereby minimising side effects while maintaining adequate analgesia/sedation. This concept of co-analgesia has become routine practice in PICU[29], although a consensus has not been reached regarding the best regimen. Furthermore, the introduction of any new agent should be supported by evidence.

Clinical practice guidelines for sedation and analgesia in critically ill adults have been established for many years [30,31]. A European survey involving 647 physicians from 16 countries has shown that there are considerable differences among countries regarding the agents most commonly used: 75% of ventilated patients in the UK received medication for analgesia and sedation continuously, whereas only 30% of Italian ventilated patients did so[32]. The most commonly used medication for continuous sedation of adults in Europe is propofol and midazolam, whereas in the USA propofol and midazolam are administered as the preferred medication for short-term sedation and lorazepam for long-term sedation. (Propofol is only authorised for long-term sedation in ICU in adults and children >16 years; it is contraindicated for long term sedation in PICU because of the risk of developing propofol-infusion syndrome). Analgesic agents differ broadly between countries, and neuroaxial techniques are not often reported [33].

Furthermore, in the field of paediatric critical care, National Surveys and multicenter observational studies have been conducted in several countries. For example in New Zealand and Australia authors conducted a multicenter study evaluating the sedation therapies in 231 children (median age of 2.75 months). Midazolam was the agent predominantly prescribed followed by dexmedetomidine and clonidine. They identified considerable variation in sedation practice with an increased incidence of early deep sedation associated with increased mortality [34].

Recently, in 2015, a survey on sedation and analgesia practices among Canadian PICU physicians was conducted (134 intensivists and 17 PICUs). The most common infusions administered to children were morphine and midazolam with clonidine being used, as required, as an adjunct therapy [35].

However, to our knowledge, consensus guidelines on sedation and analgesia in critically ill children have only recently been established in the UK and Germany (United Kingdom Paediatric Intensive Care Societies Sedation Analgesia and Neuromuscular Blockade Working Group and the German Working Group, respectively) [33,36]. However, many of these agents remain unlicensed and as such have been identified in the EMA inventory of therapeutic needs [19].

SEDATION AT EVELINA LONDON CHILDREN'S HOSPITAL'S PICU

Each PICU uses a different combination of drugs to achieve the sedation required. Until 1999 the routine practice at ELCH PICU was to administer a combination of morphine and midazolam infusions for achieving sedation in the majority of children. However, since the beginning of 2000, following agreement among all consultants, clonidine has replaced midazolam as a sedative agent in an attempt to prevent the problems of tolerance, withdrawal and respiratory/circulatory depression encountered [37,38]. Oral clonidine in combination with IV morphine and occasional IV boluses of lorazepam are used as part of the sedation protocol in the unit (see Appendix 6.2), and if the child requires more sustained levels of clonidine an IV infusion is used instead of the oral regimen. However, at the time of the change there was very little knowledge about the safety and efficacy of clonidine in this patient population, and, catalysed by the pharmacist, the multidisciplinary team embarked upon a series of studies. The first study was published in 2004, this was an important publication which has guided many units on the use of enteral clonidine for sedation and has been informative for further research in the unit and internationally, this publication is still up-to-date, being frequently cited in many other publications with over 50 citations in Web of Science and used in routine care. Clonidine is one of the drugs identified in the Inventory of Paediatric Therapeutic Needs, in both areas of anaesthesiology and pain, by the EMA [19].

CLONIDINE

Clonidine (2-[2,6 dichlorophenyl-amino] 2-imidazoline hydrochloride) is an imidazole derivative which was introduced into clinical practice in 1966 and is authorised for use throughout the EU and in the USA for the treatment of high blood pressure (adults only), migraines (adults and children over 12 years only) and attention-deficit/hyperactivity disorder (ADHD) (children 6 to 17 years – USA only).

In the UK, clonidine was already on the market before the licensing began in 1971 and was granted a full UK Marketing Authorisation on 11 July 1980 (Catapres -Boehringer Ingelheim

Limited). However, in addition to the authorised indications, clonidine use is being explored in a number of other indications, including sedation and analgesia.

Clonidine is a sympatholytic agent acting as a partial agonist of adrenergic α–receptors both within the central nervous system and in the periphery being more specific for α2 subtype than for α1 with a ratio of affinity of approximately 300:1 [39].

As clonidine is lipid soluble, it is able to cross vascular (e.g. blood brain barrier) and cellular barriers to exert its pharmacological effects. At the central level, α2-adrenoreceptors are located both presynaptically on terminals of neurons releasing different neurotransmitters (norepinephrine, epinephrine, serotonin and acetylcholine) and postsynaptically of non-noradrenergic neurons.

Clonidine is able to stimulate all α2-receptors decreasing neuronal excitability. In particular, the activation of presynaptic α2-receptors inhibits adenylate cyclase (via protein Gi), decreasing the activity of protein kinase A (PKA) and presynaptic calcium levels, and, as a consequence, blocks the release of norepinephrine, thus reducing the activity of sympathomimetic transmission. The resulting cardiovascular effect is a decrease in sympathetic tone and the consequent well-known hypotensive effect.

It has also been proposed that the antihypertensive effect of clonidine is also due to agonism on the I1-receptor (imidazoline receptor), which mediates the sympatho-inhibitory actions of imidazolines to lower blood pressure. However the main contribution to the cardiovascular action of clonidine is via α2-receptors.[39,40]

At high serum concentration, clonidine may stimulate also central α1-receptors enhancing neuronal excitability.

Besides hypotension, the activation of α2-adrenoceptors is known to produce analgesia and sedation. The analgesic effect is thought to occur at the spinal cord or peripheral nerve level [41,42]. Indeed, the locus coeruleus in the brainstem is a principal region responsible for the sedative effect of clonidine[43]. The main ascending and descending noradrenergic pathways originate from this important area. This results in increasing activity of inhibitory interneurons such as GABA- (gamma aminobutyric acid-) ergic pathway to produce CNS depression[44].

A summary of the pharmacological effects of clonidine is presented in Table 1: Clonidine has little, if any, respiratory depressant effect.

Table 1: Effects of clonidine following stimulation of different receptors[39]

Receptor	Effects of stimulation of receptors
Central α2-receptors	Hypotension, bradycardia (mainly α2-post synaptic receptors), sedation, analgesia, hypothermia, changes in motor activity & conditioned behaviour
Peripheral presynaptic α2-receptors	↓ Saliva flow, ↓ intestinal motor activity, ↓ gastric acid secretion & bradycardia, ↓ insulin secretion from the pancreatic β–cell
Imidazoline 11 (cell membrane) & 12 (mitochondrial)	Minor contribution to inhibition of norepinephrine release. Main effect of clonidine through α2-receptors
At high concentrations binds central α1-receptors	Opposite effect than central α2-receptors stimulation

Clonidine is moderately lipid soluble and is almost completely absorbed following an oral dose. Peak serum levels occur at 1-3 hours and in as little as 15-20 minutes following epidural or spinal administration. Due to its large volume of distribution, clonidine has a long half-life of elimination of 12-24 hours. Elimination is through both hepatic metabolism to inactive metabolites and direct renal excretion. Due to its bioavailability profile clonidine has been administered by almost every route [45-48].

Clearance estimates in children out of infancy are similar to those described in adults when standardised for size using allometric scaling (CL 12.8-16.7 l/h/70kg). Both the distribution half-life (t1/2α 12min) and elimination half-life (t1/2ß 9h) are also similar to those predicted in adults after standardisation for size using allometric models. Clearance in neonates is approximately one-third of that described in adults, consistent with immature elimination pathways. Maintenance dosing, which is a function of clearance, should be reduced in neonates and infants when using a target concentration approach[49].

ADMINISTRATION OF DRUGS IN PAEDIATRIC CRITICAL CARE AREAS

Neonates are highly vulnerable to medication errors with a significantly higher error rate in the Neonatal Intensive Care Unit (NICU) setting specifically around drug ordering, dosing and intravenous (IV) formulations[50].

Medication therapy in the neonatal population is complex as in addition to the regular steps of drug use, where risks can occur; there are other factors such as lack of research on drug pharmacology in this population. Treatments involving small doses require numerous precise calculations and several dilutions to achieve the prescribed dose. The most common routes of drug administration on PICU and NICU are the IV route by continuous infusion or intermittent IV bolus and the enteral route.

A systematic review of publications on medication errors in neonatal care highlighted that administration errors accounted for approximately 46% of errors and human factors were the most cited cause of error [51]. Some studies described 56% of errors involving the intravenous route [52].

Clinicians are faced with the challenge of ensuring safe and effective drug prescribing in critically ill children with the drugs available in clinical practice. At the same time, nurses often need to administer drugs not designed for children or neonates. The process involves multiple manipulations of the original presentation of the drug in order to get a dose, which often is not the exact one prescribed, especially when the volumes involved are very small and there is a lack of accurate devices in clinical settings to measure these volumes. Volumes involving decimal points and less than 0.5ml are very common when dosing neonates and infants. In Academia or in a research institution the devices used to measure these volumes will likely be precision pipettes. However, in the clinical setting when treating the most vulnerable of patients, sometimes with very high risk drugs, accurate medication devices are not developed and available. The most commonly used smallest device is the 1ml commercially available syringe primarily tested with water and not with each specific drug and doses, and showing great variability on the dead space volume [51].

In addition, to add to the complexity, in many situations the accuracy of delivering the correct dose also depends on the process. There is no systematic method to make the IV doses in clinical practice; therefore, each operator (i.e. nurse, pharmacist, doctor) will manipulate the

product for a different dose/patient and day making difficult the prediction of the exact dose that each child receives since there is no quality control process.

In order to assess pharmacological efficacy and safety parameters of drugs, understanding of accuracy of the exact drug dose received by the child is paramount.
Allegart et al [53], reported that in case of amikacin, the use of paediatric vials improved dosing precision significantly when measuring pharmacokinetic parameters. Showing that using age-appropriate formulations has direct improvement on pharmacological parameters.

ADMINISTRATION OF INTRAVENOUS INFUSIONS

Continuous, IV drug infusions are commonly used in neonatal and paediatric critical care for life-sustaining medicines such as inotropes, analgesics, muscle relaxants, etc. A variable amount of drug, based on patient's weight, is added (often at the bedside) to the diluent to produce a constant relationship between rate of administration and drug dose (for example, 1 ml/hr of a dopamine infusion prepared using a given formula equates to 10 mcg/kg/min)[54]. This is thought to facilitate bedside dose adjustment, and also limits fluid volumes.

However, this approach increases the complexity of continuous IV infusion therapy, by requiring:

(a) bespoke drug-to-diluent dose calculations based on patient weight (often aided by calculation tools)

(b) several manipulations during preparation

(c) management of multiple, simultaneous infusions requiring evaluations of drug-drug, drug-diluent compatibilities, use and management of multiple lines and connectors and pressure effects when changing fluid rates

(d) syringe sizes from the point of view of measuring the drug and the diluent as well as final syringe size volume and impact on accuracy of small fluid rates [55]. Medication errors associated with this practice are potentially harmful, and are three times more likely to occur in paediatric and neonatal populations than adults [56,57].

In addition, infusions are also made, following this method, on retrieval settings where the nurses and doctors in the back of the ambulance or on air transfer have to make the complex

infusions for a particular child during transfer, as well as caring for the child, making the retrieval even more challenging.

This practice leads to products made by different technical operators and leading to several different concentrations undergoing no quality control testing.

To be able to assess drug efficacy and safety appropriately, the doses prescribed and administered need to be accurate. Nurses and other healthcare professionals rely on the administration technique and devices commercially available to be able to ensure accuracy. However, some studies[58-60] indicate that current practices in children's hospitals may lead to inaccurate concentrations. In addition, syringe sizes commercially available in healthcare settings to measure drug volumes do not reflect the volumes required for clinical doses, especially in the youngest age group, the neonates. Often volumes required to make infusions from a drug vial, involve decimal points and quantities < 0.5ml.

International organisations such as the Joint Commission in North America[61] and even the World Health Organisation (WHO)[62] have identified as best practice the use of standard concentrations in paediatric IV therapy, however, there is no guidance on how healthcare professionals can implement this appropriately.

Morphine is the most common infusion used in our units and the main drug together with clonidine in our sedation and analgesia protocol (Appendix 6.2). In order to evaluate accuracy of morphine drug administration, an observation study of the final concentration in the syringes was carried out. Syringes made by nurses and pharmacy were analysed for accuracy of content in relation to the intended concentration on the label.

A second study looked at a safe implementation of standard concentrations of morphine infusions in a Paediatric Intensive Care Unit, all the safety steps and evaluation of medication errors reported with the change in system. Finally, this approach was extrapolated to the rest of the drugs administered as continuous infusions in the unit.

ENTERAL DRUG ADMINISTRATION

Once the enteral route is established, liquid medicines, such as clonidine, require an enteral commercially available administration device for dose administration. Regulations for dosing

accuracy of oral medicines include requirements for assay and uniformity of content and/or mass of the product for both oral solid and liquid dosage forms, as well as demonstration of dosing accuracy for oral liquids since accuracy depends on the dose delivered by administration devices. Hence, administration devices should be manufactured to national or international standards for safe and effective use of liquid dosage forms. The recommended devices for doses below 5ml are the oral/enteral syringes[63], The British Standard for Medicine Measures, refers to specification for oral syringes delivering doses up to an including 5ml and only mandates the use of water for the tests to determine capacity of syringes but it does not consider the characteristics of liquids specifically[64]. Viscosity and surface tension, for example, can affect the dosing accuracy of administration devices. This has been shown in a study with oral droppers[65] but there is no data available for oral syringes. The last study of this thesis will look at accuracy of enteral syringes for administration of commonly prescribed oral liquid medicines in the PICU, since sedatives are also administered via enteral route.

1.2: THESIS JUSTIFICATION

Analgesia and sedation in PICU is an important therapeutic area; however despite this, most of the drugs routinely used are unlicensed and there are still many knowledge gaps which may not lead to the safest and most effective therapy in children.

Many medicines in PICU, including analgesia and sedation, are administered as IV infusions for a rapid and sustained effect and especially when the child is not absorbing medicines orally or when this route is contraindicated. However, the traditional practice of prescribing and administering medicines as continuous IV infusions, as in the case of morphine, could lead to inaccurate drug delivery to children therefore unpredictable response, especially when manipulations of small volumes are required to make the infusions.

Furthermore, on other occasions when the enteral route is established, liquid medicines require an enteral administration device and the accuracy of these devices has not been properly identified.

By having a pharmacist as part of the multidisciplinary team most of these aspects are identified and explored.

1.3 HYPOTHESIS

The combination of clinically focused research and service delivery evaluation leads to a more effective use of sedation and analgesia in neonatal and paediatric critical care areas

1.4 OBJECTIVES

Main

To identify a safer and more effective use of sedatives and analgesics in Paediatric Critical Care Areas

Secondary

- To identify a safe and effective use of oral clonidine as sedative in a range of patients in PICU
- To identify the deviations from approved standards of morphine concentrations in IV continuous infusions made by nurses and pharmacy
- To identify service development steps required for the introduction of standard concentrations of Morphine in a safe manner
- To identify the accuracy of enteral syringes commonly used in PICU for the administration of oral liquids

1.5 TIMELINES of STUDIES

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Clonidine Sedation	P, D	R				R, M	M, S	P			
Morphine Accuracy							P, D	M, P			
Morphine Standard and Other Infusions		P, D				D	D	D, R	R, M	S	2 P
Enteral Syringes									P, D	D, R,M	S

Yellow: Secondment months at the European Medicines Agency 08-10 and clinical research activity at the hospital stopped until 2011.

Abbreviations:

P: Protocol Design

D: Data Collection

R: Analysis of Results

M: Manuscript in progress

S: Submitted for publication

P: Publication Accepted

1.6 RESÚMEN EN ESPAÑOL

Una Unidad de Cuidados Intensivos Pediátricos (UCIP), se considera un área de alto riesgo en uso de medicamentos. La farmacoterapia en estas unidades está directamente asociada a la complejidad de las condiciones clínicas de los pacientes además de los riesgos inherentes a la infancia y a la naturaleza heterogénea de este grupo poblacional.

La farmacoterapia, especialmente en niños de cuidados intensivos, se ve afectada por una escasez de formulaciones diseñadas para la edad del paciente disponible en el mercado obligando a los equipos clínicos a usar medicamentos no autorizados o fuera de indicación. Ésto conlleva a posibles riesgos como el de desarrollar reacciones adversas al medicamento, de no conseguir los efectos deseados o de inducir a errores de medicación.

Una farmacoterapia segura y eficaz requiere unos conocimientos sobre la variabilidad y cambios constantes en la farmacocinética y respuesta farmacodinámica a los medicamentos desde el nacimiento a la edad adulta además de retos en prescripción y administración de medicamentos durante la infancia. En las unidades de cuidados intensivos neonatales y pediátricos el rango de edad de los pacientes varía entre 24 semanas de gestación y los 18 años.

La mayoría de los ingresos en una UCIP requieren analgésicos y sedantes para facilitar procedimientos diagnósticos y terapéuticos, respiración asistida, evitar la auto-extubación, reducir el metabolismo basal y la demanda de oxígeno y potenciar la analgesia y un sueño más prolongado y con menos interrupciones. Una sedación inadecuada es inaceptable en un niño vulnerable incapaz de moverse o comunicar una situación de estrés y ansiedad. Además ha sido relacionada con pronósticos adversos a corto y largo plazo e incluso una hospitalización más prolongada de lo que sería necesario. Entre los problemas que pueden surgir se encuentran el hipermetabolismo, retención de agua y sodio, lipolisis, síntomas cardiovasculares como taquicardias, aumento de consumo de oxígeno y presión arterial como también pueden presentarse alteraciones en la motilidad gastrointestinal y en la coagulación. A pesar de estos conocimientos todavía hay una gran variabilidad en los tratamientos de sedación entre diferentes unidades.

La mayoría de los niños ingresados en la UCIP requieren analgésicos y sedantes durante la fase aguda de la enfermedad administrados como perfusión endovenosa continua pero también por ruta enteral con una dosis calculada por peso del paciente. La dosis se ajusta acorde a las observaciones fisiológicas y criterios de comportamiento. La morfina y la clonidina son dos agentes de uso común en los protocolos de sedación y analgesia en estas muchas unidades pero su uso no está autorizado lo que supone poca evidencia sobre eficacia y seguridad en sedación infantil, especialmente con un agente terapéutico como la clonidina.

La práctica tradicional de prescripción y administración de medicamentos como perfusiones endovenosas continuas, como es el caso de la morfina, puede ser poco precisa generando una respuesta clínica impredecible. Ésto puede ocurrir especialmente cuando hay una manipulación de volúmenes pequeños para preparar las bombas de infusión. En otras ocasiones cuando la ruta enteral está establecida, los medicamentos orales líquidos requieren el uso de una jeringa enteral y la precisión de éstas no está estudiada en volúmenes pequeños.

Esta tesis se centra en los tratamientos de sedación y analgesia en una Unidad de Cuidados Intensivos Pediátricos Terciaria de Londres. Se estudian dos medicamentos que son de primera línea en esta unidad, la clonidina y la morfina, desde el punto de vista farmacocinético y dinámico y desde el de la administración. La clonidina es un medicamento de uso no autorizado que ha sido identificado por la Agencia Europea del Medicamento como “Necesidad Terapéutica Prioritaria” en áreas de dolor y anestesiología pediátricas ya que no hay muchos estudios que avalen esta práctica.

Con la participación de un farmacéutico en el equipo multidisciplinar estos aspectos son identificados y explorados en detalle.

OBJETIVOS

El objetivo principal de esta tesis es la identificación de un uso seguro y eficaz de sedantes y analgésicos en el área de Cuidados Intensivos Pediátricos. Como objetivos secundarios primeramente se identificará un uso seguro y eficaz de la clonidina oral como sedante en

un grupo de pacientes de UCIP, seguidamente se estudiarán las desviaciones en las concentraciones de morfina endovenosa preparada en farmacia y en la planta por personal de enfermería respecto a estándares aprobados por la Farmacopea Británica,. A la luz de estos resultados se diseñan los pasos a seguir para un cambio en la práctica de administración de perfusiones endovenosas mediante la introducción de uso de concentraciones estándar de morfina y se evalúa la seguridad de esta intervención. Finalmente se evalúa la precisión de las jeringas orales utilizadas de forma común en la UCIP para la administración de jarabes orales.

MÉTODOS

Esta tesis comprende seis estudios en tres secciones o temas para responder al objetivo principal y a los secundarios.

Primeramente, se realizaron dos estudios para determinar la seguridad y eficacia de la clonidina (capítulo 2). Un primer estudio observacional (capítulo 2.1) usando el protocolo de sedación de la unidad seguido de un estudio de farmacocinética (capítulo 2.2) ya que este medicamento es de uso no autorizado en cuidados intensivos pediátricos y esta información no está disponible o en el mejor de los casos es escasa. Se estudió la respuesta fisiológica y de comportamiento en niños intubados con ventilación asistida después de la administración del protocolo de sedación de la UCIP mediante la escala COMFORT y también se miró la respuesta hemodinámica. El modelo de farmacocinética poblacional se diseñó primeramente para determinar la absorción enteral de la clonidina en niños postquirúrgicos cardíacos por medio del programa NONMEN de regresión no linear de efectos mixtos.

Seguidamente, el propósito de la tesis fue de asegurar una administración precisa de la sedación y analgesia (capítulo 3). Se diseñaron dos estudios para establecer la precisión en la práctica de administración clínica actual y el impacto y seguridad de la implementación de una intervención para una mejora de precisión en la administración. El primer estudio de esta sección (capítulo 3.1) evaluó la precisión de las perfusiones de morfina endovenosa preparadas en planta y en la farmacia. La concentración de la morfina en las jeringas fue determinada por cromatografía liquida de alta resolución (HPLC). El

segundo estudio (capítulo 3.2) se focalizó en el impacto de la implementación de un sistema nuevo para la administración de perfusiones endovenosas y la evaluación de seguridad durante un periodo de 8 años. Los datos obtenidos para la morfina se extrapolaron al resto de los medicamentos administrados como perfusiones en la unidad elaborando una tercera publicación (capítulo 3.3).

Finalmente, la tesis estudió la administración de medicamentos enterales y la precisión de dos marcas de jeringas enterales comúnmente usadas en los hospitales con 11 jarabes de características fisicoquímicas diferentes mediante un estudio in vitro (capítulo 4.1).

RESULTADOS

El papel de la clonidina y otros agonistas α-2 como sedantes en la UCIP cada vez está más reconocido. Nuestro régimen de sedación con morfina y clonidina y bolos de lorazepam produjo una sedación aceptable en un 82% de las horas del estudio. Los niños admitidos en el estudio tuvieron un nivel adecuado y consistente de sedación en la mayoría de los casos con unas concentraciones plasmáticas de clonidina entre 0.9–2.5 ng/mL. Los datos sugieren un efecto sinergístico con el lorazepam y la morfina cuando las concentraciones plasmáticas de clonidina estaban en este rango aunque los resultados no son significativos sin un ensayo aleatorio controlado. El perfil de efectos secundarios de la clonidina era aceptable a dosis hasta los 5 microgram/kg cada 8-h. El límite de seguridad en niños se desconoce aunque dosis más altas que éstas se toleran cuando se administran de forma endovenosa. Sin embargo, dosis altas de clonidina pueden causar hipertensión secundaria a efectos agonistas de los receptores α-1. Ésto está documentado en adultos cuando alcanzan concentraciones plasmáticas de 3–4 ng/ml, generalmente al recibir dosis mayores de los 10 microgram/kg.

Los resultados y discusión están descritos en la siguiente publicación, trabajo original publicado en la revista *Intensive Care Medicine:*

Arenas-López S, Riphagen S, Tibby SM, Durward A, Tomlin S, Davies G, Murdoch IA. Use of oral clonidine for sedation in ventilated paediatric intensive care patients. Intensive Care Med. 2004 Aug;30(8):1625-9

Este trabajo se puede considerar como un estudio pilar ya que ha informado la decisión clínica en bastantes unidades que usan la clonidina como alternativa a las benzodiacepinas y sirve de base para otros estudios científicos de nuestra UCIP. La parte inicial de este estudio, su diseño, fue la base del Master en Ciencia de la doctorando en el 2002. El artículo se ha citado en más de 50 publicaciones relacionadas con la sedación en niños de cuidados intensivos y todavía permanece como una de las publicaciones principales especialmente porque se tocan los aspectos de seguridad hemodinámica y una reducción en la necesidad de uso de opioides y benzodiazepinas. Se ha utilizado recientemente en una publicación por *Hünseler et a*l[66] donde los autores también estudiaron en el primer ensayo aleatorizado de esta naturaleza, la reducción en requerimientos de fentanilo y midazolam en la población de UCI neonatal y pediátrica hasta los dos años de edad.

Al estudiar la absorción enteral de clonidina, ésta mostró una variabilidad interindividual considerable con una C_{max} entre 0.15 to 1.55 ng ml^{-1} (mediana 0.73) y T_{max} from 12 to 478 min (mediana 190). Sin embargo, las concentraciones plasmáticas que produjeron sedación se consiguieron en un 94% de pacientes, solamente la mitad lo consiguieron 70 min después de la dosificación. Los pacientes que no recibieron medicación vasoactiva mostraron una asociación positiva entre la dosis cumulativa de morfina y la T_{max} (interaction effect P=0.03); ésto no se observó en pacientes que recibieron inotrópicos. El perfil hemodinámico fue favorable; pocos pacientes requirieron bolos de suero y ésto no tenía relación con la concentración plasmática de la clonidina.

Los resultados y discusión están detallados en la siguiente publicación, trabajo original publicado en la revista *British Journal of Anaesthesia:*

Arenas-Lopez S, Mulla H, Manna S, Durward A, Murdoch IA, Tibby SM. Enteral absorption and haemodynamic response of clonidine in infants post cardiac surgery. Br. J. Anaesth. 2014; 113(6): 964-9. doi: 10.1093/bja/aeu258

Este trabajo se llevó a cabo en los pacientes pediátricos postquirúrgicos cardíacos y responde al uso de clonidina enteral en este grupo específico de pacientes donde la

perfusión sanguínea del área gastrointestinal puede verse comprometida debido a los procedimientos quirúrgicos y a la administración concomitante de otros medicamentos como los medicamentos vasoactivos con un posible impacto en la absorción del sedante. No se observó un efecto de reducción en la cantidad de clonidina absorbida, sólo un retraso en la misma por tanto un retraso en el efecto clínico esperado. De nuevo se hicieron observaciones hemodinámicas confirmando el hecho de que la clonidina es un fármaco seguro en este grupo de pacientes cardíacos.

Seguidamente se estudiaron los métodos de administración de estos fármacos. Al investigar la precisión de la administración de perfusiones parenterales un total de 19.2% de perfusiones preparadas por enfermería en la planta y un 7.8% preparadas en farmacia estaban fuera de los límites especificados por la Farmacopea Británica (±7.5%). Una desviación en la concentración de más de un 20% se encontró en las perfusiones preparadas en planta, aunque causadas por discrepancias de volúmenes de menos de 0.2 mL. La frecuencia y la magnitud de las desviaciones que se observaron en las perfusiones preparadas en farmacia era inferior a las preparadas en la UCIN. La última mostró un número significantemente mayor de muestras fuera de la especificación (p=0.015); sin embargo, desviaciones de las concentraciones intencionadas ocurrieron en las dos áreas. Entre las razones que pueden explicar esta inexactitud se encuentra el problema de falta de equipamiento de precisión para medir volúmenes pequeños pero de uso común en dosis pediátricas.

Los resultados y discusión están detallados en la siguiente publicación, trabajo original publicado en la revista *Archives of Disease in Childhood:*

> *Aguado-Lorenzo V, Weeks K, Tunstell P,Turnock K, Watts T, Arenas-Lopez S. Accuracy of the concentration of morphine infusions prepared for patients in a neonatal intensive care unit. Arch Dis Child* 2013; 98: 975–979
>
> A continuación concentraciones estándar de perfusiones endovenosas de morfina se diseñaron para prevenir las desviaciones, se implementaron para diferentes bandas de peso y se hizo un seguimiento en los aspectos de seguridad durante 8 años. Durante

este período se registraron 126 incidentes relacionados con la morfina (dos tercios en los 3 años seguidos a la implementación). Es de destacar que un 67% (85/126) resultó en ningún daño al paciente; y el resto, un 33% resultó en daño pequeño. El análisis de errores de administración reveló que hasta un 70% podría ser eliminado refinando la tecnología con la inclusión de códigos de barras. Éstos incluyen: selección de la jeringa errónea (24%), selección de programación de la bomba erróneo (28%), y el peso del paciente programado en bomba erróneo (18%).

La experiencia en este estudio se ha extrapolado para el resto de medicamentos que se administran por bomba de infusión en la unidad. Los resultados y discusión están recogidos con detalle en las siguientes publicaciones, trabajos originales publicados en la revista *Journal of Pharmacy and Pharmacology*.

Arenas-Lopez S, Stanley I, Tunstell P, Aguado-Lorenzo V, Philip J, Weeks K, Calleja-Hernandez MA, Durward A, Tibby S. Safe implementation of standard concentrations of morphine intravenous infusions in Paediatric Intensive Care. J Pharm Pharmacol Published online June 2016. DOI 10.1111/jphp.12580.

Perkins J, Aguado-Lorenzo V, Arenas-Lopez S. Standard Concentration Infusions in Pediatric Intensive Care: The Clinical Approach. Journal of Pharmacy and Pharmacology published online August 14, 2016 doi: 10.1111/jphp.12604

El uso de concentraciones estándar de infusiones intravenosas es un tema importante para el Ministerio de Sanidad Británico y la comunidad internacional incluyendo la O.M.S[61,62,67]. Actualmente, hay evidencia suficiente que demuestra que la administración de medicamentos intravenosos en la UCI Pediátrica y Neonatal es una práctica de alto riesgo y que la ruta para mejorar la seguridad es la prescripción y la administración de medicamentos intravenosos, especialmente infusiones, como concentraciones estándar. La tecnología evoluciona hacia el uso de códigos de barras lo que reduce el principal error de medicación que es la selección de la concentración errónea, especialmente si los productos se realizan en la farmacia. Éste es un cambio

importante en las prácticas de terapia intravenosa pediátrica ya que asegura una mínima o no manipulación de volúmenes pequeños, que se puedan producir en farmacia productos de alta calidad que cumplan con un control de calidad y el uso de tecnología que disminuya el riesgo de errores en programación y la infusión de la dosis errónea.

Estos artículos sirven de base para guiar a otros hospitales en la implementación segura del sistema y para guiar a las Autoridades. También es de esperar que este trabajo sea informativo para la industria farmacéutica en la producción de estos medicamentos a nivel nacional para todas las UCI pediátricas y neonatales, siguiendo un consenso entre unidades sobre las concentraciones clínicas requeridas. Los hallazgos de esta investigación se presentarán como parte del argumento para la constitución de una red multidisciplinar con Instituciones públicas, de carácter privado y regulatorio bajo un proyecto Europeo de desarrollo científico y tecnológico COST (www.cost.eu).

Finalmente, el estudio de la administración de medicamentos enterales demostró, como se esperaba, que el espacio muerto en las jeringas enterales difería entre marcas comerciales: Medicina (punta ancha) tenía un volumen de espacio muerto aproximadamente doble a las jeringas de la marca comercial Baxa (punta estrecha) para los diferentes tamaños: 1mL (0.11 $\pm$ 0.01 versus 0.06 $\pm$ 0.003, $p<0.001$), 2.5/3mL (0.13 $\pm$ 0.01 versus 0.06 $\pm$ 0.01, $p<0.001$), y 5mL (0.15 $\pm$ 0.02 versus 0.09 $\pm$ 0.02, $p<0.001$). Volúmenes inferiores o iguales a 0.5ml presentaron una variabilidad mayor con algunos volúmenes fuera de un 90-110% del rango intencionado. Baxa descargaba una dosis mayor que Medicina y que el volumen intencionado ($p<0.0001$). Se hizo una comparación de la precisión de los mismos volúmenes medidos en diferentes tamaños de jeringas por cada marca comercial. Las características fisicoquímicas no influenciaron de forma significante la precisión de la medición del volúmen en la jeringa más pequeña (1ml).

Los resultados de este estudio se recogen con detalle en el siguiente manuscrito que se ha enviado para publicación a la revista British Medical Journal: Quality and Safety.

Arenas-Lopez S, Gurung K, Calleja Hernandez MA, Tibby SM, Tuleu C. Accuracy of Enteral Syringes with commonly prescribed paediatric oral liquids. Submitted to BMJ:Quality and Safety

Este trabajo se centra en la administración de medicamentos enterales. La idea de este proyecto surge no sólo de la práctica clínica sino también del trabajo que la doctorando realiza para el Comité de Pediatría en la Agencia Europea del Medicamento (EMA).

Algunas soluciones orales de uso en la UCI Pediátrica son muy solubles en agua y fáciles de administrar, como por ejemplo la solución oral de clonidina, y otros viscosos como la solución oral de morfina (aunque hidrosoluble). En estos últimos casos las enfermeras tuvieron la impresión de que no toda la dosis salía de la jeringa al administrarla. A raíz de ésto, se establece una estancia de colaboración con la Facultad de Farmacia y el Centro de Investigación de Medicamentos Pediátricos de la University College London para estudiar el fenómeno.

El diseño de este estudio incluyó una selección de las soluciones orales de uso frecuente en la UCI y se eligieron ejemplos de medicamentos por sus características físico-químicas y volúmenes de dosis que eran representativos de dosis clínicas pautadas en la UCIP. Sin embargo, nos encontramos con dificultades que nos impidieron el estudio de la clonidina y de la morfina oral como líquidos a evaluar.

La clonidina es un producto realizado de forma galénica en nuestra farmacia, no autorizado, por lo que no podíamos suministrar muestras a la Universidad. A su vez, la morfina está clasificada como estupefaciente y con un registro muy estricto por tanto tampoco podíamos enviarlo a la Universidad ya que infringe la Ley con lo que se eligieron medicamentos de uso común en la UCI de características similares entre el rango de medicamentos a estudiar.

Este estudio aclaró tres conceptos de aplicación clínica; primeramente, la marca de jeringas no es intercambiable ya que se comportan de diferente manera. Además se tiene que elegir el tamaño correcto de jeringa para la administración de cada dosis.

Este estudio tiene también un mensaje importante para la industria y los Órganos Reguladores a la hora de comercializar medicamentos para el uso pediátrico ya que es importante estudiar el producto junto al dosificador. Es importante realizar estudios de validación de jeringas para el medicamento líquido oral durante el proceso de Autorización de Marketing, especialmente si se prevé la necesidad de utilizar volúmenes pequeños en la dosificación. Las jeringas comúnmente comercializadas no son precisas para volúmenes pequeños para todos los tipos de jarabes orales. Además sería deseable que las Autoridades Sanitarias, productores y Órganos Reguladores incorporasen protocolos clínicos reconocidos nacionalmente al proceso de manufactura de las jeringas. Por ejemplo, en el ámbito hospitalario, la administración enteral de medicamentos tiene que diferenciarse de la parenteral para evitar errores fatales de equivocación en la ruta de administración. Ésto implica que las jeringas que se incluyen como parte del envasado del medicamento en la mayoría de los casos no puedan usarse en el hospital, ya que no cumplen con estos protocolos de seguridad a pesar de ser las jeringas autorizadas en el proceso de Autorización de Marketing.

Seguidamente sería recomendable que la industria farmacéutica diseñara las concentraciones de los medicamentos a la luz de las dosis requeridas evitando volúmenes pequeños que resulten en una administración inexacta.

Finalmente un mensaje para los pacientes y los profesionales de la Salud en el ámbito de Atención Primaria es el de usar siempre la misma marca y tamaño de jeringa para la misma dosis de un medicamento y si hay una jeringa en el envasado del medicamento autorizado es la que se debería usar ya que contaría con estudios de precisión para el producto específico autorizado en una determinada indicación pediátrica.

CONCLUSIONES

La clonidina es una agente sedante seguro aunque la administración enteral en un paciente hemodinámicamente estable entre 2h y 6 h después de una intervención quirúrgica cardíaca puede ir asociado a un perfil de absorción lento. La mayoría de los pacientes consiguen eventualmente concentraciones plasmáticas terapéuticas. Por tanto,

se recomienda la administración enteral aunque si se necesita un efecto analgo-sedante rápido la administración parenteral es preferible.

La práctica actual de preparación de perfusiones endovenosas utilizando concentraciones que se han diseñado para adolescentes o adultos involucra la dilución de volúmenes pequeños en una jeringa y lleva a imprecisiones en la concentración final de la perfusión para la administración especialmente en neonatos. Se propone la implementación de las concentraciones estándar en pediatría para eliminar estos errores como una opción más segura.

La precisión en la dosificación con las jeringas enterales comúnmente utilizadas en los sistemas sanitarios es heterogénea para volúmenes de dosificación pequeños (<0.5ml) los cuales se usan regularmente en pediatría. La seguridad en la práctica clínica de administración de medicamentos enterales se mejora utilizando el tamaño correcto de jeringa para la dosis a administrar y siempre usando la misma marca comercial ya que las jeringas no son intercambiables. Preferiblemente la recomendación es la de usar siempre la jeringa testada en los procedimientos de autorización de marketing del medicamento.

Conocer exactamente la dosis que recibe el paciente es esencial a la hora de planificar y llevar acabo estudios farmacológicos y en la farmacoterapia asistencial del paciente pediátrico. Actualmente la dosis que el paciente recibe está sujeta a muchas variables en la práctica clínica. Esta tesis ha cubierto, de forma parcial, este problema para dos medicamentos, clonidina y morfina, proponiendo medidas para una mejora en la práctica clínica. Sin embargo, el alcance del problema requiere atención a nivel de la comunidad internacional de forma colaborativa.

REFLEXIÓN

Los estudios que comprenden esta tesis han sido realizados por la farmacéutica de la Unidad de Cuidados Intensivos pediátricos, El farmacéutico que desarrolla una labor asistencial en un área clínica de alta complejidad como la UCIP tiene una posición privilegiada para el avance en conocimientos fármaco-terapéuticos ya que una vez que

se adquieren conocimientos clínicos de la especialidad, el farmacéutico tiene unos conocimientos amplios en farmacología y comportamiento farmacéutico de los medicamentos pudiendo identificar problemas y áreas de vacío en conocimientos sobre el uso de estos fármacos y así poder ayudar a encontrar soluciones. El aspecto importante es la documentación de dichos problemas para poder construir evidencia científica. Sin embargo, la planificación de proyectos de investigación científica en clínica es una labor intensa y cada vez más compleja que requiere financiación y aprobación por los diversos comités de investigación y ética, y requiere una dedicación fuera de la asistencia clínica. Generalmente ésto es difícil de encontrar en los farmacéuticos que desarrollan una actividad asistencial si no hay un reconocimiento de esta necesidad por parte del equipo multidisciplinar.

CHAPTER 2: CLONIDINE FOR SEDATION IN CRITICALLY ILL CHILDREN

CHAPTER 2.1: Use of Oral Clonidine for Sedation in Ventilated Paediatric Intensive Care Patients

Arenas-López S, Riphagen S, Tibby SM, Durward A, Tomlin S, Davies G, Murdoch IA.

Intensive Care Med. 2004 Aug;30(8):1625-9

ABSTRACT

Objectives: We aimed to document our experience with oral clonidine when used as a sedative in combination with intravenous morphine and lorazepam in a group of mechanically ventilated children with single-organ, respiratory failure. In particular, our objectives were to establish the relationship between oral dose, plasma concentration, and sedative effect, and second, to document the side-effect profile.

Design: Prospective, cohort study over a 72-h period.

Setting: Regional paediatric intensive care unit.

Patients and participants: Twenty-four children were enrolled (median age 3 months) of whom ten were excluded (six due to extubation before 72 h, three sedation failures, one protocol violation).

Measurements and Results: Plasma clonidine was measured using gas chromatography mass spectrometry, and sedation assessed using the COMFORT score. Using a dose of 3–5 microgram/kg every 8 h, plasma concentrations appeared to plateau at approximately 41 h giving a mean value of 1.38 ng/ml (95% confidence interval 1.0–1.8). Adequate sedation was achieved during 82% (837/1022 h) of the study period; however, this decreased to 70.3% when analysed on an intention-to-treat basis. There was a concomitant overall decrease in the average hourly requirements for both morphine ($P = 0.02$) and lorazepam ($P = 0.003$). There were no documented episodes of bradycardia, hypotension or hyperglycaemia.

Conclusions: Oral clonidine may be a safe and effective sedative in combination with morphine and lorazepam for young children with single-organ, respiratory failure. This agent may also exhibit opioid and benzodiazepine sparing effects in this patient group. A full pharmacokinetic study is warranted.

Keywords: Clonidine · Sedation · Paediatric · Intensive care

INTRODUCTION

Patients requiring mechanical ventilation in the Paediatric Intensive Care Unit (PICU) frequently need a combination of analgesic and sedative drugs to facilitate ventilator synchrony, reduce anxiety, and decrease oxygen consumption. This is commonly achieved with combination therapy, usually an opioid and a benzodiazepine [1]. Unfortunately, many benzodiazepines carry a significant side-effect profile, including tolerance, withdrawal, and respiratory/circulatory depression [2, 3].

Clonidine is an alpha-2 partial agonist with sedative properties offering advantages over other agents, as it does not produce respiratory depression, decreases the dose requirements of other sedatives, facilitates opiate withdrawal, and can be administered orally [4, 5, 6]. The majority of studies in children have examined the use of clonidine as a co-analgesic prior to surgery [7, 8, 9, 10,11, 12, 13]; only one study has documented its use in the PICU as an intravenous sedative [14].

To date, no study has reported the use and pharmacokinetics of oral clonidine for routine sedation in PICU.

Since 2000, oral clonidine has been used with morphine as a first-line sedative agent in our 20-bed, tertiary PICU. Our annual admission rate is between 850 and 1,000 patients, and approximately 85% of patients receive clonidine at some stage during their admission. The aims of this study were thus to document our experience with oral clonidine in a group of children with single-organ (respiratory) failure. In particular, our objectives were to establish the relationship between oral dose, plasma concentration, and sedative effect, and second, to document the side-effect profile.

METHODS

The study was conducted over 1 year (January 2002 to January 2003). Inclusion criteria included any child up to 5 years of age requiring intubation for primary respiratory failure who was likely to need mechanical ventilation for longer than 72 h.

Exclusion criteria included:

- renal impairment (serum creatinine >100 mmol/l)

- liver impairment (total bilirubin >85 mmol/l and serum ALT or AST >100 U/l) [15]
- gastric intolerance
- administration of inotropes, arrhythmias, complex congenital heart disease, and severe neurological impairment.

For the purpose of this study, an arrhythmia was defined as any non-sinus tachycardia, junctional or idioventricular rhythm, or sinus bradycardia less than the lower limit of normal for age. The study was approved by the local research ethics committee, and informed consent obtained from patients' parents or guardians.

Study protocol

Sedation

All patients were treated using the standard PICU sedation proto- col. This included bolus intravenous morphine (100 microgram/kg), followed by infusion (20–40 microgram·kg·h for children, 10–20 microgram·kg·h for neonates). Clonidine was administered via the nasogastric tube at time 0 h as a test dose (1 microgram/kg) to assess the blood pressure response, followed 1 h later by 3 microgram/kg every 8 h. This could be adjusted up to 5 microgram/kg, depending upon the patient's sedation requirement. Clonidine was administered as an oral solution, formulated as a 10-microgram/ml preparation by the Pharmacy, St. Thomas' Hospital which holds an MHRA "specials" manufacturing license. The stability of the preparation was confirmed using a stability indicating assay. Lorazepam bolus doses (50–100 microgram/kg) were used whilst determining the optimal clonidine dose, and prior to invasive procedures. Neuromuscular blockade was not routinely used. Adequacy of sedation was assessed objectively using the COMFORT score on an hourly basis. The COMFORT score is a validated numerical scale comprising eight physiological and psychological domains, each graded as 1–5, producing a range between 8 (comatose) and 40 (hyperalert) [16]. An adequate level of sedation was agreed a priori as 13 to 23. This range was chosen to target a level of sedation that would produce a patient who was under analgesics, calm, with minimal risk of self-extubation, but able to maintain an appropriate cough reflex and spontaneous respiratory effort to achieve ventilator synchrony.

Sedation failure was defined as the need for greater than 400 microgram/kg of lorazepam in a 24-h period while receiving the maximal morphine (40 microgram·kg·h) and clonidine (5 microgram/kg every 8 h) doses.

Clonidine sampling and analysis

Blood sampling was limited to four occasions due to ethical considerations. As a detailed pharmacokinetic profile was not possible, we elected to measure clonidine trough concentrations only. A baseline sample was taken at time 0-h, and subsequently at times 17-h, 41-h, and 65-h. These time points represented 16-h after the initial dose and thereafter at 24-h intervals, and were chosen to accommodate the likely range of time to achieve steady state (41 h and 65 h samples), with the inclusion of a mid-point sample (17-h sample). Blood samples were collected in lithium/heparin tubes, centrifuged within 1-h at 13,000 rpm for 5 min, and the supernatant transferred to a clear tube and frozen at –20^{o}C until analysis. Plasma samples were assayed via gas chromatography mass spectrometry (ABS laboratories, London). The limit of detection of this method is 0.1 ng/ml, and the limit of quantification is 0.5 ng/ml. Sample preparation included addition of the internal standard (d4-clonidine), basification with sodium hydroxide, extraction into dichloroethane, and then derivatisation to form a pentafluorobenzyl derivative. The derivative was then cleaned via an acid wash and hexane extraction performed.

Side-effect profile

Potential side effects of clonidine include bradycardia, hypotension, and hyperglycaemia. An electrocardiogram was performed prior to commencing clonidine. Blood pressure and heart rate were monitored as per routine PICU practice. Blood glucose was measured 4–6 hourly using the Advantage Blood Glucose Monitoring System (Boehringer-Mannheim).

Statistical analysis

Continuous, temporal data were analysed using one-way, repeated measures analysis of variance, with post hoc Bonferroni-corrected t-tests where appropriate (Instat, Graphpad Software, San Diego, Calif., USA).

RESULTS

Twenty-four patients were enrolled (13 male) with a median (interquartile) age of 3 months (1.3–15.9 months), weight of 5.0 kg (4.5–5.6 kg) and PIM-derived mortality risk of 8.0% (5.3–9.8%). The commonest reasons for admission were acute viral bronchiolitis (n =13), pneumonia (n = 4), and croup (n = 3). Ten patients were excluded from final analysis, six because of extubation before 72 h, three secondary to sedation failure and one due to protocol violation. All three sedation failures occurred within 24 h and were subsequently managed successfully using intravenous clonidine infusions at 1 microgram·kg·h. The median length of ventilation among the remaining 14 patients was 81 h (78–111 h).

Clonidine dose and plasma concentration

All patients were commenced on clonidine as per protocol. There were no episodes of hypotension following the test dose. However, by 24 h 9/14 patients were receiving the maximum dose (5 microgram/kg). Table 1 shows the relationship between clonidine dose and plasma concentration. Although this increased with time (ANOVA P <0.001), the concentration appeared to reach a plateau by 41 h (P >0.05 compared to 65 h). The majority (23/28) of the plasma concentrations measured at time 41 h and 65 h were in the range 0.9–2.5 ng/ml.

Table 1 Temporal values for cumulative dose, plasma concentration and area under the curve (clonidine plasma concentration versus time) following oral clonidine administration. The area under the curve is evaluated on the trough (pre-dose) plasma concentrations only, as a full pharmacokinetic profile was not obtained. As such, it represents the minimum exposure to clonidine. Data are mean (95% confidence interval)

Time	Cumulative dose	Plasma concentration	Area under curve
(h)	(mg/kg)	(ng/ml)	(ng·ml·h)
0	0	0	0
17	8.1 (7.3–8.9)	0.9 (0.7–1.1)	7.9 (6.2–9.6)
41	20.3 (18.4–22.2)	1.38 (1.0–1.8)	34.9 (27.3–42.5)
65	32.7 (29.0–36.4)	1.4 (1.2–1.6)	68.6 (54.8–82.4)

Efficacy of sedation

The mean COMFORT score remained within the specified range throughout the study period (Fig. 1). Adequate sedation was achieved in 837/1,022 (81.9%) study h, while over-sedation and under-sedation occurred in 75/1,022 (7.3%) h, and 110/1,022 (10.8%) h respectively. However, the number of study hours where adequate sedation was achieved decreased to

70.3% (1023/1456) when analysed on an intention to treat basis. This figure incorporates the COMFORT scores for the six patients extubated before 72-h, and assumes a failure rate of 72-h for each of the three patients who required intravenous clonidine.

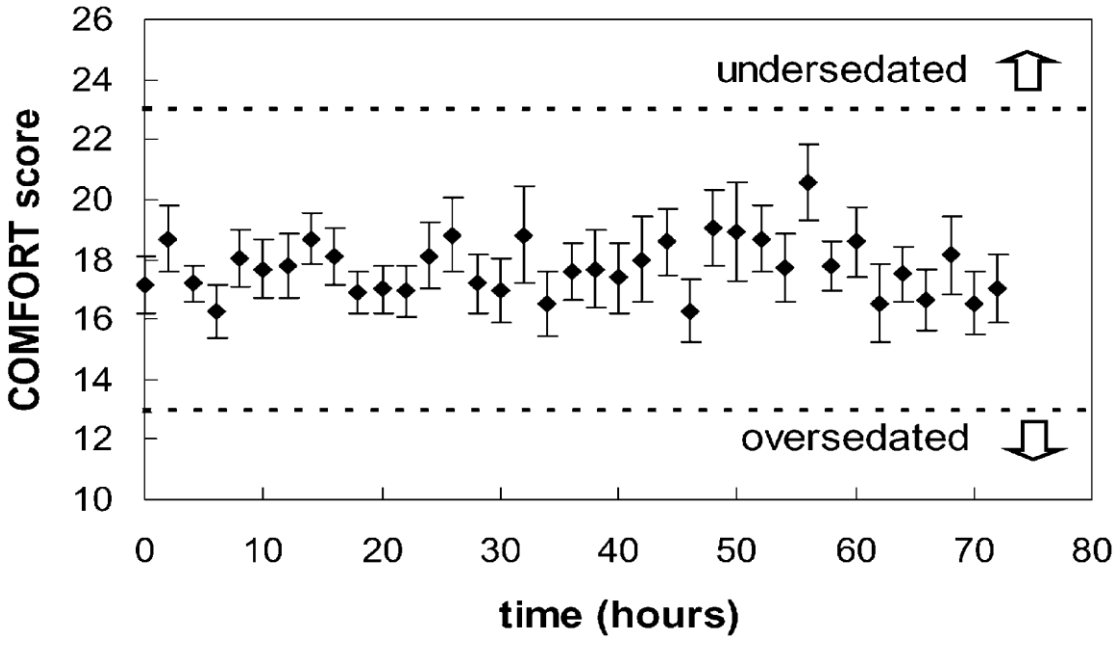

Fig. 1 Group sedation scores (COMFORT) over the study period. Data are mean, error bars SEM. Adequate sedation was defined as a COMFORT score of 13–23

There was a concomitant overall decrease in the average hourly requirements for both morphine (ANOVA P = 0.02) and lorazepam (ANOVA P = 0.003) when analysed over the first 64 h for the fourteen patients who completed the study (Fig. 2). This time interval was chosen for statistical analysis (rather than the complete 72 h study period) as it excluded a period of at least 12 h prior to the first patient extubation and was thus unlikely to be confounded by planned sedative weaning to facilitate extubation. Figure 2b also shows that by 56 h, the majority of the lorazepam was administered prior to invasive procedures, rather than for sedation.

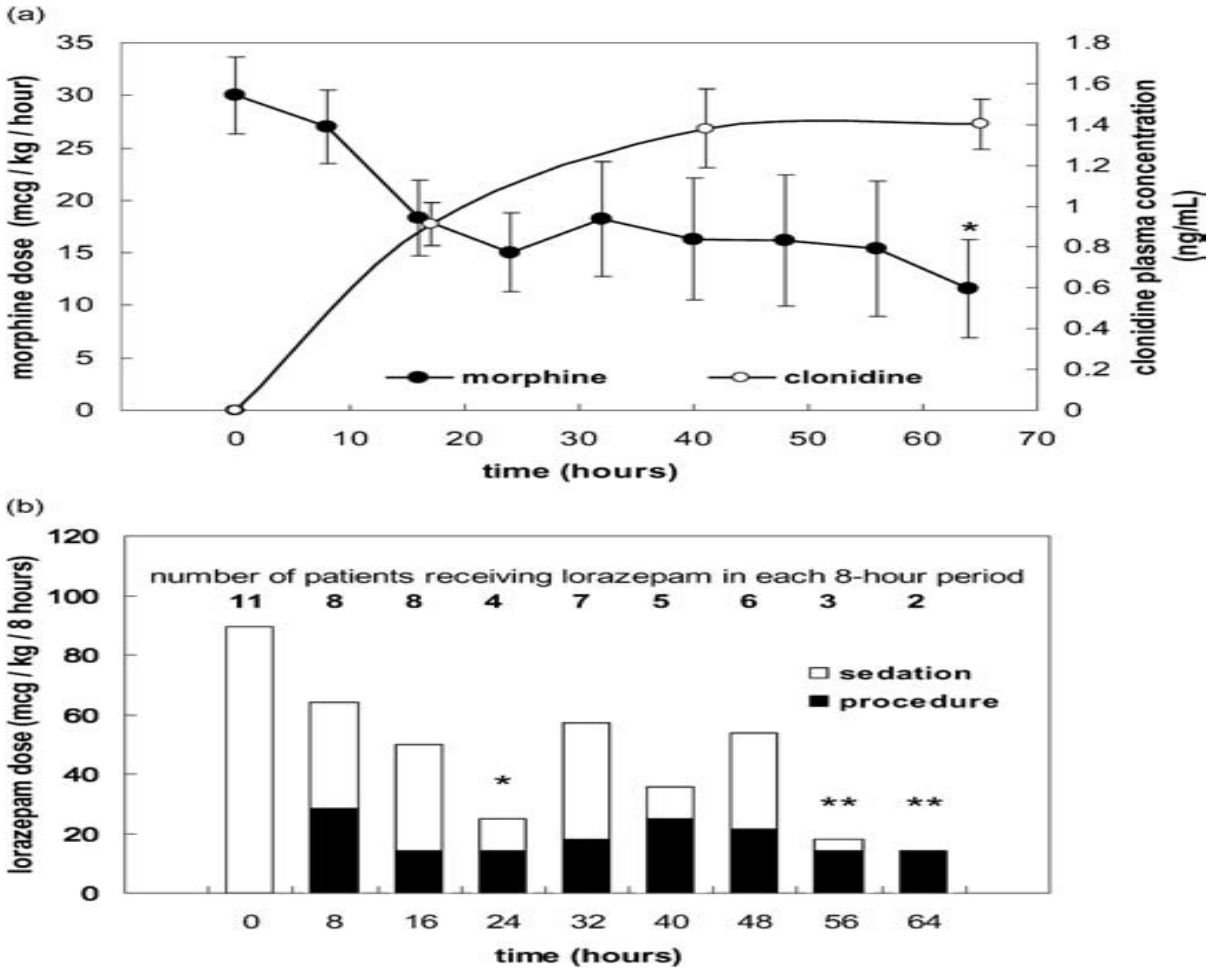

Fig. 2A,B A Average hourly morphine dose, plasma clonidine concentration; B average 8-h lorazepam dose with time. There was an overall decrease in both morphine (ANOVA P = 0.02) and lorazepam use (ANOVA P = 0.003). Bonferroni-corrected t-tests were performed, comparing time 0 with all subsequent time points (* P< 0.05, ** P< 0.01). Data are mean, error bars SEM

Side-effect profile

Table 2 shows the mean heart rate, blood pressure, and blood glucose profiles over the study period. Although the heart rate decreased significantly, this may have been influenced by other factors such as disease resolution. Of note, there were no episodes of bradycardia requiring treatment, and the lowest recorded heart rate was 85 beats per minute. Similarly, there were no recorded episodes of hypotension or hyperglycaemia.

Table 2 Heart rate,mean blood pressure, and blood glucose values. The ANOVA P values were as follows: heart rate (P <0.001), mean blood pressure (P = 0.03), blood glucose (P = 0.54). Data are mean (95% confidence interval).

Time (h)	Heart Rate (Beats Per Min)	Mean Blood Pressure (mmHg)	Blood Glucose (mMol/L)
0	152 (143–160)	69 (62-76)	4.1 (3.8-4.4)
8	137 (129-146)	60 (54-66)	4.3 (3.9-4.7)
16	134 (126-142)	62 (56-68)	4.6 (4.2-5.0)
24	137 (129-146)	62 (55-69)	4.6 (4.2-5.0)
32	134 (122-146)	59 (53-66)	4.9 (4.2-5.6)
40	139 (131-146)	61 (56-65)	4.8 (4.5-5.2)
48	132 (122-143)	60 (55-65)	4.6 (4.3-4.9)
56	130 (118-142)	63 (56-70)	4.4 (4.3-4.5)
64	129 (119-139)	63 (58-68)	4.6 (4.4-4.8)
72	126 (117-135)	66 (61-70)	5.0 (4.5-5.5)

DISCUSSION

Clonidine was introduced over 30 years ago as a centrally acting antihypertensive agent [17]. More recently, its role in analgesia, sedation, and opioid withdrawal has been highlighted in adult practice [5, 18, 19]. Over the last decade, many reports have examined its use in children primarily as a co-analgesic, usually prior to surgical procedures [7, 8, 9, 10, 11, 12, 13, 20].

To date, one study has reported its use as an intravenous sedative in the PICU [14]. On the basis of this study, and its known excellent absorption profile in adults, we adopted the oral preparation of this agent into our sedation regime in 2000, replacing intravenous midazolam. Although our clinical impression was favourable, we felt it necessary to formally assess and document its clinical efficacy and safety in reference to plasma concentration.

The clonidine dose range used in this study was 3–5 microgram/ kg, which was extrapolated from previous paediatric pre-medicant studies [13, 20] and adult schedules on a dose/kg basis. This produced an initial temporal increase in plasma concentration, which appeared to plateau by 41-h, suggesting that steady state values were achieved by this time. However, this cannot be ascertained with certainty from our data as a full pharmacokinetic profile was not obtained, nor were identical clonidine doses given to each patient. Nonetheless, steady state approximating 41-h is conceivable if we assumed the half-life of oral clonidine to be similar to that following intravenous and rectal administration in children (6–12- h) [7, 8], knowing that steady state is typically achieved at four to five times the drug half-life. The plasma concentrations reported in our study represent 8-h trough values following oral administration, and are similar to previous paediatric reports. Lonqvist documented a median maximum plasma concentration of 0.7 ng/ml following rectal administration (2.5microgram/kg) [8], while Bergendhal reported median levels of 0.38 ng/ml and 0.76 ng/ml 15 min after single intravenous doses (0.625 microgram/kg and 1.25 microgram/kg, respectively)[9]. Although our study differs from these in regard to route of administration, patient age, and timing of samples, the comparable plasma concentrations suggest a favourable absorption profile with oral use. Again, a full pharmacokinetic study is warranted.

The sedation routine used in this study was the standard regime for our unit. Our sedation regime produced acceptable sedation in 82% of the study hours, remarkably similar to that

reported by Ambrose [14]. However, direct comparison between these two studies is difficult because of differences in sedation scores used, endpoints, and adjunctive sedatives. We demonstrated a consistent and adequate level of sedation in the majority of cases at clonidine plasma concentrations of 0.9–2.5 ng/ml. This is comparable to that reported in adults, where maximal sedative effect is achieved at concentrations of 1.5–2.0 ng/ml [17]. Our data also suggest a benzodiazepine and morphine sparing effect when the plasma clonidine concentration approaches this range, although this cannot be proven without a randomised controlled study. However, the antinociceptive effects of clonidine have been well known for over 20 years [21], and the benzodiazepine sparing effects of this agent in healthy volunteers have been shown recently [22].

We found an acceptable side-effect profile using oral clonidine at doses of up to 5 microgram/kg every 8-h. The safe upper limit in children remains unknown, although doses higher than this have been tolerated when used intravenously [14, 23]. However, high-dose clonidine can cause hypertension secondary to agonistic effects on alpha-1 receptors. This has been reported in adults achieving plasma concentrations of 3–4 ng/ml, typically receiving doses greater than 10 microgram/kg [17].

There are several limitations to our study. As stated earlier, we did not perform a full pharmacokinetic profile because of the excessive volume of blood required relative to patient size. This means that detailed information on peak plasma concentration, half-life, and clearance are lacking. We cannot extrapolate our findings with confidence to the wider PICU population, particularly those with multiple organ failure for several reasons. First, hepatic and renal impairment are likely to alter clonidine pharmacokinetics, as approximately 40% of an administered dose undergoes oxidative metabolism in the liver leading to inactive metabolites, while the remaining 60% is excreted unchanged by the kidney. Second, the apparent volume of distribution (0.96L/kg) [7, 8] may change in critical illness.

Third, although haemodynamic side effects have not been demonstrated following cardiac surgery [14], this may differ in patients with cardiac failure from other causes such as sepsis. Fourth, it is difficult to separate the sedative effects of clonidine from the other two agents used, namely morphine and lorazepam. We did not measure plasma concentrations of either of these compounds or their active metabolites; however, the doses used were modest, as can be seen from Fig. 2.

In summary, we have shown that oral clonidine is a safe and effective sedative in combination with morphine and lorazepam for young children with single-organ, respiratory failure. Over time, this agent demonstrates morphine- and benzodiazepine-sparing effects. Using a dose of 3–5 microgram/kg every 8-h, plasma concentrations appear to plateau at approximately 41-h, usually in the range of 0.9–2.5 ng/ml. Further studies are warranted to elucidate the full pharmacokinetic profile of clonidine and to explore its use in the wider PICU population.

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Chapter 2.2: Enteral absorption and haemodynamic response of clonidine in infants post cardiac surgery

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ABSTRACT

Background

Clonidine is a useful analgesic-sedative agent; however, few data exist regarding its use in infants after congenital heart disease surgery. We thus aimed to assess the absorption and safety of enterally administered clonidine in this setting.

Methods

Sixteen infants (median age 6.7 months) received a single nasogastric dose of 3 microgram kg^{-1} clonidine 2–6- h after surgery. Blood samples were obtained at seven time intervals (up to 480 min). Plasma concentration profiles were obtained, and then pooled with a previous study (137 samples, 30 infants) for estimation of population pharmacokinetic parameters (NONMEM version 7.2).

Results

Enteral absorption showed considerable inter-individual variability, with clonidine C_{max} ranging from 0.15 to 1.55 ng ml^{-1} (median 0.73), and T_{max} from 12 to 478 min (median 190). Although therapeutic sedative plasma concentrations were achieved in 94% of patients, only half had attained this by 70 min post-dose. Patients who did not receive inotropes exhibited a positive association between cumulative morphine dose and T_{max} (interaction effect P=0.03); this was not seen among those receiving inotropes. The haemodynamic profile was favourable; few patients required fluid boluses, and this bore no relationship to plasma clonidine concentration. Population pharmacokinetic parameter estimation yielded results similar to previous paediatric studies: clearance 13.7 litre h^{-1} 70 kg^{-1} and V_d 181 litre 70 kg^{-1}.

Conclusions

Early postoperative enteral clonidine produces favourable haemodynamic profiles and therapeutic plasma concentrations in the majority of cardiac surgical infants; however, the time to achieve this can be erratic. Thus, parenteral administration may be preferable if rapid analgo-sedative effects are needed.

Keywords:

cardiac surgical procedures; clonidine; infants

INTRODUCTION

The importance of optimizing the balance between oxygen delivery and consumption after surgery for congenital heart disease is widely acknowledged.[1] Several studies have evaluated strategies for optimizing oxygen delivery;[2–4] however, comparatively little attention has been devoted to exploring therapies that minimize oxygen consumption. A major component of oxygen consumption in the immediate postoperative period is the degree of sedation/analgesia. Surprisingly, there is lack of consensus regarding the optimal sedative regime in critically ill children; as a result, a wide variety of agents are used.

Clonidine has several properties which make this drug a potentially useful agent in the cardiac postoperative period. It is a partial agonist of central and peripheral a-2 receptors with analgesic, sedative, and antihypertensive effects.[5] Thus, it may both reduce oxygen consumption and prevent deterioration in oxygen delivery secondary to sustained increases in afterload. The majority of paediatric reports have evaluated clonidine use in the general perioperative or paediatric intensive care settings,[6,7] with only two reports assessing clonidine administration after cardiac surgery.[8,9] In addition, reports have primarily assessed clonidine when administered via i.v., intrathecal, and/or rectal routes.[10 – 12] Recently, a team from Karolinska University Hospital has published an observational study investigating oral bioavailability of clonidine in children when used as a premedication for adenotonsillectomy.[13]

We have been using an oral preparation of this agent in critically ill patients since 2000, and demonstrated its safety and efficacy in a group of mechanically ventilated infants with respiratory failure.[14] However, as the beneficial effects of early use of the gastrointestinal tract in cardiac patients are increasingly recognized, we wished to evaluate the enteral absorption of clonidine when used in the immediate postoperative period after congenital heart disease surgery. Our primary aim was to characterize absorption profiles for clonidine after enteral administration, with a secondary aim of assessing haemodynamic stability. In addition, these data could be used to

refine previously estimated pharmacokinetic parameters of oral clonidine when used in critically ill infants.

METHODS

The study was conducted over a 6-month period (March– August 2006) and approved by the Guy's local research ethics committee (ref: 2004/02/12), with informed consent obtained from patients' parents or legal guardians.

Inclusion criteria were any infant (>28 days to 1 yr of age) undergoing surgery for congenital heart disease that required postoperative monitoring with central venous and arterial lines. Exclusion criteria included: pre-existing renal or hepatic impairment, or clinically significant haemodynamic instability.

Conduct of the study

Patients who were haemodynamically stable (defined as not requiring an increasing inotropic dose or more than 15 ml kg^{-1} fluid boluses in the previous hour) received a single, nasogastric dose of 3 microgram kg^{-1} clonidine at between 2 and 6-h after surgery. Clinical observations were as per routine care. Clonidine solution was manufactured by Guy's & St Thomas' manufacturing unit under a special manufacturing licence (10 microgram ml^{-1} solution).

Arterial blood samples (2 ml) for plasma clonidine assay were obtained immediately before clonidine administration (t0), and at the following post-administration time intervals: 5–20 min (t1), 25–40 min (t2), 50–70 min (t3), 110–130 min (t4), 180– 300 min (t5), and 420–480 min (t6). Time points were chosen using information derived from two prior studies.[15 16] Designation of sampling time intervals, rather than single points, allows for greater accuracy in estimation of pharmacokinetic profiles using population-based pharmacokinetic software (provided the time of sampling was recorded accurately).

Blood specimens were immediately centrifuged for separation of plasma and stored at -70^{0}C. Plasma clonidine concentration was assayed using high performance liquid chromatography mass spectrometry at the Advanced

Bioanalytical Service Laboratories Ltd, Hertfordshire. Sample preparation included addition of the internal standard (d4-clonidine), basification with ammonium hydroxide, extraction into dichloroethane:isopropanol (90:10), drying, and then reconstitution in 1% (v/v) formic acid solution for quantitative determination using high performance liquid chromatography tandem mass spectrometry with selected reaction monitoring of the protonated molecular ions using a CTC autosampler (CTC Analytics, Zwingen, Switzerland), Agilent 1100 liquid chromatograph (Agilent Technologies, Wokingham, UK), interfaced to an API4000 tandem mass spectrometer (AB SCIEX, Framingham, MA, USA). The samples were analysed with duplicate calibration standards containing clonidine in control human plasma prepared at 0 (blank), 0.1, 0.2, 0.5, 1, 2, 5, 10, and 20 ng ml^{-1} and duplicate quality control samples (QCs) at 0.3, 2.5, and 15 ng ml^{-1}. The limit of quantification of this method is 0.1 ng ml^{-1}, with the range of linearity 0.1–20 ng ml^{-1}, and intra- and inter-assay coefficients of variation of <10 and <15%, respectively. We were unable to detect metabolites of clonidine, as the above method is highly specific, and no reference standards for metabolites were available at the time of analysis.

Pharmacokinetic methodology and statistics

Plasma concentration profiles after the single oral dose of clonidine were first examined for the post-cardiac surgical patients in the current study. These data were then pooled with trough plasma concentrations from our previous study in infants with respiratory failure, and pharmacokinetic parameters recalculated. The population pharmacokinetic model was developed using the mixed effects non-linear regression modelling programme, NONMEM (version 7.2; Icon) and a gfortran compiler. Post-processing of NONMEM output was conducted using the software Perl-speaks-NONMEM (v 3.4.1), R (v2.13.0), and Xpose (v4.3.2). A detailed description of the modelling method including model selection, development, and validation is provided in the Supplementary material.

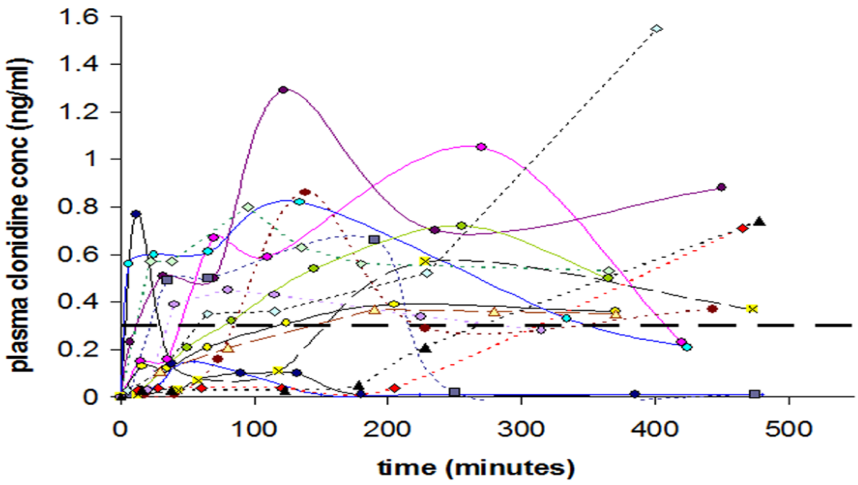
RESULTS

Sixteen infants post-cardiac surgery were studied, with a median (IQR) age of 6.7 months (5.9–8.6) and weight 6.9 kg (5.4 – 7.8). Diagnoses included: tetralogy of Fallot repair (n=8), ventricular septal defect (n=4), ventricular and atrial septal defect (n=2), and atrioventricular septal defect (n=2). Eleven of 16 patients were receiving the phosphodiesterase inhibitor milrinone (dose range 0.3–0.7 microgram kg^{-1} min^{-1}); no other inotropes were used during the study period. The median (IQR) dose of morphine at each time point was 30 microgram kg^{-1} h^{-1} (20–40).

Enteral absorption

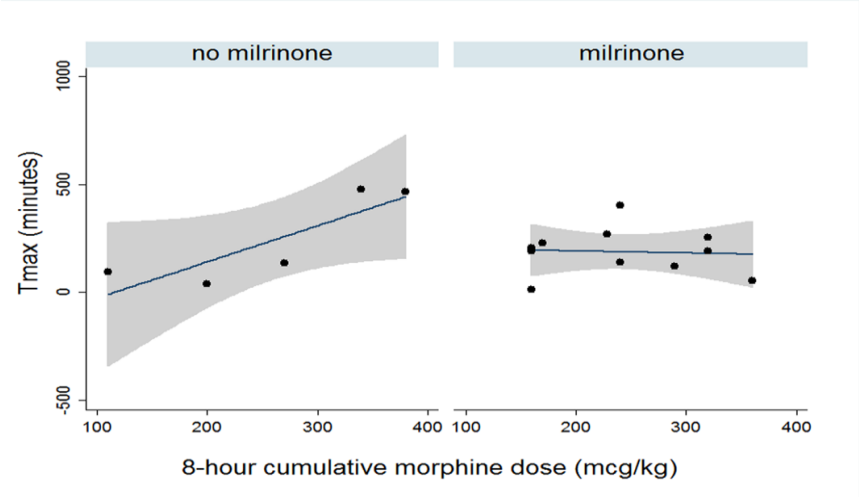
Enteral absorption profiles showed considerable variability (Fig. 1), with the maximum measured plasma clonidine concentration ranging from 0.15 to 1.55 ng ml^{-1} (median 0.73), and the time to maximum measured concentration (T_{max}) ranging from 12 to 478 min (median 190). Of note, 94% of patients (15/16) achieved the minimum therapeutic sedative plasma concentration of >0.3 ng ml^{-1}.[14] However, this was achieved relatively slowly, in that only half of the patients had attained this concentration by 50 – 70 min (t3), and three-quarters by 110 – 130 min (t4).

Figure 1: Enteral Absorption Profiles for all patients. The dashed horizontal line represents a plasma concentration of 0.3ng ml-1, which is the desired minimum therapeutic concentration at which sedative effects are seen



Multiple linear regression revealed an interaction effect between cumulative morphine dose (over the first 8 postoperative hours) and milrinone use in terms of their relationship with T_{max} (Fig. 2). There was a positive association between cumulative morphine dose and T_{max} among patients who did not receive milrinone (coefficient 1.68, P=0.009); with no such relationship for patients receiving milrinone (coefficient -0.09, P=0.86, interaction P=0.03).

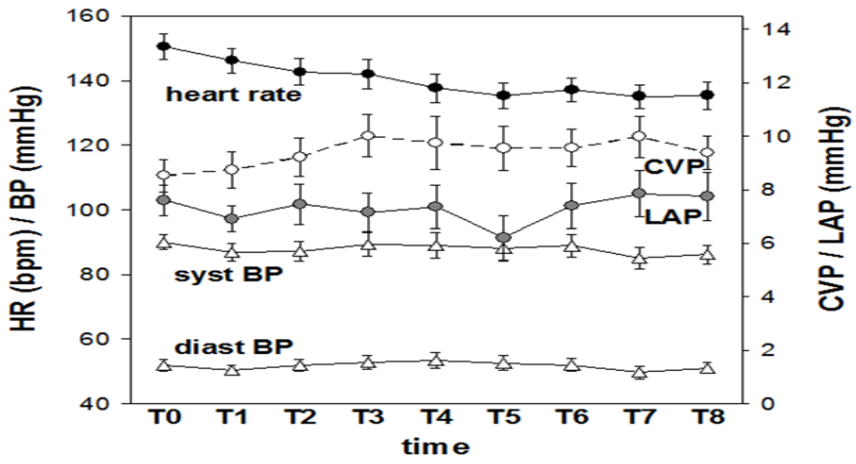
Figure 2: Relationship between time to maximum plasma concentration of clonidine (Tmax) and cumulative morphine dose. An interaction is seen with the use of the phosphodiesterase 3 inhibitor, milrinone. Regression lines are shown with the shaded areas representing 95% confidence intervals



Haemodynamic effects

Haemodynamic profiles are shown in Figure 3. Five patients required a total of seven fluid boluses for hypotension; four of these occurred at t1. Timing of fluid bolus bore no relationship to the plasma clonidine concentrations; five boluses were given when plasma clonidine was below the limit of quantification; for the remaining two, the plasma clonidine concentrations were 0.15 and 0.63 ng ml^{-1}.

Figure 3: Haemodynamic effects after clonidine administration. CVP, central venous pressure; LAP, left atrial pressure; AP, arterial pressure. Symbols represent mean values, error bars are SEM



Pharmacokinetic parameters

Estimation utilized data pooled from this and our previous study.[14] A total of 137 samples from 30 children were available for analysis (97 from the current study, the remaining 40 coming from 14 respiratory patients).

A three-transit compartment absorption model coupled with a one-compartment disposition model was found to be the most appropriate structural model. Estimation of the between-subject variability in the absorption model parameters was not possible as it resulted in model convergence difficulties. The mean (SD) of individual subjects absorption half-life was 3.3 (1.2) h.

Significant improvement in model fit was achieved when weight (standardized to 70 kg) was associated linearly with both clearance and volume. In the case of clearance, weight was allometrically transformed by setting weight to a

power of 0.75. No other covariate was found to have significant influence in the model. The population estimates (and associated between-subject variability) of clearance and volume of distribution were 13.7 (56.3% CV) litre h^{-1} 70 kg^{-1} and 181 (37.8% CV) litre kg^{-1}, respectively.

The parameter estimates from the final model along with their associated 95% confidence intervals are shown in Table 1. Both the absorption and disposition parameters were estimated with reasonable precision. The bootstrapped values show no real bias in comparison with the final model suggesting model stability.

Table 1: Pharmacokinetic parameter estimates from the final model. *Bias % calculated using the following equation: % bias= (final model estimate/bootstrap estimate)/final model estimate x 100. † Absorption rate constant, $K_a=K_{a1} + K_e$. Where $K_e=CL/V$. Parameterized in this way to avoid "flip-flop". ±Absorption half-life=0.693/K_a presented as mean (SD). This was determined using a posthoc individual subject's Bayesian estimate of K_a. ¶Study 1, postoperative cardiac children (current study); Study 2, ventilated respiratory children [14]

Parameter	Study Dataset		Bootstrap (500 replicates)		Difference [a](bias %)
	Estimate	**95% CI**	**Estimate**	**95% CI**	
CL (L h^{-1} 70kg^{-1})	**13.7**	**10.1 – 17.3**	**14.1**	**9.9 – 21.8**	**7.1**
V (L 70kg^{-1})	**181**	**143 - 219**	**182**	**138 – 235**	**0.5**
Ktr (per h)	**94.0**				
Ka1 (per h)*	**0.07**				
Absorption Half Life (h)** **Mean(SD**)	**3.32 (1.16)**				
BSV in CL (% CV)	**56.3**	**22.9 – 76.7**	**61.2**	**31.9 – 113**	**1.6**
BSV in V (%CV)	**37.8**	**24.9 – 47.3**	**36.7**	**20.9 – 50.8**	**2.7**
Residual error, additive (SD) ng ml^{-1}					
Study 1[b]	**0.21**	**0.15 -0.26**	**0.21**	**0.15 – 0.28**	
Study 2[b]	**0.26**	**0.16 -0.33**	**0.26**	**0.15 – 0.33**	

*Absorption rate constant, Ka = Ka1 + Ke, where Ke = CL/V. Parameterised in this way to avoid 'flip-flop'.

**Absorption half-life = 0.693/Ka presented as mean (SD). This was determined using post-hoc individual subject's Bayesian estimate of Ka.
[a]Bias % calculated using following equation:
% bias = (final model estimate / bootstrap estimate) / final model estimate * 100
[b]Study 1 = Postoperative cardiac children (current study); Study 2 = Ventilated respiratory children (ref 14)

Plots of the observed vs the final model-predicted plasma clonidine concentrations indicated excellent correlation (see Supplementary Fig. S1). Plots of weighted residuals vs both time and predicted serum clonidine concentrations revealed no systematic error (data not shown). The ability of the final model to simulate (and hence describe) the observed data is illustrated by the visual predictive check (Fig. 4). Overall, the median and 5th and 95th percentile 'capture and envelope' the observed data reasonably well, suggesting model appropriateness.

Figure 4: Prediction-corrected visual predictive check of model performance based on n=1000 replicates. The figure utilizes combined data from the current and previous studies. [14] See supplementary material for further explanation

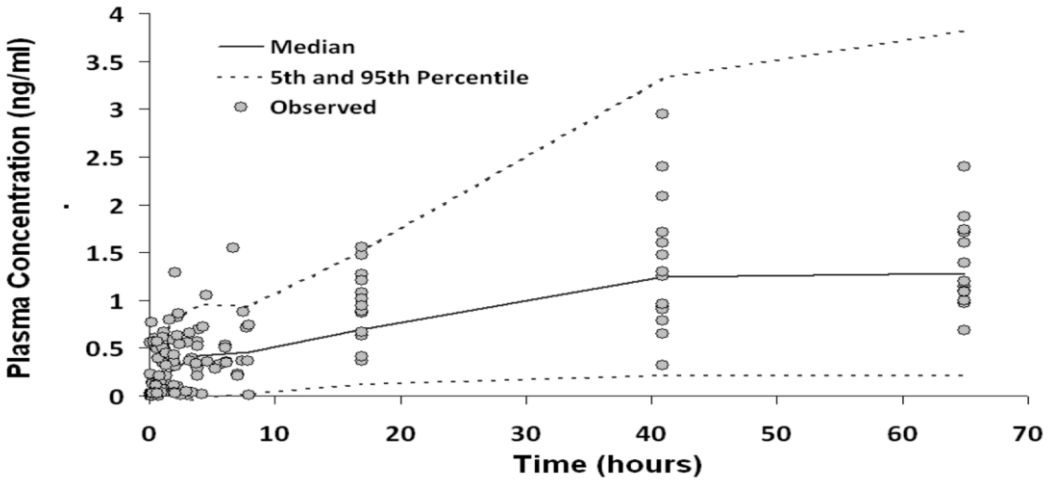
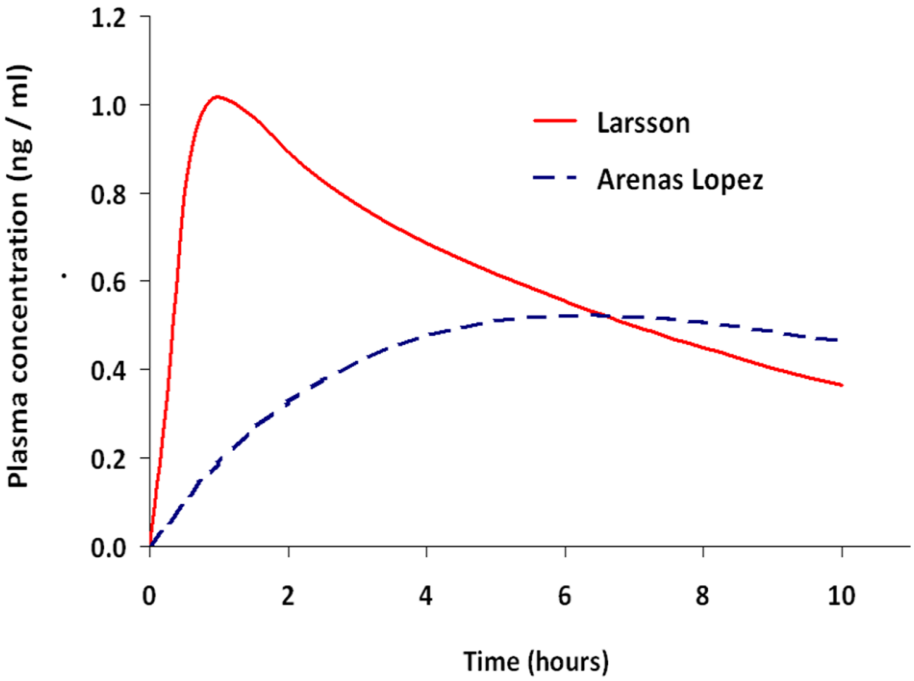


Figure 5: Comparison of simulated plasma clonidine concentrations vs time for a 1year-old infant after a single dose of 3microgram kg^{-1} clonidine using absorption profiles derived from our and Larsson and colleagues [13] studies.



DISCUSSION

The value of clonidine and other α-2 agonists as sedatives in the intensive care unit are increasingly recognized.[14 17] Over the last decade, enteral and i.v. clonidine have been used in our unit as first-line sedative agents, including patients post-cardiac surgery. Limited pharmacological data exist on clonidine use in paediatric intensive care, with the majority of reports detailing i.v. use. However, there are several reasons why enteral administration may be preferable in the intensive care setting (e.g. reduced infection risk, drug compatibility, fluid restriction), which provided the impetus for our study.

Our results show that although the majority (94%) of patients achieved therapeutic plasma clonidine concentrations, the absorption was often slow, with half of the patients requiring longer than 1-h to reach these values. Compared with healthy children in the study by Larsson and colleagues,[13] our T_{max} was approximately three times longer (190 vs 63 min), with a longer absorption half-life (3.3 vs 0.45-h) and more variable peak plasma concentrations. Simulated plasma concentrations illustrating the difference in typical absorption profiles between our and Larsson and colleagues' studies are shown in Figure 5. The reduced rate of absorption in our population may be due to reduced splanchnic blood supply post- cardiac surgery, which can be exacerbated by pharmacological effects of drugs such as opioids which delay gut transit time.[18] This is consistent with our findings, whereby increasing morphine doses were associated with higher T_{max} only in patients who were not receiving inotropic support (Fig. 2); it is possible that these patients had an unappreciated lower cardiac output state. Conversely, this relationship was not seen for patients who were receiving inotropes. An additional difference is the administration method; unlike the study by Larsson and colleagues, our patients received the clonidine solution nasogastrically without further dilution in water or juices.

The population estimates of oral clearance and volume of distribution in our postoperative cardiac children are very similar to those reported by Potts and colleagues[9] in their pooled population pharmacokinetic analysis of i.v.,

epidural, and rectal clonidine data, 13.7 vs 14.6 litre h^{-1} 70 kg^{-1} and 181 vs 182 litre 70 kg^{-1}, respectively, and also similar to values reported in adults.[9] However, whereas Potts and colleagues identified an effect of age on the clearance parameter, no such effect of age or any other covariate was found during model development, perhaps a reflection of our limited sample size and restricted age limit.

Our data also add to previous work documenting the safe haemodynamic profile with this drug when used after cardiac surgery. Ambrose and colleagues[8] studied the use of i.v. clonidine infusion in a cohort of 10 post-cardiac surgery patients. They specifically investigated the effects on cardiac index, heart rate, and arterial pressure after a dose of 1 microgram kg^{-1} h^{-1}. Most of the patients received concomitant low-dose inotropic support which either stayed the same or was reduced during the 8-h study period. They found no significant change in trends over 6 h in heart rate [166 (SD 17.9) to 154 (20.2) beats min^{-1}], arterial pressure [60 (SD 9.8) to 64 (11.1) mm Hg], or derived cardiac index [5.7 (SD 2.2) to 6.0 (1.51) ml m^{-2} min^{-1}]. These results are consistent with our haemodynamic findings (Fig. 3). In addition, we found no relationship between need for treatment with fluid boluses and neither timing of clonidine administration nor plasma clonidine concentrations. This was also shown in our previous study in children with respiratory failure,[14] where the arterial pressure did not decrease over time, although heart rate exhibited a small temporal reduction, this could have been explained by disease resolution, and never fell outside the normal limits for patients' age. In summary, the findings from these three studies suggest that clonidine has a safe haemodynamic profile in critically ill children.

The slow and erratic absorption profiles for enteral clonidine shown in our study patients are somewhat countered by two potentially beneficial effects. Firstly, this appears to largely avoid the biphasic arterial pressure changes associated with i.v. bolus administration. Secondly, once the potentially sedative plasma concentration of 0.3 ng ml^{-1} is achieved, this appears to be sustained. These findings suggest that there may be some advantage to early

enteral administration in this patient group.

Limitations

Several limitations of this study require acknowledgement and elaboration. Firstly, we did not attempt to measure the primary desired pharmacodynamic effect of clonidine, sedation, but rather chose to target achieving a pre-defined minimum plasma concentration of >0.3 ng ml^{-1}. However, we feel that this was a reasonable assumption, as it was based upon pharmacodynamic assessment (via the COMFORT score) in our previous study, conducted on infants of a similar age.[14] Furthermore, accurate assessment of sedation in this patient group is confounded by many factors, such as cardiovascular status, cerebrovascular status, and recent emergence from prolonged general anaesthesia. The study design could have been strengthened by concurrent measurement of oxygen consumption, of which level of sedation is a major contributor.

Secondly, we could not estimate bioavailability, as patients did not receive i.v. clonidine. However, we feel this is a minor limitation. Furthermore, as our C_{max} was similar to Larsson and colleagues,[13] it is possible that bioavailability is broadly comparable.

Finally, as this was a single-dose study, it is thus difficult to extrapolate to steady state. In addition, the erratic and occasionally reduced rate of enteral absorption for clonidine may become less important after multiple dosing.

CONCLUSION

Clonidine is a safe sedative agent in the postoperative cardiac surgery period. However, enteral administration between 2 and 6-h after surgery in haemodynamically stable patients may be associated with a delayed absorption profile, with the majority of patients eventually achieving therapeutic plasma concentrations. Thus, we would recommend early enteral administration, or, if rapid analgosedative effects are needed, parenteral administration may be preferable.

Acknowledgement

We would like to thank Ms Mira Doig of the Advanced Bioanalytical Service Laboratories Ltd, Hertfordshire, for assaying the plasma clonidine concentrations

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Online Supplementary material

Pharmacokinetic Modelling Methodology and supplementary figures

All modelling was carried out using the First Order Conditional Estimation method with interaction between the residual and between-subject variability (NONMEM, v7.2, Icon). Model selection involved both statistical and graphical methods but ultimately the most parsimonious model which best explains the data was to be selected. Comparisons were to be based on improvements in model fitting. The objective function value (OFV), calculated using minus twice the log likelihood of the data, details the amount of variation explained in the model. If there was a difference of more than 3.84 when two nested models were compared then this was to be considered to be a statistically significant ($p<0.05$, 1 df) and relevant change. Other selection criteria used included improvement in the goodness of fit and residual plots, increased precision in parameter estimation, and reduced variance of between subject and residual errors. Final model appropriateness was assessed using the techniques of bootstrapping and visual predictive check.

Structural model

In the preliminary analysis a one or two compartment model with first order elimination was fitted to all data from all subjects simultaneously. The profiles from the cardiac children revealed significant variability in the absorption phase with subjects displaying differences in the rate and extent of absorption and in addition many patients revealed a lag phase. Initial attempts to model this part of the profile using first order, zero order or mixed first/zero order with or without lag phase resulted in poor fits and imprecision in parameter estimates. An alternative approach is to implement a transit compartment model, where the absorption delay is modelled by passage of drug through a series of hypothetical transit compartments. The transit compartments mimic the delay in absorption and a gradual increase in the absorption rate in a more physiological manner than lag times. Drug is transferred between the transit compartments according to the first order rate constant, Ktr, and from

the final transit (absorption) compartment to the central compartment, according to the first-order rate constant, Ka. The optimum number of transit compartments was determined iteratively. This method may have advantages of providing a better model fit by capturing the absorption phase more precisely, as well as being more numerically stable than implementing a lag phase since there is no change-point.

The between subject variability (BSV) in all parameters were modelled as exponential variance parameters. Residual variability (RV), comprising unspecified within subject variability, model misspecification and experimental error was described using additive, proportional and combined error structures. A separate RV model was estimated for the cardiac and respiratory datasets, acknowledging the different provenance of residual error. The mean transit time through the compartments and the number of compartments are estimated as parameters of the model.

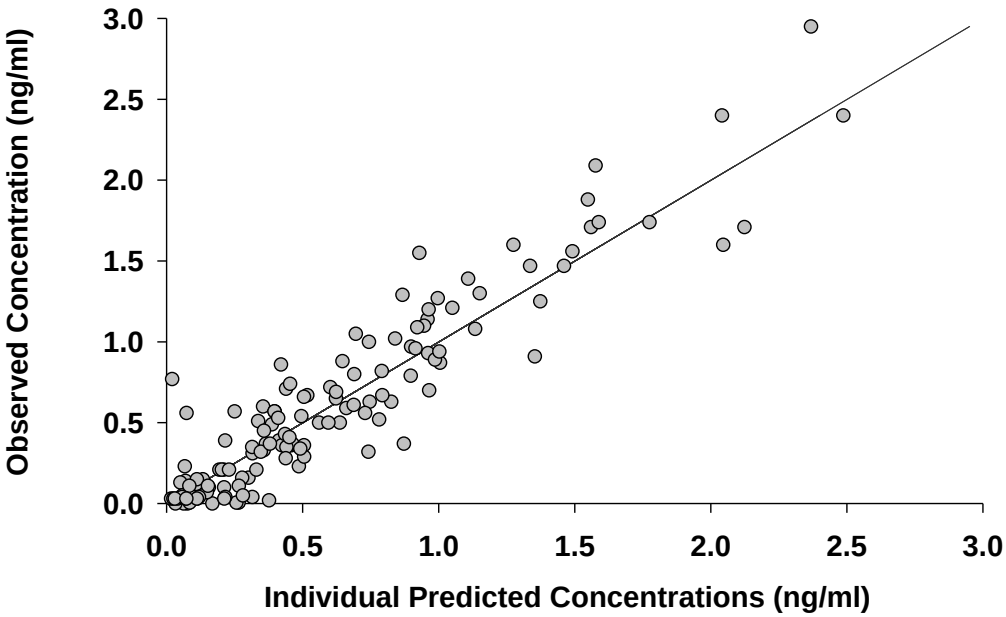
Covariate analysis

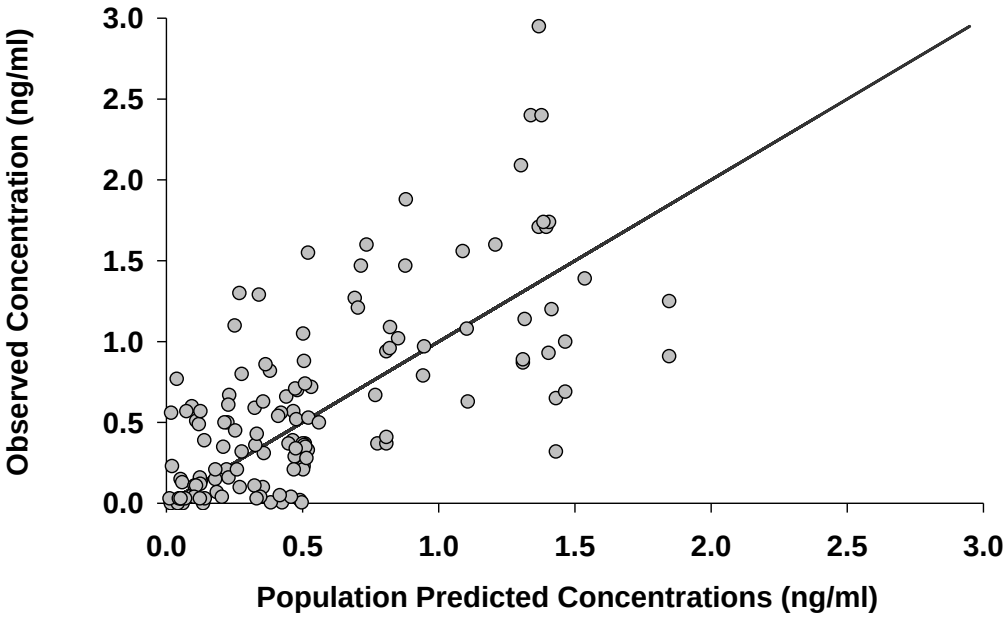
Allometrically scaled transformations of bodyweight were included in the model before evaluation of all other covariates. The parameter values were standardised to a bodyweight of 70kg. This standardisation allows a comparison of parameter estimates in the present population with previous reports in children and adults. Scatterplots of covariates against initial parameter estimates were examined to identify those factors that may have a potential influence in the model. Covariates screened included age, urea, creatinine, albumin, ALT, GGT and co-administration of morphine and milrinone. Following the inclusion of weight, covariates were then added sequentially to the initial regression model. A multivariable analysis was then performed in a forward addition and backward elimination fashion. For the forward addition step, a change in the OFV > 3.84 ($p<0.05$, 1df) was accepted as statistically significant whereas during the backward elimination step, a change in the OFV > 10.84 ($p<0.005$) was required for retaining a covariate in the model.

Model Validation

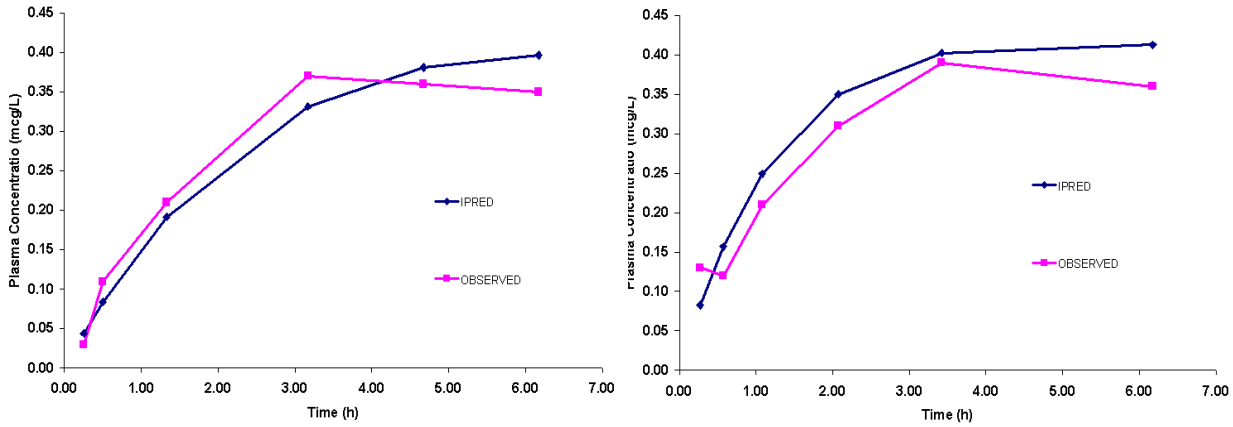
The software tool Perl-speaks-NONMEM was used to generate 500 replicates of the data by bootstrap (i.e. resampling from the original data with each individual subject as a sampling unit) for NONMEM analysis and to provide mean and %CV of the fixed-effect and random-effect parameters, and between subject variability estimates. The predictive performance of the model was evaluated by performing the prediction corrected-visual predictive check. The final model was used to simulate clonidine plasma concentrations (1000 replicates) and the distribution compared with the distribution of observations.

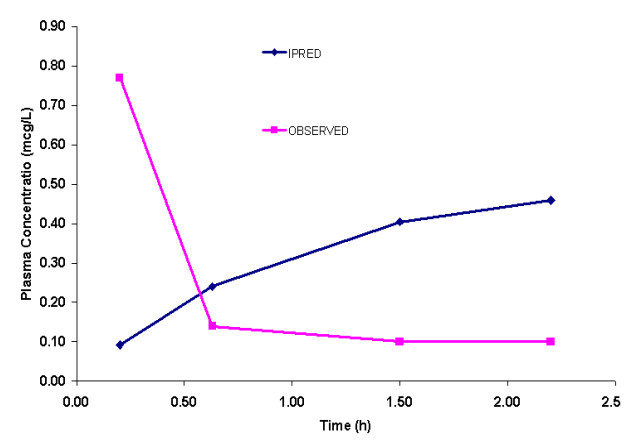
Electronic Supplement Figure 6. Observed versus the final model-predicted individual and population plasma clonidine concentrations. The figure and estimates utilise combined data from the current and previous studies (reference 14).

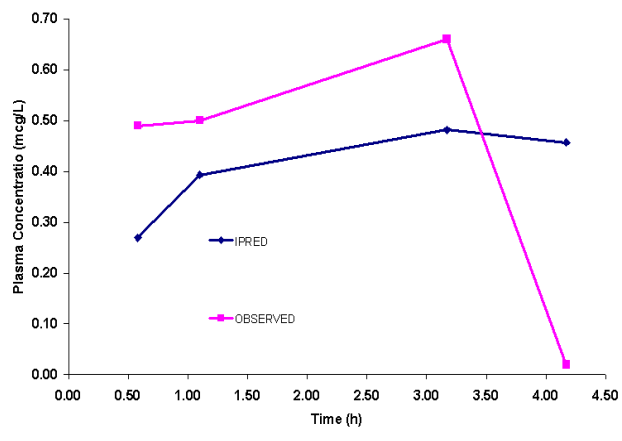




Electronic Supplement figure 7. Example plots of the best (upper 2 plots) and worst (lower 2 plots) model fits based upon individual posterior Bayesian parameters.







CHAPTER 3:

ADMINISTRATION OF IV INFUSIONS

CHAPTER 3.1: Accuracy of the Concentration of morphine infusions prepared for patients in a neonatal intensive care unit

Aguado-Lorenzo V, Weeks K, Tunstell P, Turnock K, Watts T, Arenas-Lopez S.

ArchDisChild2013;98:975–979.

ABSTRACT

Objective To investigate the accuracy of morphine infusions prepared for neonates in relation to the label strength and to identify the differences in deviation between infusions made in neonatal intensive care unit (NICU) and those dispensed ready-to-use from pharmacy.

Methods Unused portions of morphine solution for infusion were collected over a 6-weeks period and used to determine the concentration of the drug by high- performance liquid chromatography (HPLC).

Results A total of 19.2% of infusions prepared by nurses in the ward and 7.8% prepared in the pharmacy were outside the limit required by the British Pharmacopoeia (±7.5%). Moreover, a deviation in concentration of more than 20% was found in ward prepared infusions, although this was caused by volume discrepancies of less than 0.2 mL. The frequency and magnitude of deviations found in infusions prepared in pharmacy was lower than in those prepared by NICU. The latter showed significantly higher number of out-of-specification samples (p=0.015); however, deviations from intended concentration occurred in both settings. Significant differences between pharmacy and NICU for volumes of less than 0.5 mL or for less than 1 mL were not identified probably due to small sample size, but statistical data show a trend for differences.

Conclusions Current practice of preparation of infusions from strengths intended for older children and adults involves dilution of small volumes in a syringe and leads to inaccuracy in the final concentration of infusions for neonatal use. We propose the implementation of standard concentrations for this patient group to effectively eliminate these errors.

What is already known on this topic:

- Errors occur during preparation of intravenous drugs in paediatric and neonatal clinical areas
- The intravenous products available are frequently inadequate for administration of doses required in children
- The use of standard concentrations has been recommended to reduce risk

What this study adds:

- Incorrect concentrations occur both in ward and pharmacy prepared infusions.
- The use of small drug volumes to prepare infusions correlates to an increased frequency and magnitude of deviation from the intended concentrations

INTRODUCTION

Errors with intravenous medications are common, and drug preparation has been identified as one of the steps of the process where errors are more frequent.[1] Multiple-step preparation processes, in particular, have been associated with an increased occurrence of error.[2]

The preparation of morphine infusion for neonates is a complex procedure that involves using an open system during the dilution process, which requires syringe-to-syringe transfer of the drug. Morphine sulfate continuous infusion is prepared on individualised doses, both in pharmacy and at ward level, prescribed using a calculation tool in an attempt to reduce errors during preparation and administration.[3–5] The concentration of morphine sulfate infusion prepared using this method varies from patient to patient as it is determined by weight. Routine practice in neonatal units is to withdraw the required amount of morphine sulfate to a syringe of the appropriate size and then transfer to a second syringe to dilute to a larger volume of 50 mL with glucose 5%.[6]

Morphine infusions were chosen for this project because it is a high-risk drug widely prescribed for neonates as first-line analgesic, doses frequently require use of small volumes and there is strict controlled documentation of this drug. Previous studies have reported that two-thirds of morphine infusions prepared in clinical areas were outside pharmaceutical standards.[7]

The preparation of intravenous therapy by a pharmacy-run centralised intravenous admixture service (CIVAS) is intended to reduce errors and microbiological risk of preparation of injectable drugs in clinical areas. However, a significant number of the treatments continue to be prepared by nursing staff on the wards[8,9] mainly due to limited capacity of pharmacy services, leading to impractical turnaround time for first doses and lack of an out-of-hours service.

The objective of this study was to investigate the accuracy of morphine infusions prepared for neonates in relation to the label strength and to identify the differences in deviation between infusions made in neonatal intensive care

unit (NICU) and those dispensed ready-to-use from pharmacy.

METHODS

Morphine syringes containing the unused portion of morphine solution for infusion administered to patients in NICU (typically neonate with a weight range between 0.5 and 4 kg) were collected over a 6-weeks period and used to determine the concentration of the drug. Hospital policy is to run intravenous infusions for a maximum of 24-h. Nurses were asked to retrieve syringes containing unused portion of solution from all morphine infusions administered in NICU during the study period. The syringes were stored in a refrigerator prior to analysis for a maximum of 10 days. Little or no degradation would be expected as morphine sulfate has been shown to be stable, less than 3% loss over 4 months stored in syringes in previous studies performed in-house (unpublished work).

The concentration of morphine in the syringes was determined by high-performance liquid chromatography (HPLC) using Hewlett Packard HP 1100/1200 HPLC System attached to a HP Computer system with Hypersil ODS 5μm 100 mm×4.5 mm id+20 mm guard column (particle size 5 μm) at 20°C. Mobile phase was 0.005 M dioctyl sodium sulphosuccinate+0.01 M sodium acetate (pH=5) and methanol (40:60); flow rate 1.5 mL/min and detection by ultraviolet at 285 nm. The limit of detection for the method was determined to be 14.4 ng/μL, and the limit of quantitation for the method was determined to be 48.0 ng/μL.

Morphine sulfate B.P. was used to prepare the solution standard for the analysis. The method has been validated for stability testing by means of forced degradation using acid, alkali, heat, light and oxidation (unpublished work). External standards were used for all assays. Linearity was shown over the range of concentrations injected as part of method validation performed in-house (r^2=0.9994). Triplicate readings were obtained for each of the samples analysed, and the average was used as the measured concentration of morphine sulfate.

Data analysis

Using as reference the British Pharmacopoeia (BP) concentration limits for morphine sulfate injection, a maximum deviation of ±7.5% of the concentration in product label was considered acceptable.[10] For interpretation of results in this study, we consider that a deviation has occurred when an infusion fails BP quality standards (out of specification).

The clinical significance of the deviations identified on the concentration of the infusions was not the purpose of the study, and, therefore, the results obtained were not linked to individual patients or staff.

Statistical analysis

A Fisher's test was carried out to determine if there was a significant difference between errors found in infusions prepared on the ward and CIVAS.

RESULTS

A total of 214 samples of morphine infusions were collected. They were prepared either in pharmacy CIVAS (n=115, 54%) or by nurses in the ward (n=99, 46%). Morphine 10 mg in 1 mL was the starting material used in all cases to prepare the infusions, as confirmed by Controlled Drug (CD) registers.

The concentrations recorded of morphine infusions prepared for NICU patients during the study period ranged from 0.5 mg to 52 mg in 50 mL, median concentration was 8.65 mg in 50 mL (interquantile range 4–17 mg in 50 mL).

Theoretical volumes of morphine sulfate 10mg/mL used during preparation of the infusions were as small as 0.05 mL. In 60% of the infusions, withdrawal of volumes of less than or equal to 1 mL of morphine sulfate was required, being less than or equal to 0.5 mL in 37% of the cases.

Accuracy of morphine sulfate concentration

The concentration of 19.2% of infusions prepared by nurses on the ward and 7.8% of infusions prepared in the pharmacy were outside the ±7.5% BP limit. The difference between preparations in both settings was significant (p=0.015, OR 2.79), indicating that the probability of out of specification of ward infusions is nearly three times higher.

The rate of errors in relation to volumes of morphine sulfate withdrawn to prepare the solutions is shown in table 1.

Table 1. Distribution of errors with respect to theoretical volume of morphine withdrawn

		No. samples analysed	No. samples outside BP limits (%)
Ward			
	≤0.5mL	42	13 (31)
	0.5 - ≤1mL	24	4 (16.7)
	1- ≤3mL	31	2 (6.5)
	>3mL	2	- (0)
Total Ward		99	**19 (19.2)**
CIVAS			
	≤0.5mL	37	7 (18.9)
	0.5 - ≤1mL	25	2 (8)
	1- ≤3mL	52	- (0)
	>3mL	1	- (0)
Totals CIVAS		115	**9 (7.8)**

Infusions prepared using volumes of the starting material less than or equal to 1 mL of morphine accounted for 93% (26/28) of results out of specification and 71% (20/28) when using volumes of less than 0.5 mL.

No significant differences were found on frequency of out-of-specification results in CIVAS and NICU for less than 1 mL and 0.5 mL (p=0.184 and 0.301, respectively). However, a trend was observed indicating that out-of-specification infusions are more likely to occur on the ward for subgroups

(ORs 1.497 and 1.921, respectively).

Concentration accuracy in relation to strength in label

The deviation of morphine volumes withdrawn to prepare the infusions was calculated from the difference between measured concentration of the solution in syringe and concentration in label.

Table 2 shows the calculated volume deviations for each of the 28 samples found to be outside BP limits. The calculated deviation was 0.01–0.08 mL for infusions prepared by CIVAS and up to 0.19mL for infusions prepared on the ward. Furthermore, a deviation of more than 20% in relation to the strength on the label was found in 3/99 infusions prepared on the ward, including one infusion in which morphine concentration was 66.5% more than expected.

Table 2. Morphine infusion samples with a concentration outside BP limits

Prepared	Morphine concentration in label (mg in 50mL)	Measured deviation (%)	Theoretical volume required (morphine 10mg/mL) (mL)	Calculated volume withdrawn* (mL)	Difference in volume (mL)
CIVAS	9.3	**-7.6**	0.93	0.86	**0.07**
NICU	10	**-7.6**	1.00	0.92	**0.08**
NICU	4.5	**-7.7**	0.45	0.42	**0.03**
NICU	9	**-7.9**	0.90	0.83	**0.07**
NICU	4.75	**-8.0**	0.48	0.44	**0.04**
NICU	21	**-8.1**	2.10	1.93	**0.17**
NICU	1.6	**-8.1**	0.16	0.15	**0.01**
NICU	1.68	**-8.1**	0.17	0.15	**0.01**
CIVAS	1.68	**-8.2**	0.17	0.15	**0.01**
NICU	4.1	**-8.2**	0.41	0.38	**0.03**
NICU	4.5	**-8.4**	0.45	0.41	**0.04**
NICU	22	**-8.6**	2.20	2.01	**0.19**
NICU	8.65	**+8.8**	0.87	0.94	**0.08**
CIVAS	9.3	**-9.0**	0.93	0.85	**0.08**
CIVAS	2	**-9.5**	0.20	0.18	**0.02**
CIVAS	4	**-9.7**	0.40	0.36	**0.04**
CIVAS	5	**-10.0**	0.50	0.45	**0.05**
NICU	4.6	**+10.1**	0.46	0.51	**0.05**
NICU	1.6	**-10.2**	0.16	0.14	**0.02**
NICU	9.4	**-10.2**	0.94	0.84	**0.10**
NICU	3	**+10.4**	0.30	0.33	**0.03**
CIVAS	2.6	**+10.6**	0.26	0.29	**0.03**
CIVAS	2.63	**-11.7**	0.26	0.23	**0.03**
NICU	4.95	**-14.3**	0.50	0.42	**0.07**
CIVAS	1.92	**+16.2**	0.19	0.22	**0.03**
NICU	1.68	**+25.3**	0.17	0.21	**0.04**
NICU	1.92	**-26.4**	0.19	0.14	**0.05**
NICU	2.4	**+66.5**	0.24	0.40	**0.16**

* based on calculation from the assay result obtained

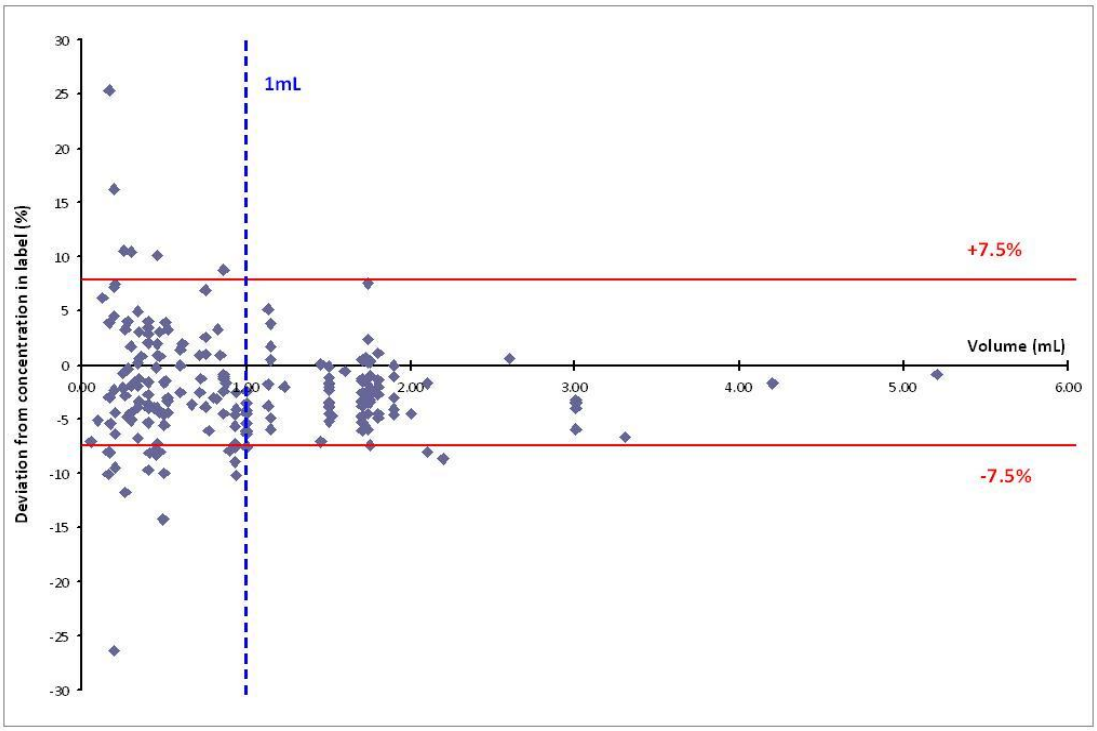
A similar volume deviation was observed in other infusions that were

compliant with BP limit (figure 1). All the three infusions showing a volume deviation of 0.1 mL or greater were prepared on the ward.

Figure 1 Relationship between concentration deviations observed and volume of morphine withdrawn.

*Outlier result 66.5% deviation not shown in chart (volume of morphine 0.24 mL).

BP, British Pharmacopoeia.



DISCUSSION

A difference in accuracy of syringes in relation to strength in label, outside the BP limits, was found in syringes prepared for the neonatal unit. The frequency of error found in syringes made on the ward was significantly higher than in pharmacy (p=0.015), but deviations were found in both settings.

Variation of the magnitudes described may result in morphine delivery that is significantly higher or lower than that prescribed. It is difficult to predict the

clinical effects on neonates following these deviations as this population presents an additional challenge with the pharmacokinetic and pharmacodynamic morphine profile compared with term neonates and older children.

These neonates are more vulnerable to the effects of morphine due to a decreased glucuronidation capacity and excretion. Therefore, increases of more than 10% higher concentrations than intended could potentially put the baby at increased risk of side effects such as respiratory depression.[11]

However, the main problem is that individualised syringes made by weight either by nurses or in pharmacy cannot reliably deliver the intended prescribed concentrations (in up to 20% of the cases in our study). This makes dose adjustments and interpretation of clinical effects challenging as they rely on the label concentration and may not correlate the observed effect due to the deviation in concentration. The variation between syringes prepared daily could compromise clinical response in neonates.

There are no international guidelines as to safe rounding of doses in paediatrics; therefore, having the correct concentration according to pharmacopoeial standards as a starting point is paramount.

Previous authors have reported incidence of error higher than those observed in this study, even when limits are based on US Pharmacopeia (±10%),[7 12] or preparation was taken place in non- clinical settings for the study.[13] In this study, calculation errors or wrong volume measurements may have been prevented by independent double check by two registered nurses during preparation and administration of the morphine infusions, documented on CD records. The standard procedures for selection of materials and manipulations, documented supervision of each preparation step and automated validated systems in CIVAS contribute to eliminate certain sources of error, thereby minimising inaccuracies during preparation. Wheeler et al[12] reported fourfold to fivefold errors attributable to calculation mistakes. The magnitude of the deviations observed in this study, with only three volume errors over 0.1 mL and none over 0.2 mL, suggests those were due to

inaccuracies during preparation of the infusion rather than due to calculations or volume measurement errors.

There is evidence that most errors occur during the preparation process and are associated to multiple steps and the use of small volumes.[14,15] Although in our study most volumes measured were greater than 0.1mL compared with previous studies,[15] small deviations in a volume measured up to 0.5 mL or even 1 mL caused a significant concentration error.

Our results showed that even when preparation is carried out by experienced supervised staff there seems to be a residual number of infusions that still lay outside pharmacopoeial limits. Deviations in volume were less than 0.1 mL in 86% out-of-specification morphine infusions, and they were as low as 0.01 mL in some of them. Statistical analysis showed that these were twice as likely to occur in the ward as in CIVAS for volumes up to 0.5 mL and 1.5 times more likely for volumes up to 1 mL.

Discrepancies in volume could be attributable to accumulated factors: syringe accuracy,[16] volume in syringe dead space (0.07 mL in BD 1 mL and 3 mL syringes used)[17,18] or mixing of the final product, as the content of drug may not be uniformly distributed in the syringe.[13] In addition, the choice of syringe size can also have an impact,[19] with smallest syringes providing more accurate and reproducible results.[20 21]

These findings can also be applied to other infusions such as inotropes, protaglandines, etc., using a similar preparation method and a range of volumes in this patient group.[22] We propose the implementation of batch manufactured standard concentrations of morphine infusions. This would guarantee compliance with pharmacopoeia limits and reduce microbiological risks.[23]

The use of standardised concentrations is recommended on numerous safety alerts [24–26] by the US Government in 2008 [27] and has demonstrated reduced administration errors.[28,29] However, in order to implement this change in

paediatric practice safely, careful considerations such as agreement on clinically appropriate concentrations and diluents, introduction of a change in prescribing and administration practice, labelling of different strengths to avoid mis-selection and safety of storage are required. The main risk envisaged with the implementation of this new system is the mis-selection of the prefilled syringes. Therefore, the use of barcoding and smart pump technology need to be considered for a successful implementation of standardised concentrations.[30]

CONCLUSIONS

Current practice of preparation of infusions from strengths intended for older children and adults involves dilution of small volumes in a syringe and leads to inaccuracy of final concentration of infusions in neonatal use. We propose the implementation of standard concentrations for this patient group to effectively eliminate these errors.

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Contributors VA-L and SA-L were the lead authors, providing design of the study, supervision data collection, analysis and interpretation of the data and wrote manuscript. KW and PT contributed with data collection and analysis of samples and review of the manuscript. KT and TW were responsible for the interpretation of the data from the clinical perspective and review of manuscript.

Competing interests None.

Ethics approval This study was registered as an audit following trust procedures. No patient data were retrieved from any sample, and therefore no ethics permission was required.

Provenance and peer review Not commissioned; externally peer reviewed.

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CHAPTER 3.2: Safe implementation of standard concentrations of morphine intravenous infusions in Paediatric Intensive Care

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ABSTRACT

OBJECTIVE: To evaluate safety, following introduction of standard concentrations of morphine infusions in paediatric critical care.

METHODS:

Implementation: A multidisciplinary team was convened, and several workstreams designated, including derivation of concentrations, manufacturing, supply, prescribing, administration using smart pump technology, training and evaluation.

Safety Evaluation: Retrieval of all existing data on medication errors linked to morphine use using our hospital incident reporting system and risk assessment of errors in relation to standard concentration implementation

KEY FINDINGS: The pilot identified several areas for improvement, stock control, reasons for reverting from standard to variable concentrations and sources of error. Improvements included the following: refining morphine concentrations and weight limits for bands, pump reprogramming and education.

Long term Safety: Over an 8 year period, 126 morphine-related incidents occurred (two-thirds in the 3-years around introduction). Of note, 67% (85/126) resulted in no patient harm; the remainder 33% resulted in low harm. Analysis of administration errors revealed that up to 70% could be eliminated by refining technology to include bar-coding. These included the following: wrong syringe selection (24%), wrong pump mode (28%), and wrong patient weight inputted (18%).

CONCLUSION: Introduction of standard infusions is safe and effective. We are exploring ways to further refine safety, and extending to other drugs.

INTRODUCTION

Continuous, intravenous (IV) drug infusions are common in neonatal and paediatric critical care, and are used for life-sustaining medicines such as inotropes, analgesics, muscle relaxants, nutrition and antibiotics.[1, 2] Routine practice in paediatric and neonatal intensive care units is to withdraw an individualised dose of the required drug (calculated by weight) to a syringe of the appropriate size and then transfer to a second syringe, diluting to a larger volume for example 50mL with Glucose 5% or Sodium Chloride 0.9%. This process occurs often at the bedside and produces a constant relationship between rate of administration and drug dose (for example, 0.1 mL/h of a morphine infusion usually equates to 5 mcg/kg/min if 2.5 mg/kg body-weight is diluted to a final volume of 50 mL) [3]. This is thought to facilitate bedside dose adjustment, and also limits fluid volumes.

However, this approach increases the complexity of continuous IV infusion therapy, by requiring: (a) bespoke drug-to-diluent dose calculations based on patient weight (often aided by calculation tools) [4-6], (b) several manipulations during preparation, and (c) management of multiple, simultaneous infusions requiring evaluations of drug-drug and drug-diluent compatibilities. Medication errors associated with this practice are potentially harmful, and are three times more likely to occur in paediatric and neonatal populations than adults [7-10].

Over a decade ago, the Joint Commission on Accreditation of Healthcare Organizations in the United States made standardised IV solutions a medicines management standard.[11] All accredited US hospitals were required

to meet this mandate by 2009, including introduction of smart pump technology to facilitate its safe implementation[12]. A similar practice change has taken place in Canada [13] and Australia[14]. In the United Kingdom, the National Patient Safety Association recognised this complexity in 2007, and recommended the use of standardized IV solutions provided in ready-to-use forms[7].

Many of the issues with traditional prescribing and administration practice as described above would be addressed with the introduction of standard concentrations. However, standard concentrations could potentially bring new risks such as mis-selection of ready-to use formulations resulting in drug dose error or administration of an inappropriate diluent (for example, Sodium Chloride 0.9% to a patient at high risk of hypoglycaemia). Following a risk appraisal in 2007, our pediatric intensive care unit (PICU) concluded that the potential benefits outweighed the risks and decided to implement standard concentration IV infusions. We recognised that this represented a major change in drug delivery, and were surprised to discover that no published guidance existed on change management in this specific setting.

The aims of this study are thus twofold:

(i) to describe our process for introducing standard concentration IV infusions, and

(ii) to evaluate the ongoing safety of this initiative.

Of note, we hope that, by detailing a carefully evaluated, step-by-step approach to introducing standard concentration of infusions in a high risk area, could serve as a template for other units considering similar initiatives.

METHODS

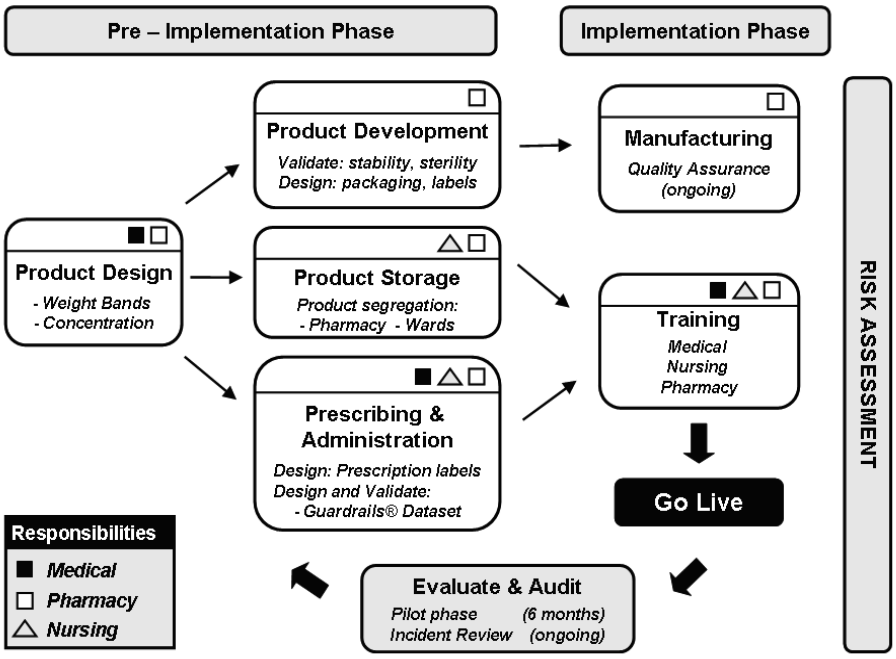
The study met the criteria for service evaluation as defined by the Governance Arrangements for Research Ethics Committees document, and thus did not need Research Ethics Committee approval. However, the work was registered as a service evaluation via our usual hospital procedure.

Prior to implementation, we agreed on several key principles:

- The project team must be multidisciplinary, with one overall lead
- Implementation would initially involve a single drug
- We identified several workstreams, including: drug concentration banding, manufacturing, labelling and storage, prescribing, software configuration, staff training and safety monitoring
- Members could belong to several workstreams; however there would be a clear description of responsibilities for each workstream
- The process would be iterative, involving an interim assessment after 6 months, with ongoing safety assessment beyond this time
- Risk assessment would be formalised, and occur across all project stages

The overall process is summarised in figure 1. Clinical leads were identified from medicine, pharmacy (clinical and manufacturing) and nursing. The chosen drug was morphine, as it was the most frequent infusion, carried a favourable risk-benefit profile (e.g. compared to an inotrope), and had pre-existing accurate traceable records due to its status as a controlled drug. Morphine used for nurse- or patient-controlled analgesia was excluded, as these infusions were commonly initiated outside the PICU, and administered via different infusion pumps.

FIGURE 1: Implementation Process Diagram



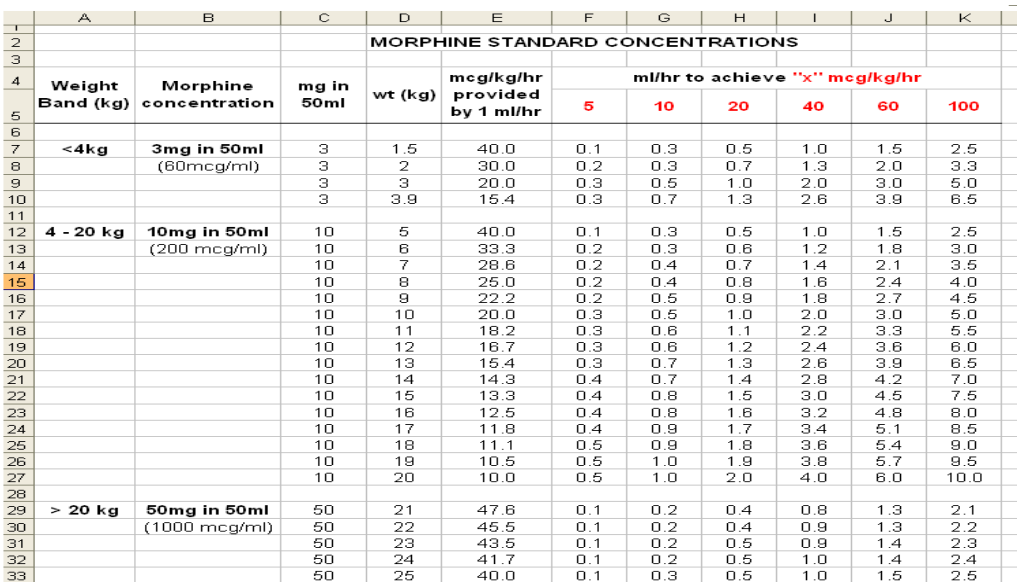
Standard concentration bands were designed and iterated using an Excel-based matrix that considered typical age-related morphine dose ranges, the range and frequency distribution of patient weight in our PICU population (for example, 25% of our patients are neonates), age-appropriate diluents and the common clinical requirement for fluid restriction (see figure 2). A further consideration was minimising variability in drug delivery by not deviating from fluid volume ranges that can be delivered accurately, this was derived from the infusion pumps specification and evidence from the literature[15]

Once the standard concentrations were agreed, the product was developed to British Pharmacopoeia standards for morphine injection, including validation

of stability and sterility during the product shelf-life. In addition, risk assessment of labelling syringes was also undertaken. Further details of manufacturing and labelling are given within the Supplemental Digital Content: appendix S1. An important risk was identified whereby the bedside nurse may inadvertently select a syringe of the wrong concentration band. This was addressed in two ways: (1) label design to facilitate differentiation of strengths emphasising total amount of drug in syringe and using reverse type (light text on a dark background) or warnings such as “high strength” (see Supplemental Digital Content: appendix S1) and (2) segregated storage of each concentration band in specified labelled areas within both pharmacy and PICU.

Prescribing was simplified by designing weight band-specific prescription labels which included the following: concentration strength, starting dose and dose range (see results). The shift from variable to standard IV concentrations meant that the relationship between volume administration rate and dose was no longer constant for all patients (e.g. 1 mL/h no longer means 20 microgram/Kg/hr). This now required complex bedside calculations immediately prior to patient administration and with each dose change on the pumps. To obviate the need for calculation (carrying a high probability of human error), we introduced the ALARIS-CC syringe pump, incorporating Guardrails® software (CareFusion, Basingstoke, United Kingdom). No calculations are needed to obtain the rate of infusion; pump programming requires selecting syringe strength from pump library and inputting patient weight only.

FIGURE 2: Clinical design using a matrix weight/dose and concentration



	A	B	C	D	E	F	G	H	I	J	K
2				MORPHINE STANDARD CONCENTRATIONS							
3											
4	Weight Band (kg)	Morphine concentration	mg in 50ml	wt (kg)	mcg/kg/hr provided by 1 ml/hr	ml/hr to achieve "x" mcg/kg/hr					
5						5	10	20	40	60	100
6											
7	<4kg	3mg in 50ml	3	1.5	40.0	0.1	0.3	0.5	1.0	1.5	2.5
8		(60mcg/ml)	3	2	30.0	0.2	0.3	0.7	1.3	2.0	3.3
9			3	3	20.0	0.3	0.5	1.0	2.0	3.0	5.0
10			3	3.9	15.4	0.3	0.7	1.3	2.6	3.9	6.5
11											
12	4 - 20 kg	10mg in 50ml	10	5	40.0	0.1	0.3	0.5	1.0	1.5	2.5
13		(200 mcg/ml)	10	6	33.3	0.2	0.3	0.6	1.2	1.8	3.0
14			10	7	28.6	0.2	0.4	0.7	1.4	2.1	3.5
15			10	8	25.0	0.2	0.4	0.8	1.6	2.4	4.0
16			10	9	22.2	0.2	0.5	0.9	1.8	2.7	4.5
17			10	10	20.0	0.3	0.5	1.0	2.0	3.0	5.0
18			10	11	18.2	0.3	0.6	1.1	2.2	3.3	5.5
19			10	12	16.7	0.3	0.6	1.2	2.4	3.6	6.0
20			10	13	15.4	0.3	0.7	1.3	2.6	3.9	6.5
21			10	14	14.3	0.4	0.7	1.4	2.8	4.2	7.0
22			10	15	13.3	0.4	0.8	1.5	3.0	4.5	7.5
23			10	16	12.5	0.4	0.8	1.6	3.2	4.8	8.0
24			10	17	11.8	0.4	0.9	1.7	3.4	5.1	8.5
25			10	18	11.1	0.5	0.9	1.8	3.6	5.4	9.0
26			10	19	10.5	0.5	1.0	1.9	3.8	5.7	9.5
27			10	20	10.0	0.5	1.0	2.0	4.0	6.0	10.0
28											
29	> 20 kg	50mg in 50ml	50	21	47.6	0.1	0.2	0.4	0.8	1.3	2.1
30		(1000 mcg/ml)	50	22	45.5	0.1	0.2	0.4	0.9	1.3	2.2
31			50	23	43.5	0.1	0.2	0.5	0.9	1.4	2.3
32			50	24	41.7	0.1	0.2	0.5	1.0	1.4	2.4
33			50	25	40.0	0.1	0.3	0.5	1.0	1.5	2.5

Guardrails® Software datasets were agreed for each weight band. It was envisaged that a 'variable strength' option would also be required (in addition to standard concentrations) for situations when a more concentrated solution was needed (e.g. severe fluid restriction). The datasets included a drug library with patient weight, minimum and maximum concentrations and dose rates, occlusion alarm pressures and bolus limits. Once uploaded to the pumps, the datasets were validated by running the programs for various hypothetical patients.

An electronic ward protocol was developed, specifying the step-by-step process from prescribing to administration of the prefilled syringe, including who had responsibility for each step (see Supplemental Digital Content:

appendix S2). The protocol was available at each bed space, and functioned initially as the core document for staff training. A rolling program of training and competency assessment was implemented, involving thirteen key trainers, with at least one rostered on duty each day and night shift for the first week to support staff through the initial implementation period. This resulted in 80% of frontline staff (120 nurses, 30 doctors) being “signed off” over the initial fortnight.

Risk analysis for the ordering to administration stages was conducted by a multidisciplinary team using the National Patient Safety Agency “Failure Mode Risk Analysis” matrix[16]. This identified risk areas and implemented process controls to minimise the probability of error (see Supplemental Digital Content: appendix S3).

Finally a 6-month surveillance of banding, stock levels, wastage, datasets and soft and hard alert limits by pumps was conducted via electronic forms filled by bedside nurses for each patient per shift, and data downloaded from Guardrails® pumps.

Post implementation, an ongoing safety assessment was conducted via incident reports from the hospital database (DATIX®) and reviewed over 8 years. Medication errors identified were classified and assessed in relation to the use of standard concentration syringes or variable strengths.

STATISTICAL METHODS

Data are described as counts and percentages. The association between the type of administration error and mode of drug administration (Table 1) was evaluated using Fisher's exact test. Elsewhere, formal statistical testing was not used. The statistical program used was Stata v13.1 (StataCorp, Texas).

RESULTS

Evaluation of six-month pilot

Morphine was used on 472 occasions between July and December 2007; however 53/472 (21.2%) did not use standard concentrations, as morphine infusion was commenced prior to PICU admission. In the cases where standard concentrations were used (n = 419), this was subsequently altered to variable strength infusions on 79 occasions (18.9%). Reasons for this included the following: morphine infusion doses required above the preset limits (n = 45), higher diluent strength due to hypoglycemia (10% versus 5% glucose, n = 19) and fluid restriction (n = 15). Most episodes occurred in patients who were in the smallest weight band.

Data downloaded from the pumps revealed 535 alerts (1 alert per 15 infusions), with 197 (37%) occurring in the first month. Eighty eight per cent of the alerts were due to attempts to enter dose rates above the limits, with approximately half of these above the hard limit (maximum programmed dose). For hard limit violations, there were 170 attempts to program >1.5 times over the hard limit: this included nine attempts >2 times, 18 attempts >5 times and one attempt at 10 times the limit. The majority of violations that were between 1.5 to 2 times the hard limit occurred for patients who were between 4 and 7 kg, suggesting our hard limit was too low for their clinical requirements.

Following the pilot, two changes were made. (1) Four weight bands (and concentrations) had been designated initially: 1.5 - 6.9 kg (2.5mg in 50mL), 7 - 19.9 kg (10mg in 50mL), 20 - 34.9 kg (30mg in 50mL) and >35kg (50mg in 50mL). These were reduced to three after elimination of 30mg in 50mL, which was rarely used due to the small number of patients, resulting in 60% wastage due to product expiry. (2) The weight cut-off between the two smallest bands was adjusted from 6.9 to 4 kg. This meant that patients >4kg could now receive a higher dose of morphine infusion with less volume. The final weight bands are shown in figure 3.

FIGURE 3: Prescription labels for final weight bands

		Patient Weight	MORphine Concentration	Starting Dose	Dose Range	Doctor Signature
IV	C/P	**<4 kg**	3mg in 50ml Glucose 5%	**10** mcg/kg/hr	**5 - 40** mcg/kg/hr	

		Patient Weight	MORphine Concentration	Starting Dose	Dose Range	Doctor Signature
IV	C/P	**4 - 20 kg**	10mg in 50ml Sodium Chloride	**20** mcg/kg/hr	**5 - 60** mcg/kg/hr	

		Patient Weight	MORphine Concentration	Starting Dose	Dose Range	Doctor Signature
IV	C/P	**> 20 kg**	**50mg in 50ml** Sodium Chloride	**20** mcg/kg/hr	**5 - 60** mcg/kg/hr	

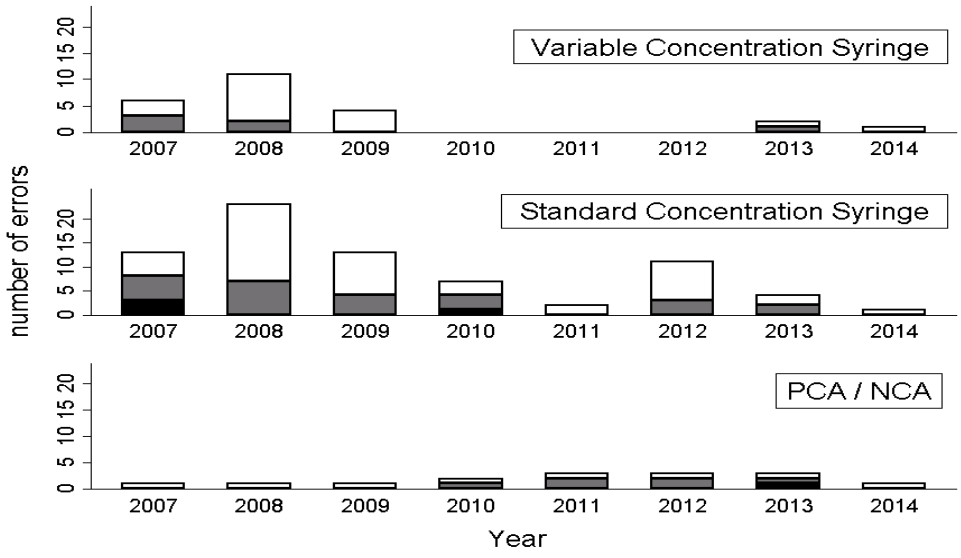
Eight year safety evaluation

Between 2007 and 2014, 126 morphine-related incidents were reported, of which 18 (14%) were categorised as supply-related (involving procedures for ordering stock or controlled drug documentation), 36 (29%) were prescription related, and 72 (57%) involved drug administration. Of note, no error resulted in moderate or severe patient harm, and only 32.5% (41/126) resulted in low harm. The yearly breakdown is shown in figure 4, further categorised by method of administration (variable strength infusions, standard concentrations

and nurse/patient controlled analgesia). Approximately two-thirds of errors occurred in the 3 year period around implementation (2007-09). In comparison, the yearly number of total drug errors rose from 60 to 137 over the same period, meaning that morphine-based as a percentage of total drug errors decreased from 45% in 2007 to 2.2% in 2014.

Although prescription errors occurred most commonly with standard concentrations (24/36), the majority (22/24, 92%) did not result in patient harm (i.e. patient receiving an incorrect dose). These were primarily due to a prescription sticker not being signed. Administration errors were twice as frequent (n = 72, table 1), and varied between mode of drug administration (p = 0.025, Fisher's exact test). The three commonest were as follows: (1) 28%, combining delivery modes (e.g. using a variable concentration syringe whilst in standard strength mode on the pump), (2) 24%, choosing an incorrect banded syringe whilst in standard concentration mode, and (3) 18%, pump programming errors (e.g. inputting the wrong patient weight).

FIGURE 4: Morphine Incidents by year and mode of delivery



Key: Black, supply-related; Grey, prescription; White, administration.
PCA, patient controlled analgesia; NCA, nurse controlled analgesia.

Errors were ascribed according to the intended method of administration. Thus, for example, if a standard strength syringe was used for intended PCA/NCA administration, the error was ascribed to the PCA/NCA category.

Table 1. Morphine administration errors by type and mode of administration

	Mode of Administration			
Error Type	NCA / PCA	Standard	Variable	Total
No Signature	2 (25%)	2 (4.4%)	2 (11.1%)	6 (8.3%)
Programming	2 (25%)	7 (15.2%)	4 (22.2%)	13 (18.1%)
Wrong Syringe	1 (12.5%)	16 (34.8%)	0 (0%)	17 (23.6%)
Compatibility	0 (0%)	3 (6.5%)	1 (5.6%)	4 (5.6%)
Wrong Mode	2 (25%)	9 (19.6%)	9 (50%)	20 (27.8%)
Other	1 (12.5%)	9 (19.6%)	2 (11.1%)	12 (16.7%)
Total	8	46	18	72

DISCUSSION

We offer a suggested framework for implementing standard concentration infusions in a paediatric critical care area. We developed this whilst considering several likely challenges. First, the initiative represented a change from a long-established practice, thus potentially meeting resistance from practitioners.[3-6] Second, there was a need to identify a limited number of concentrations while maintaining an acceptable fluid load across a wide range of patient weight. Third, there was limited evidence supporting the safety and

most appropriate standard concentrations compared with traditional weight-based prescribing.

We addressed the first potential challenge (resistance) by: (1) utilising a multidisciplinary implementation group, (2) providing sufficient advance notification to the entire clinical team, (3) facilitating a structured training program, and (4) actively involving end-users in feedback, via the six-month evaluation and also informally. In addition, our unit has a well-established mechanism for incident reporting, which provided reassurance to staff about safety monitoring[17].

Meeting the second and third challenges (banding selection and evidence appraisal) was more exacting, with published evidence emerging primarily after our implementation. *Christie-Taylor*[14], reported in 2012, the introduction of neonatal dopamine and dobutamine standard concentrations. Although providing information about the implementation process, the two concentration bands proposed by Christie-Taylor for each inotrope were not applicable to our population as concentrations needed to be based on clinical requirements of patients, and our population had a larger variation in weight (40-fold versus 10-fold). In addition, *Christie-Taylor* recommended bedside nurse reconstitution, which has several disadvantages compared to batch manufacturing, including a requirement for complex calculations with potential for calculation error, and greater microbiological risk.[18] Even when reconstituted correctly, final drug concentrations are inherently inaccurate and this is accentuated when small drug volumes are used, which is common in paediatrics. This was demonstrated in a neonatal population by *Aguado*

Lorenzo,[19] where the measured morphine concentration of approximately one in five (19.2%) of bedside syringes prepared by nurses were outside the British Pharmacopoeia acceptable limits for accuracy. The majority of errors occurred when the smallest drug volumes (<0.5 mL) were used for reconstitution.

Hilmas et al[20] developed a paediatric mathematical algorithm in 2010, which derived two to four clinical standard concentrations for 39 continuous infusion medications, aided by a computerized prescribing system and smart pump introduction. Their process was similar to ours; however we lacked the computerised prescribing element.

Our results have shown that introduction of standard morphine concentrations was both feasible and safe, with no serious errors reported (in terms of patient harm) up to 8 years post introduction. However, error analysis highlighted several interesting findings. First, smart technology is essential. The pump technology both intercepted, and provided valuable information on potential administration (programming) errors, whereby staff were attempting to administer doses above the pre-set limits. This represented “true” error (e.g. 10x dosing) on some occasions, but also highlighted areas for improvement in terms of adjusting our weight cut-off for bands, allowing infants to receive higher upper doses than neonates. This was demonstrated by Manrique-Rodriguez in a 17-month PICU study, where smart pumps intercepted 92 infusion-related programming errors in 486,875 infusions, with 49% classified as potentially having severe or catastrophic consequences[21]. Almost all (97%) involved programming infusions rates above the upper hard limits predefined

in the dataset.

Second, the majority of errors occurred in the 3 years after standard concentration introduction, and allowed us to focus on areas such as education, stock control and refining the process (e.g. via adjusting weight bands). Of note, there appeared to be a resurgence of error in 2012, primarily administration-related. This was the result of a quality improvement initiative, whereby we focused on “tightening up” bolus morphine prescribing, and was thus not related to the standard concentration process per se. Another interesting observation was the absence of error involving variable concentrations between 2010 and 2012, followed by a small resurgence in 2013-14. The former may have been due to a reduction in the number of variable infusions used after initial standard concentration introduction, with the subsequent resurgence of error being due to staff being less familiar with this method in later years.

Third, classification of administration error by type (table) has highlighted two initiatives, which could potentially eliminate up to 70% of this error category: extending standard concentrations to patient/nurse-controlled analgesia and bar-coding. We are currently expanding the standard concentration program to patient/nurse-controlled analgesia, and rolling this out beyond PICU[22]. Bar-coding the standard concentration syringes would effectively negate the “wrong syringe” selection error (24%), and also reduce the “wrong mode” error (28%), as the smart pumps would recognise when a standard strength syringe was being used in variable programming mode and vice-versa. A second aspect of bar-coding could input patient weight automatically via linking the smart pumps to a computerised clinical information system;

thereby largely eliminating the commonest program error (incorrect weight, 18%). The effectiveness of bar-coding is increasingly recognised. Poon[23] demonstrated that it can lead to a relative reduction of 41.4% in administration errors. Hospitals in the United States have introduced this technology for paediatric oral syringes,[24] and the Joint Commission has highlighted the importance of introducing this technology with intravenous drugs[25]. To our knowledge this is still under development in the U.K. and providers need to address the specific needs for the paediatric population.

CONCLUSION

The use of ready-to-use prefilled syringes has been encouraged as a way to minimise risk exposure in paediatrics and neonates since preparation of individualised infusion manipulating small volumes are a high risk. This study adds a carefully clinically evaluated step approach to introduce standard concentration of infusions in a paediatric high risk area in an effective and safe manner. We are exploring ways to further refine safety, and extending this to other commonly used drugs as the principles and results of this study can be extrapolated to other medicinal products administered as continuous IV Infusions, and offer special benefits to those infusions involving calculations and manipulation of small volumes.

Limitations: Two major limitations of our study relate to reporting medication errors. First, we do not have robust electronic data capture for the years before the introduction of the standard concentrations; thus we are unable to quantify the impact in terms of potential change in morphine drug error rate. The decrease in number of drug errors in the latter years following

implementation (figure 4) may have reflected a change in PICU reporting culture (i.e. we were no longer focused on the initiative, so may be less likely to report incidents). However we feel this is unlikely, as our overall drug incident reporting actually increased this time (see Results).

At time of writing this manuscript, we are aware of discussions among regulatory agencies at national and international levels regarding harmonising standard concentrations for commonly used IV medications in children. This may improve cost efficiency by optimizing production lines, making it more economical for the health service. We hope that our implementation and safety data may help to inform such decision making.

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Conflict of interest: None

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Online Supplementary Material

APPENDIX S1: PRODUCT DEVELOPMENT and MANUFACTURING

A product specification for manufacturing was approved by Quality Assurance (QA) for pre-filled syringes of morphine infusions at the established concentrations.

The product was developed to British Pharmacopoeia (BP) standards for morphine injection, including validation of stability and sterility during the product shelf-life.

Product development took place in three phases:

Physicochemical stability: Determined by visual inspection, pH and HPLC.

The HPLC method used and its validation was extensively described in our first article [1]

Six samples of each concentration studied were analysed, three were at 4°C and three at 25°C. Testing was carried out at the start point, at six weeks and at 12 weeks from the date of preparation.

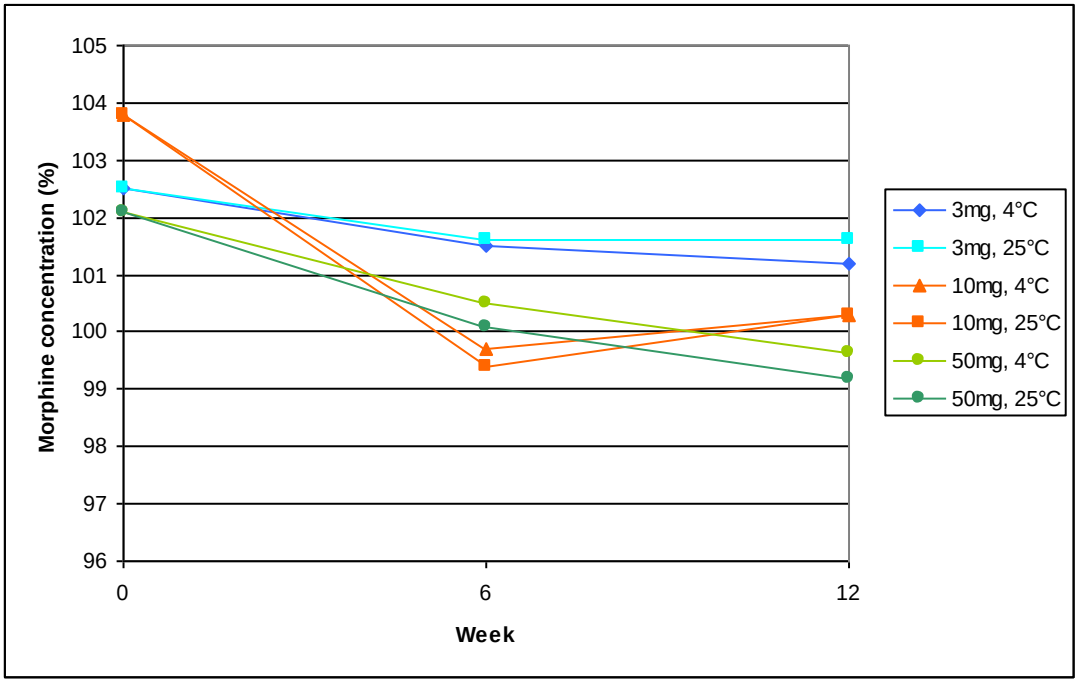
BP concentration limits for morphine sulphate injection were followed and a maximum deviation of ±7.5% of the concentration in product label was considered acceptable [2].

Microbiological risk: Pre-filled syringes were tested at the end of storage period for both storage conditions to validate storage in a syringe following aseptic preparation of this product.

Results:

Morphine infusion stored in pre-filled syringes was stable over a 12-week period at 4^{o}C and 25^{o}C. No significant changes on the concentrations were observed during the study period. Concentration of all samples tested was within BP limits. The average concentrations of morphine stored at 4C and 25C are shown in figure 3a. No changes of pH neither signs of precipitation or change of colour of the solution were observed for any of the concentrations or storage conditions tested (Figure 3b) and all samples were sterile.

FIGURES 1a: Average concentrations of morphine stored at 4C and 25 C



1b: AVERAGE pH at 4C and 25 C

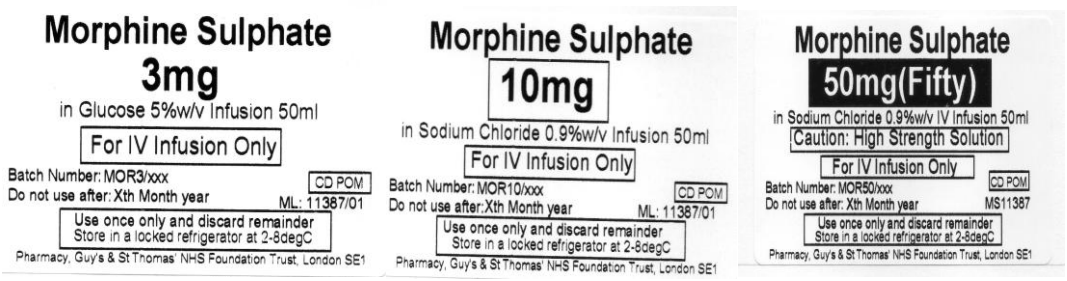
pH	***Stored 4°C***			**Stored 25°C**		
	3mg	**10mg**	**50mg**	**3mg**	**10mg**	**50mg**
Week 0; (t=0)	4.3	5.2	5.4	4.3	5.3	5.5
Week 6	4.3	5.6	5.5	4.3	5.8	5.8
Week 12	4.4	5.2	5.4	4.5	5.6	5.8

Risk assessment of labelling of syringes

Labels of the syringes were designed to help differentiating the different strengths and prevent mis-selection of the syringes. This was a key patient risk given the 25 fold difference in concentrations between the high and low strength syringe.

A number of sample labels (Figure 2) were developed and tested using a panel of nursing and medical staff and the final labels used the following features to prevent mis-selection risk: Reverse print to highlight the strength, warning ‘high strength’ for the 50mg in 50mL strength. In addition a procedure was developed for the nurses to use when selecting syringes including independent check by a second nurse.

FIGURE 2 : Design of labels for three different concentrations



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APPENDIX S2: WARD PROTOCOL

PICU MORPHINE PRE-FILLED SYRINGES
WARD PROCEDURE

Process

A) Ordering stage

- Specific designated order and record book for pre-filled syringes
- Use a separate page in the ordering book for each strength (as per current CD practice) to a maximum of 20 syringes per page
- Liaise with PICU pharmacist for order levels
- Order book to be filled by night nurse in charge and handed over to PICU pharmacist on designated days (Mon-Wed-Fri) before 12 noon otherwise they will be processed the following day (as per current CD practice)
- Order each strength in batches of 10

B) Delivery/Collection

- Pharmacist or qualified nurse depending on week day. Nurses should present proof of ID on collection (as per current CD practice)

C) Registration of pre-filled syringe CD's

- 2 qualified nurses to log in pre-filled syringes as soon as delivery arrives. Log in CD record book on corresponding page of serial number in CD order book (as per current CD practice)

D) Storage

- Registered morphine syringes will be stored in the lockable CD fridge in PICU pharmacy room
- Each strength will be stored in a separate designated labelled box

E) Prescribing

- PICU doctor to prescribe standard concentration syringe appropriate to patient's weight, the starting dose and dose range using the pre-printed stickers
- Doctor to sign the sticker as this is the legal prescription

Example:

(a) for a 4 kg infant, a pre-printed sticky label appropriate for the patient's band (in this case 4-19.9kg) is placed on the fluid chart. This sticker states the morphine concentration, the starting dose and the dose range

(b) The doctor then signs the prescription

(c) The nurse programs guardrail accordingly (see below under administration)

Table 1: Prescription label example

		Patient Weight	MORphine Concentration	Starting Dose	Dose Range	Doctor Signature
IV	C/P	**4.0-20 kg**	**10 mg** in 50ml Sodium Chloride 0.9%	**20** mcg/kg/ hr	**5 - 60** mcg/kg/hr	

Exceptions

- Patients who are severely fluid restricted, whereby the banded syringe will provide excessive fluid. **In this case, abandon the banding and revert to the traditional method of morphine prescribing (mg/kg basis) for double strength infusions (1ml/hr =40mcg/kg/hr)**
- An alternative diluent is required (again, revert to traditional method)
- A greater concentration of morphine is required

Table 2: Morphine standard concentrations and weight bands

Patient Weight (kg)	MORphine Standard Concentration	Starting Dose	Dose Range	Doctor Signature
< 4kg	**3mg** in 50ml Glucose 5%	**10** mcg/kg/hr	**5 - 40** mcg/kg/hr	
4.0-20 kg	**10mg** in 50ml Sodium Chloride 0.9%	**20** mcg/kg/hr	**5 - 60** mcg/kg/hr	
> 20kg	**50mg** in 50ml Sodium Chloride 0.9%	**20** mcg/kg/hr	**5 - 60** mcg/kg/hr	

F) Administration (2 qualified nurses, required to check at all following stages)

- Check morphine is correctly prescribed according to table 2
- Read the drug and strength off the prescription out loud
- Select correct syringe from **labelled** fridge box (check luer lock of syringe is intact and not leaking)
- Pick up the syringe and read the drug and strength off the syringe label out loud
- Confirm that syringe matches prescription
- Log out of CD record book as per current practice
- Follow prescription checking procedure and patient details as per current practice
- Select a designated **labelled** morphine infusion pump with guardrails installed
- Connect syringe to infusion line and prime
- Follow Alaris guardrail procedure for programming infusion pump (if patient on old system mg/kg basis choose option “Morphine Variable” otherwise choose the prescribed standard concentration)

G) Procedure for programming Alaris infusion pump with guardrails (2 nurses)

1. Insert syringe into infusion pump
2. Insert pressure disc into pump
3. Switch on infusion pump
4. Confirm profile (yes: if same patient, no: if new patient)

5. Select drug

ml/h
Dosing only
Drugs A - F

→

Drugs G - M
Drugs N - S
Drugs T - Z

6. Select Drugs G-M
7. Select **Morphine strength** if using a standard concentration (cross check that syringe in pump matches the concentration selected) **or Morphine variable** if using non-banded (old system) syringe. If non-banded, the actual Morphine concentration and diluent volume will need to be entered manually. Press OK
8. Check the concentration and press OK if correct
9. Enter patient's weight and press OK
10. Confirm setup and press OK
11. Confirm syringe type
12. Purge if required
13. Check dose and adjust if required
14. Connect infusion line to patient's IV access
15. Press infuse

APPENDIX S3: RISK ASSESSMENT

Prescribing, selecting and administration of Morphine standard concentrations in PICU

Process Failure Mode Analysis

	Failure	Potential consequence	Likelihood	Risk score	Process controls	Process qualification
1	Incorrect prescribing	Moderate	Possible	9	• Doctors training in new prescribing method • Ward S.O.P produced • Prescription labels designed as current I infusion chart has different headings • Double checking from nurses before administration • Guardrail calculates the infusion rate based on patient weight and dose prescribed.	Process qualification of guardrail calculations
2	Incorrect selection of syringes	Major	Possible	12	• Pharmacy ECH to send different strengths on different days • 2 nurses to log in CD record books on CD order arrival to the ward immediately • 2 nurses to put the syringes in allocated lockable boxes in locked fridge • Ward S.O.P produced • Labelled boxes in fridge • Training to nurses • 2 nurses to check prescription and read a loud concentration prescribed • 2 nurses to go to fridge and pick the right syringe • 2 nurses to check the luer lock in syringe and confirm that is not defective (sometimes stored syringes put pressure on each other & may lead to leakage) • When programming pump, one step prompts nurses to confirm strength • Guardrail prompts for the syringe strength to select based on patient weight band	Process qualification of guardrail to confirm correct syringe strength prompt for a given weight band

	Failure	Potential consequence	Likelihood	Risk score	Process controls	Process qualification
3 & 4	Incorrect installation of infusion device	Insignificant	Unlikely	2	• nurses checking each other • Staff training • Pump would not run if wrongly installed • Confirm the luer thread intact before connection to pump.	
5	Pump programming: Choosing incorrect weight band	Major	Possible	12	• Doctors Prescription • Ward S.O.P. produced • 2 Nurses checking each other • Staff training • Guardrail configuration does not allow proceeding if the band chosen doesn't correspond with entered patient weight. Therefore the patient weight has to also be entered incorrectly for this error to occur	
6	Pump programming: Choose Incorrect drug	Major	Rare	4	• Staff training • Only one drug programmed in Guardrail® at the moment	Confirm during process qualification
7	Pump programming: Incorrect concentration chosen in Guardrail	Major	Rare	4	• Staff training • Only two options per weight profile programmed: one is the standard concentration relevant to weight and second is "Morphine Variable". If morphine variable chosen they need to check prescription individualised for that patient and nothing would be prescribed	
8	Pump programming: Incorrect patient´s weight	Major	Possible	12	• Two nurses to check each other • Staff training • Ward S.O.P. Produced • Guardrail configuration does not allow proceeding if the band chosen doesn't correspond with entered patient weight. Therefore the patient weight has to also be entered incorrectly for this error to occur	

	Failure	Consequence	Likelihood	Risk score	Process controls	Process qualification
9	Pump programming: Incorrect starting dose and maintenance doses	Moderate	Unlikely	6	• Ward S.O.P. Produced • Prescribed in sticker on IV fluid chart • Prescribed in mcg/kg/hr instead of old system in ml/hr • 2 nurses checking each other • Pump is configured with soft and hard limits to avoid overdoses • the recommended starting dose is set as default	Confirm default dose set up during process qualification
10	Incorrect overall programming of Guardrail (Incorrect calculations of dose in volume from weight, concentration and dose in mass units)	Major	Rare	4	• Hospital validation of guardrail • Alaris validation of guardrail	Confirm the correct infusion rate in ml/hr calculated on the basis of the data entered into guardrail.
11	Incorrect programming of bolus dose	Major	Rare	4	• Hospital validation of guardrail • Alaris validation of guardrail	Confirm during process qualification that multiple bolus cannot be administered
12	Incorrect press of bolus button	Minor	Rare	2	• Staff training • Ward S.O.P. Produced • Guardrail would not deliver the bolus	
13	Incorrect press and hold	Minor	Rare	2	• Staff training • Ward S.O.P. Produced • Guardrail would not deliver the bolus	
14	Incorrect delivery & display of bolus dose in volume	Major	Rare	4	• Hospital validation of guardrail • Alaris validation of guardrail	Confirm the correct bolus infusion volume calculated on the basis of the data entered into guardrail.

Risk Matrix*

	Consequence					
Likelihood	**Score**	**1**	**2**	**3**	**4**	**5**
	1	**1**	**2**	**3**	**4**	**5**
	2	**2**	**4**	**6**	**8**	**10**
	3	**3**	**6**	**9**	**12**	**15**
	4	**4**	**8**	**12**	**16**	**20**
	5	**5**	**10**	**15**	**20**	**25**

http://www.npsa.nhs.uk/nrls/improvingpatientsafety/patient-safety-tools-and-guidance/risk-assessment-guides/risk-matrix-for-risk-managers

CHAPTER 3.3: Standard concentration infusions in paediatric intensive care: The Clinical Approach

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ABSTRACT

The use of standard concentrations of intravenous infusions has been advocated by international organisations to increase intravenous medication safety in paediatric and neonatal critical care. However, there is no guidance on how to identify and implement these infusions leading to great inter-unit variability

OBJECTIVE

To identify the most appropriate clinical concentrations required by our paediatric intensive care unit (PICU) population with regard to accuracy of delivery and overall fluid allowance.

METHODS

Firstly, a matrix was used to balance the concentration, dose and infusion volume (weight range 1.5kg to 50kg). Results were further refined considering: Patient fluid allowance based on fluid volume targets, infusion pump accuracy and challenging each infusion against clinical scenarios requiring administration of multiple drug infusions found in PICU.

Consideration was given to the standard concentrations routinely used in adults, in order to assess whether alignment with paediatrics was possible for some of the concentrations proposed. Finally a risk assessment of the infusions was conducted using the NPSA 20 tool.

KEY FINDINGS

Twenty five drugs identified as the most commonly used intravenous infusions in the unit. For the majority of the medicines, three weight bands of standard concentrations were necessary to cover the children's weight ranges and kept within predefined fluid requirements and accuracy of delivery.

CONCLUSIONS

This works shows a patient focused systematic approach for defining and evaluating standardised concentrations in intensive care children

INTRODUCTION

Intravenous (IV) medication therapy in the neonatal and paediatric population is complex. Treatments involving small doses require numerous precise calculations and several dilutions to achieve the prescribed dose. A systematic review of publications on medication errors in neonatal care highlighted that administration errors accounted for approximately 46% of errors and human factors were the most cited cause of error[1]. Some reports showed that the intravenous route was involved in 54-56% of the administration errors in children [2,3]. For many reasons children are more likely to suffer harm from a medication error than adults. This occurs particularly at extremes of age, neonates and adults cared for in paediatric intensive care unit (PICU) settings and adolescents. Possibly due to weight based dosing of high risk medications (i.e inotropes and analgesics) resulting in doses for adolescents exceeding adult standard dosing practices [3,4] .

Clinicians are faced with the challenge of ensuring safe and effective drug prescribing in critically ill children with the drugs available in clinical practice. At the same time, nurses often need to administer drugs not designed for children or neonates. Intravenous drugs are commonly designed for adults, providing high strengths and recommendations on preparation of infusions which would give a fluid volume not appropriate for children in PICU. Adults have a range of weights from 40-120kg (three times difference) whereas in children the range is much wider from 0.5kg-100kg (200 times difference) therefore when in adults one concentration suits all weights, in children, a range of concentrations is required to suit the different patients requirements.

At present, the process to prepare an intravenous drug to an individual child involves multiple manipulations of the original presentation of the drug especially when the volumes involved are very small as there is a lack of devices in clinical settings to measure these volumes accurately[5]. There is no systematic method to make the intravenous doses in clinical practice; therefore the preparation of infusions by different healthcare professionals may lead to inconsistent dosage provided on successive infusions.

Few studies related to preparation errors have been reported to date involving patients of any age group. Four study groups specifically looked at the accuracy of the dilution process when medications designed for adults were administered to neonates and infants. Parshuram et al [6] analysed morphine infusions prepared for children weighing 0.7-60kg and identified an error rate of 65%. *Popescu et al*[7] investigated the difference between the vancomycin concentration prescribed and that prepared by nurses at the bedside in a paediatric unit. They found measured drug concentrations before administration to be an average of 7% lower than concentrations prescribed by the doctor. *Aguado et al*[8] looking at accuracy of concentration of morphine infusions, reported a mean deviation from intended concentration of more than 20%, in 19.8% of cases the deviations were found in infusions made by nurses and in 7.8% infusions made in pharmacy. *Campino et al* [9] conducted a study in 10 neonatal units and one hospital pharmacy looking at vancomycin, gentamicin, caffeine and phenobarbital preparations individually prepared for each patient. They detected calculation errors in 1.35% of samples and accuracy errors in 54.7% of samples (n=444) made at ward level whereas when samples were made in the hospital pharmacy setting no calculation errors were found and 38.3% of samples had accuracy errors. They further defined the errors and identified that calculation errors could be eliminated using protocols based on standard drug concentrations. However accuracy errors depended on several variables that affect both settings intensive care units and hospital pharmacy services since they are linked to syringe specifications, homogenisation process and drug manufacturing legislation involving total volume in the commercially available vials[10]

In addition, *Allegaert et al* [11] conducted a study looking at the administration accuracy and its impact on pharmacological parameters. They reported that in case of amikacin, the use of paediatric vials improved dosing precision when measuring pharmacokinetic parameters, showing that having an age appropriate formulation has direct improvement on pharmacological parameters.

Intravenous (IV) drug infusions are common in neonatal and paediatric critical care, and are used for life-sustaining medicines. Routine practice in these units is to withdraw an individualised dose of the required drug (calculated by weight) to a syringe of the appropriate size and then transfer to a second syringe, diluting to a larger volume of for example, 50mL with glucose 5% or sodium chloride 0.9%. The preparation process occurs normally at the bedside and produces a constant relationship between rate of administration and drug dose (i.e 0.1 mL/h of a morphine infusion usually equates to 5 µ/kg per minute if 2.5 mg/kg body-weight is diluted to a final volume of 50 mL). This is thought to facilitate bedside dose adjustment, and also limits fluid volumes [12,13].

Many leading organisations have advocated the use of standard concentration infusions to improve patient safety. The National Patient Safety Alert NPSA20 (March 2007), recommended the use of standardised intravenous (IV) solutions provided in ready-to-use forms[14.] Over a decade ago, the Joint Commission on Accreditation of Healthcare Organisations in the United States made standardised IV solutions a medicines management standard. All accredited US hospitals were required to meet this mandate by 2009, including introduction of smart pump technology to facilitate its safe implementation[15]. A similar practice change has taken place in Canada [16] and Australia[17].The Intensive Care Society (ICS) published guidance on medication concentrations in critical care areas in 2009 [18]. Despite of this encouragement little guidance is provided to clinical teams on how to identify the appropriate concentrations.

In 2007, our PICU decided to implement standard concentration IV infusions. Initially we focused on morphine and milrinone. A framework for implementing standard concentration infusions in a critical care area was developed [19]. This initiative represented a change from a long-established practice, thus potentially meeting resistance from practitioners. There was limited evidence at the time supporting the safety and most appropriate standard concentrations compared with traditional weight-based prescribing. After successful implementation of standard concentrations of these two drugs, we decided to aim for implementation of standard concentrations across the full

range of infusions used in our PICU with the clinical needs of the patient as the main focus.

MATERIALS AND METHODS

A core team was established consisting initially on a PICU Consultant and a senior PICU Pharmacist who designed a matrix to be used with all the commonly used PICU infusions as described in our recent publication[19]. The matrix would allow us to balance the concentration, dose and infusion volume across a range of weights from 1.5kg to 50kg. Weights above 50Kg were not included in matrix calculations as infusion rate in this patient group is caped in line with protocols in adults. This encompasses the weight ranges found within our PICU population. Consideration was given to the diluents regarding the age of the child as well as compatibility concerns with the drug. The matrix was built to deliver IV therapy following current practice and taking into consideration local and national guidance such as the Trust Paediatric formulary [20], the national injectable medicines guide-Medusa[21] and the BNF-C [22].

We interrogated each result against

1. Patient fluid allowance based on the fluid volume targets established within our unit: Concentrations required delivering therapy not exceeding maximum volumes taking into consideration routine multiple infusions routinely prescribed in this setting.

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PICU Fluid Allowance Consensus

(Adapted from Holliday-Segar equation[30])

Weight	Fluid Allowance
<9.9kg	2mls/kg per hour
10-40kg	1ml/kg per hour
>40kg	Max of 40mls/hr

2. Infusion pump accuracy: Minimum volumes that are accurately delivered with present pump technology derived from the infusion

pumps specification and evidence from the literature taking into account the impact of the syringe size[23,24]

3. This was further refined by a validation process challenging each single infusion against real clinical scenarios requiring administration of multiple drug infusions commonly found in PICU. These clinical scenarios were identified from the PICU database of case mix as the most common conditions treated in the unit
4. The proposed concentrations and clinical cases were then approved by the PICU consultants group

The concentrations obtained were further compared with IV infusions used in adult critical care to identify whether alignment was possible for some of the concentrations proposed [18,21].

A risk assessment of the infusions was carried out using the NPSA 20 risk assessment tool[14]. This provides a risk classification of each infusion in relation to the following eight factors of preparation and administration of infusions: Therapeutic risk, use of a concentrate, complex calculation, complex method of preparation, need to reconstitute drug, use of multiple or part vials, use of infusion pump and use of non-standard devices. This tool was applied at three different stages: Current practice of preparation of variable concentrations depending on patient's weight, use of standard concentrations prepared at ward level using drugs available in the UK, and use of the same standard concentrations supplied as a ready-to-use pre-filled syringes.

Statistical Methods

Formal statistical testing was not applicable for this study.

RESULTS

Twenty five drugs were identified as the most commonly used IV infusions in the unit, and the matrix was applied to them. For the majority of the medicines, three weight bands of standard concentrations were necessary to cover the children's weight ranges seen in the PICU and kept within predefined fluid requirements and accuracy of delivery.

Table 1 details the resulted proposed concentrations of the infusions for each weight band and diluents.

A risk assessment carried out for infusions prepared following current practice, that is. individualised infusions per patient, resulted on a classification of high (NPSA20 score 6 to 8) or moderate risk (with a NPSA20 score 5, moderate range is 3 to 5) for most of the infusions (Table 1). The use of standard concentrations contributes to reducing the risk, even when infusions are still prepared on the ward, eliminating the need of complex calculations on preparation of the infusions. In addition, calculation of rate of administration can be also eliminated with the use of smart pump technology. Preparation of infusions is also simplified (i.e less rounding required than with previous calculated doses) with standard concentrations designed to be prepared using, wherever possible, volumes with no decimals or even whole vials or ampoules.

Table 1 shows the risk reduction achieved from one up to three score points depending of the concentrations available to prepare the infusions for each drug and administration using smart pumps. When supplied as ready-diluted or ready-to-use pre- filled syringe, all infusion fall into the low risk category (NPSA score 1 to 2), or in the low side of the moderate risk band (NPSA score 3) if conventional infusion pumps are used. Glucose 5% was the preferred diluent for low weight children to provide some calories and to prevent sodium overload in the case of renally impaired neonates. Furthermore, for the majority of the products a final volume of 20mL was proposed for syringes to be used in children of < 5 kg taking into account accuracy of pumps when infusing small volumes.

Table 1. Standard Concentrations of PICU Infusions and NPSA risk score

Clinical scenarios were designed based on the patient population we see on our mixed PICU: Congenital and acquired cardiac disease, septic shock and acute metabolic decompensation are groups commonly seen. Each scenario was further adapted to include the extremes of age and weight found within the PICU population (i.e 25% of our PICU admissions being in the neonatal age) as well as severity of disease.

Table 2 describes the fluid contribution from predefined standard concentrations of infusions for a specific weight in relation to clinical fluid requirements in extremely unwell cardiac, metabolic or septic patients.

Table 2: Clinical scenarios and fluid contribution of standard concentrations (PICU Neonate 3kg) Extreme clinical cases

Clinical Scenarios PICU Neonate		
A) Post cardiac Surgery		
Fluid Allowance= 2mls/kg/hr (Strict)		
Drugs	Doses	Fluid Rate (mL/hr)*
Morphine	20 µ/kg per hour	1.2
Clonidine	1 µ/kg per hour	0.4
Milrinone	0.3 µ/kg per minute	0.5
Dopamine	10 µ/kg per minute	0.9
Adrenaline	0.1 µ/kg per minute	0.36
Noradrenaline	0.05 µ/kg per minute	0.18
Levosimendan	0.1 µ/kg per hour	0.36
Heparin	25 units/kg per hour	0.75
Furosemide	1mg/kg per hour	1
TOTAL INFUSIONS volume per hour		**5.65 mL**
Equivalent to		**1.88 mL/kg per hour**
B) Septic Neonate		
Fluid Allowance= 2mls/kg/hr (Strict)		
Drugs	Doses	Fluid Rate (mL/hr)*
Morphine	20 µ/kg per hour	1.2
Clonidine	1 µ/kg per hour	0.4
Milrinone	0.5 µ/kg per minute	0.9
Dopamine	10 µ/kg per minute	0.9
Adrenaline	0.1 µ/kg per minute	0.36
Noradrenaline	0.1 µ/kg per minute	0.36
Heparin	25 units/kg per hour	0.75
Furosemide	1mg/kg per hour	1
TOTAL INFUSIONS volume per hour		**5.87 mL**
Equivalent to		**1.95 mL/kg per hour**
C) Metabolic decompensation		
Fluid allowance= 2mls/kg/hr		
Drugs	Doses	Fluid Rate (mL/hr)*
Morphine	20 µ/kg per hour	1.2
Milrinone	0.5 µ/kg per minute	0.9
Midazolam	1 µ/kg per minute	0.36
Sod Benzoate	25 µ/kg per hour	1.5
Sod Phenylbutyrate	25 µ/kg per hour	1.5
L-Arginine	25 µ/kg per hour	1.5
Insulin	0.1 units/kg per hour	0.3

TOTAL INFUSIONS volume per hour 7.26 mL
Equivalent to 2.4 mL/kg per hour

DISCUSSION

Medication errors and adverse drug events are common in the paediatric population. The event rate is comparable to adult numbers but the potential for harm may be greater[3]. In addition, adverse drug events (ADE) per patient in the PICU setting is almost three times higher than reported rates found in multicentre studies of paediatric patients (reported ADE of 0.3 per patient versus 0.11 per patient) [4].

Analysis of the concentrations of infusions drawn up in NICU has shown inaccuracy of almost 20% [8], especially when the manipulation of small volumes is required. The use of standard concentrations have been shown to reduce the errors in administration without affecting therapeutic effectiveness [25,26].

While some institutions have moved to standard concentrations or are in the process, there is limited data on the rational for each concentration chosen [17, 27] as well as limited international guidance from international organisations on how to determine the concentrations despite their encouragement to adopt this practice [15, 28-29]. Similarly, there is no harmonisation between institutions locally, nationally or internationally on identified concentrations; therefore, each unit has come up with different ones. Even within our own institution we find variations in practice between different critical care areas for example NICU and PICU. It was this inconsistency that drove us to approach implementation of standard concentrations from a clinical and patient centred prospective.

Fluid restriction is common practice in Paediatric Intensive Care to ensure better patients' clinical outcomes. Practice varies within PICU's with reductions from 25-50% from the Holliday-Segar equation which still remains the standard method for calculating maintenance fluid requirements in paediatrics[30]. There is growing evidence of the adverse impact of early fluid

overload administration on clinical outcomes in paediatric critically care patients [31,32].

In our work, we tested all our concentrations in clinical scenarios to confirm that the concentrations used would not exceed our fluid regime. This confirms previous studies, which have shown that moving to standard concentrations does not increase the fluid volume administered , even in lower weight patients[25]. The concentrations developed would be applicable in units with more liberal fluid regimes.

As technology develops we have new mechanisms to help us to reduce errors associated with drug administration. These include the use of drug libraries built into our pumps; Dose Error Reduction Software (DERS) technology[27] with hard and soft limits on the amounts of drug which may be administered and barcoding[33] may all play an important role in improving safety and the quality of care we deliver to our patients.

Standard concentrations for morphine and milrinone have already been introduced successfully over the past 7 years in our PICU. At present our unit is in the process of introducing the rest of the agreed drug standard concentrations on table 1 on a step approach following the model described on our recent publication [19].

CONCLUSIONS

This work presents a systematic approach of defining and evaluating standardised concentrations that is patient-centred and establishes a benchmark methodology for future interventional studies. It also presents and opportunity to develop national recommendations and guidance although this requires national and international harmonisation between units to ensure optimisation and economy of scale in production and to facilitate the support of our industry partners and regulators.

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Table 1: Standard Concentrations of PICU Infusions and NPSA risk score

					NPSA20 risk score		
Drug	**Drug Preparation**	**Concentration**	**Preferred diluent (*)**	**Central (C) *vs* Peripheral (P) administration**	**Current (variable strenght)**	**Ward (std. conc.)**	**Ready to use (std. Conc.)**
ADRENALINE (Epinephrine)					6		
<5kg	1mg in 20mL	50 micrograms/mL	S, G	C only		5	2
5-20kg	4mg in 50mL (+)	80 micrograms/mL	S, G	C only		5	2
> 20kg	16mg in 50mL (+)	320 micrograms/mL	S, G	C only		4	2
CLONIDINE					6		
<5kg	150 micrograms in 20mL	7.5 micrograms/ml	G	C/P		4	2
5-20kg	750 micrograms in 50mL (+)	15 micrograms/ml	S	C/P		4	2
>20kg	2,000 micrograms in 50mL	40 micrograms/ml	S	C/P		3	2
DINOPROSTONE					6		
< 5kg	20 micrograms in 20mL	1 microgram/mL	G	C/P		5	2
DOBUTAMINE					5		
<5kg	40mg in 20mL	2mg/mL	G	C only		5	2
5-20kg	250mg in 50mL (+,#)	5mg/mL	S	C only		3	2
>20kg	600mg in 50mL	12mg/mL	S	C only		3	2
DOPAMINE					5		

<5kg	40mg in 20mL	2mg/mL	G	C only	5	2
5-20kg	200mg in 50mL (+)	4 mg/mL	S	C only	5	2
>20kg	600mg in 50mL	12mg/mL	S	C only	5	2
ESMOLOL					5	
<5kg	200mg in 20mL	10 mg/mL	G	C only	3	2
5-20 kg	500mg in 50mL (#)	10 mg/mL	G	C only	3	2
>20kg	1000mg in 50mL	20mg/mL	G	C only	5	2
FENTANYL					6	
<4 kg	500 micrograms in 50mL	10 micrograms/mL	S, G	C/P	3	2
4-20kg	1,500 micrograms in 50mL	30 micrograms/mL	S, G	C/P	4	2
>20kg	2,500 micrograms in 50mL (+, #)	50 micrograms/mL	S, G	C/P	2	2
FUROSEMIDE					5	
1.5-6 kg	60mg in 20mL	3 mg/mL	S	C/P	4	2
6-13kg	250mg in 50mL (+)	5 mg/mL	S	C/P	3	2
>13kg	500mg in 50mL (#)	10 mg/mL	S	C/P	3	2
HEPARIN				C/P	5	
<6kg	2,000units in 20mL	100 units/mL	G	C/P	5	2
6-15kg	10,000 units in 50mL	200 units/mL	S, G	C/P	3 or 4	2
>15kg	50,000 units in 50mL (+ #)	1,000 units/mL	Neat (in WFI)	C/P	4	2
INSULIN SOLUBLE (ACTRAPID®)					6	
<5 kg	20 units in 20mL	1 unit/mL	S	C/P	5	2
5 – 20 kg	50 units in 50mL (+)	1 unit/mL	S	C/P	5	2

> 20 kg	100 units in 50mL	2 unit/mL	S	C/P		5	2
L-ARGININE					5		
All Weights	2000mg in 40mL	50 mg/mL	S, G	C/P		4	2
LABETALOL							
All Weights	250mg in 50mL	5mg/mL	S, G	C/P			2
LEVOSIMENDAN					6		
>1.5 kg	2.5mg in 50mL	50 micrograms/mL	G	C only		5	2
LORAZEPAM					6		
>1.5 kg	10 mg in 50ml	200 micrograms/mL	G only	C/P			2
MIDAZOLAM					6		
<5kg	10mg in 20mL	0.5 mg/mL	S	C/P		5	2
5-10kg	50mg in 50mL(+, #)	1mg/mL	S	C/P		3	2
>10kg	100mg in 50mL(+, #)	2mg/mL	S	C only		4	2
MILRINONE					6		
<5kg	2mg in 20mL	100 micrograms/mL	G	C only		5	2
5-20kg	20mg in 50mL	400 micrograms/mL	G	C only		4	2
>20kg	50mg in 50mL(#)	1 mg/mL	G	C only		4	2
MORPHINE					6		
<4kg	1mg in 20mL	50 micrograms/mL	G			5	2
4-20kg	10mg in 50mL	200 micrograms/mL	S			5	2
>20kg	50mg in 50mL(+, #)	1 mg/mL	S			2	2
NORADRENALINE (Norepinephrine)					6		
<5kg	1mg in 20mL	50 micrograms/mL	G	C only		5	2
5-20kg	4mg in 50mL(+)	80 micrograms/mL	G	C only		4	2

>20kg	16mg in 50mL(+)	320 micrograms/mL	G	C only		4	2
OCTREOTIDE					6		
<5kg	100micrograms in 10mL(+)	10 micrograms/mL	S	C only		4	2
5kg-20kg	500micrograms in 10mL(+)	50 micrograms/mL	S	C only		4	2
> 20kg	1000 micrograms/ 50mL	20 micrograms/ mL	S	C only		5	2
POTASSIUM CHLORIDE Concentrated					6		
> 1.5 kg	20 mmol in 50mL(+)	0.4 mmol/mL	S, G	C only		4	2
PROPOFOL							
> 1.5 kg	200mg in 20mL (+, #) 500mg in 50mL (+, #)	10 mg/ml	Neat	C/P		2	2
SALBUTAMOL					5		
> 6kg	10mg in 50mL	0.2 mg/mL	G	C/P		4	2
	25mg in 50mL	0.5 mg/mL	G	C only		5	2
SODIUM BENZOATE					5		
All Weights	2000mg in 40mL	50 mg/mL	S, G	C/P		3	
SODIUM NITROPRUSSIDE					7		
<5kg	4mg in 20mL	200 micrograms/mL	G only	C only		6	2
>5kg	50mg in 50mL	1mg/mL	G only	C only		5	2
SODIUM PHENYLBUTIRATE					5		
All Weights	2000mg in 40mL	50 mg/ml	S, G	C/P		3	2

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CHAPTER 4: ADMINISTRATION OF ENTERAL DRUGS

CHAPTER 4.1: Accuracy of Enteral Syringes with commonly prescribed paediatric oral liquids

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ABSTRACT

Aim

To investigate the paediatric volumetric accuracy for two enteral syringe brands, using commercially available liquid drug formulations, across a range of clinically relevant volumes and physicochemical properties.

Method:

In vitro experiment under laboratory conditions. Ten drug formulations were tested for two syringe brands (Baxa, Medicina) using a range of formulation volumes (0.05 to 5 mL) and syringe sizes (1 to 5 mL). The weight of syringes, empty, filled and after expelling liquids were accurately measured and converted into volume, based on the known formulation densities. Ten replications were performed for each combination of drug, syringe and volume. Accuracy of the delivered volume was expressed as a percentage of desired volume, with desired range being within ±10% for all replications.

Results:

The two brands showed a different type of error, with Baxa demonstrating a slight positive bias (excess average volume delivered) at the smallest volumes tested in each syringe size, while Medicina had poorer precision (greater variability) at the smaller volumes (ANOVA 2- and 3-way interactions all $P < 0.005$). Using these results we were able to identify a lower limit for volume accuracy for each syringe size and each brand. Of note, the 1mL syringe for both brands was inaccurate below volumes of 0.25 mL. The physicochemical properties of pH (range 2.82 to 7.45), surface tension (30.2 to 86.7 mN/m) and viscosity (2 to 299 mPaS) did not influence error in a discernible pattern.

Conclusion:

Volumetric dosing was inaccurate when the smallest volumes were used across all syringe sizes and brands. Syringe brands are not interchangeable for small doses and the correct size of syringe should be used for a specific dose.. These volumes reflect those used in clinical practice; thus error could potentially be reduced by manufacturers revising formulation concentrations for certain drugs as well as delivery device testing for the specific oral liquids and clinical doses.

INTRODUCTION

Paediatric medications are administered most commonly via the oral route, accounting for approximately 60% of hospital prescriptions in children. Although a variety of oral medications are available, liquid dosage forms are commonest, comprising approximately two thirds of hospital oral administrations[1], They are appropriate for infants, and any child who has difficulty swallowing tablets or capsules. They also provide a means of adjusting the drug dose to patient's weight or surface area [2-4].

There are two main factors with liquid formulations which may compromise paediatric drug dosing. The first concerns the preparation of the formulation, and includes issues such as uniformity of content of the product when the drug is suspended and not solubilised, unknown bioavailability of extemporaneously prepared products, and the use of potentially toxic excipients such as ethanol. The second aspect relates to the accuracy of administration device used; these include measuring spoons, oral droppers, dosing cups (some of which contain etched calibrations) and oral syringes [5,6]. The majority of studies indicate that oral syringes provide greater accuracy than other devices, if used correctly [7-10].

A variety of Agencies and publications now recommend syringes as the preferred oral administration device for infants and children especially when volumes of less than 5ml are required, including the British National Formulary for Children, the United Kingdom (UK) National Service Framework for Children and the Council of the Canadian Academies [11-13] In addition, it is recommended that syringes be specific for oral administration, rather than utilising those designed for parenteral use. [14,15] In 2007 in the UK, the National Patient Safety Agency issued a safety alert, recommending the use of clearly labelled oral/enteral syringes that (a) cannot be connected to parenteral lines, (b) are unable to accommodate needles by having female luer lock tips, and (c) can be differentiated from parenteral syringes via the use of colour, such as purple [14]. This is now standard practice in many UK hospitals. In addition, these syringes are often used in preference to product-

specific syringes supplied by the manufacturer as part of the packaging for certain drugs, especially in hospital settings.

Currently, two brands of oral syringes predominate in the UK. Interestingly, two aspects that could potentially compromise accuracy of drug delivery with these syringes in paediatric clinical practice have not been evaluated to our knowledge. The first relates to physicochemical characteristics of liquid formulations for various drugs. Viscosity and surface tension, for example, can affect the dosing accuracy of administration devices; as demonstrated in a study with oral droppers [16] The European Committee for Medicinal Product for Human use has acknowledged this, recommending that oral administration devices be suitable for drug dosage forms in terms of the characteristics of the liquid [5].The second aspect is that therapeutic dosing requirements, and hence the administered formulation volume can vary greatly in paediatric patients. In practice, it can often be difficult to measure; hence must be rounded to the nearest syringe graduation to provide a practical volume [17]. However, the extent to which dose rounding can take place without clinical consequences depends on therapeutic window of drugs and the accuracy of administration devices [18]. Administration devices such as oral syringes can further increase the dose variability if they are not suitable for the specific drug/dose; this could lead to under dosing with diminished treatment efficacy or overdosing with potential for toxic effects [19].

With this in mind, the aim of our study was to evaluate the volumetric accuracy of drug delivery using two common oral syringe brands in the UK, over the range of syringe sizes, drug volumes, and liquid types (comprising viscosity, surface tension and pH) which mirror clinical paediatric practice.

METHODS

Two common syringe brands which are licensed for enteral administration of drugs that comply with National Patient Safety Agency recommendations were evaluated. Medicina® syringes presented a wide tip and are of 1ml, 2.5ml and 5ml capacities (smallest graduations 0.01ml, 0.1ml and 0.2ml respectively) whereas Baxa® syringes had a narrower tip, and are of 1ml, 3ml

and 5ml capacity and they present the same smallest graduations as the Medicina brand per syringe size. (See figure 1S online supplement)

Materials:

Ten oral liquid medicinal products were selected as representative of the formulations used in paediatric clinical practice, encompassing a broad range of viscosity, pH and surface tension. These were classified into:

- Aqueous liquid (Calcium carbonate BP suspension – Guy's & St Thomas' NHS foundation trust; Amoxicillin sugar-free suspension 125mg/5ml - Athlone laboratories limited; Peppermint water BP 1973 - Viridian Pharma Ltd; Nifedipine oral drops® - Ratiopharm and deionized water as control)
- Hydroalcoholic liquid (Digoxin elixir, Lanoxin®; Sodium Iron edetate elixir, Sytron®; Alfacalcidol oral drops, One Alpha®; Phenytoin suspension, Epanutin®)
- or Lipidic liquid (Cyclosporine solution, Neoral®; Ciprofloxacin suspension, Ciproxin®)

The pH was measured with a pH meter 209 Hanna®. A rotational rheometer (Gemini HR ^{nano} by Malvern) was used to derive the viscosity at a shear rate at 100 s^{-1}. Surface tension measurements were carried out on a Delta-8 multichannel microtensiometer (Kibron Inc.) and conductivity on a Primo 5 Hanna ® Conductivity meter. Baseline measurements of the physicochemical properties for each formulation (pH, viscosity and surface tension) were made at room temperature in triplicate.

Measurements of volume accuracy:

Ten measurements were made for each combination of syringe brand, syringe size, type of drug and formulation volume. The results are expressed as mean percentage (± SD) of the expected capacity indicated by the graduations. Accurate dosing was defined as within 10% of the intended volume [17, 20].

The weight of the syringes' content was measured with a Balance Precisa® 180A [accuracy of 0.002g with readability and repeatability of 0.1 mg and

linearity of 0.2 mg] by subtracting the weight of the filled syringe and the weight of the syringe after expelling the liquid.

This weight was then converted into volume using the density:
density (g/ml) = mass(g)/volume(ml)

The density was determined experimentally (n=3) at room temperature for all liquids by weighing 5ml in a clean and dry tarred measuring cylinder (capacity 10ml).

All ten drug formulations were measured in the 1ml syringes. Six formulations (Lanoxin, Amoxicillin, Ciproxin, Peppermint water, Calcium Carbonate BP, Sytron) were measured in the medium size syringes (2.5ml and 3ml), and only five medicines (Amoxicillin, Ciproxin, Peppermint water, Calcium Carbonate BP, Sytron) were measured with the largest syringe size (5ml). Water was used as control. This was in order to mimic clinical doses administered in practice. Table 1S (electronic supplement) describes the range of volumes measured for each syringe size.

Statistical Analyses

Unadjusted data are expressed as mean +/- standard deviation. The relationships between syringe brand, syringe size and formulation volume were evaluated using factorial analysis of variance (ANOVA). Brand, syringe size and formulation volume were treated as categorical variables, and the outcome variable (% desired volume actually delivered) was modelled as continuous. All 2- and 3-way interactions were assessed as part of the ANOVA. This approach was taken to assess whether the relative error between brands differed according to syringe size and volume. To test whether the formulations' physicochemical properties affected accuracy of delivery, we undertook multiple linear regression using the 1 ml syringe size only, testing interactions between formulation volume, brand and each of the physicochemical properties (surface tension, viscosity and pH). Post hoc differences following ANOVA and regression were evaluated using marginal

means with 95% confidence intervals. Analyses were performed using Stata v13.1 (StataCorp, Texas).

RESULTS

As expected, the dead space differed between brands. Medicina (wider tip) showed approximately double the dead space volume than Baxa (narrower tip) across each syringe size: 1mL (0.11 ± 0.01 versus 0.06 ± 0.003, p<0.001), 2.5/3mL (0.13 ± 0.01 versus 0.06 ± 0.01, p<0.001), and 5mL (0.15 ± 0.02 versus 0.09 ± 0.02, p<0.001).

Table 1 shows the physico-chemical characteristics of the formulations. The ranges for each property were: pH (2.82 to 7.45), surface tension (30.2 to 86.7 mN/m) and viscosity (2 to 299 mPaS).

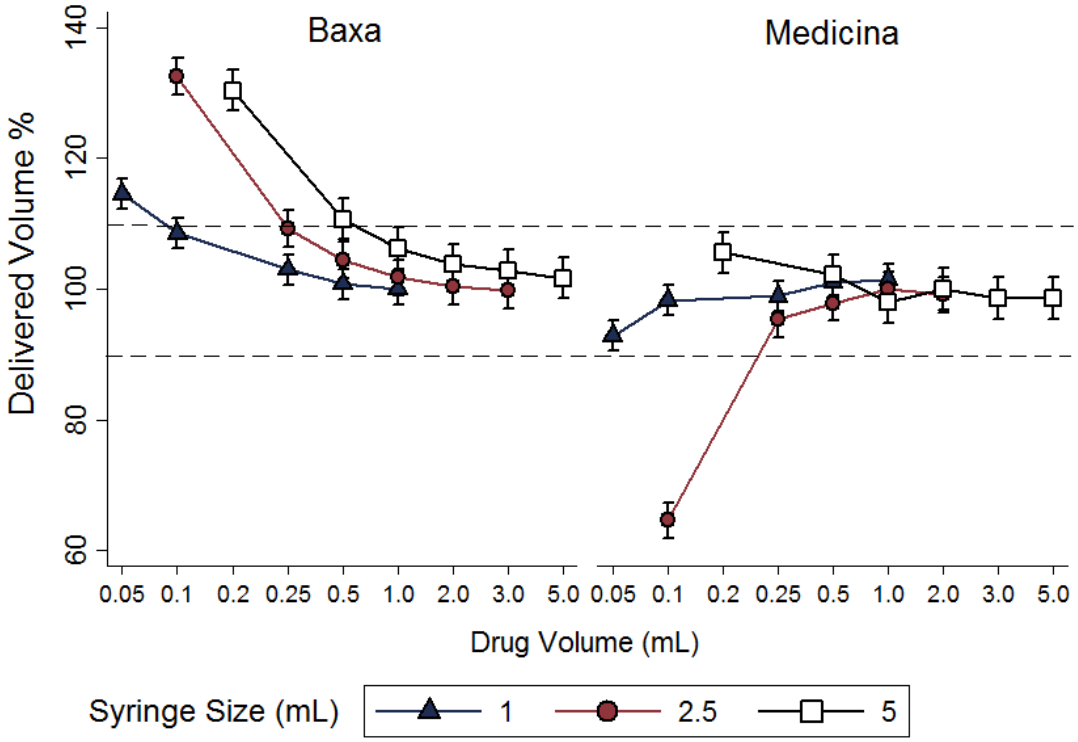
Table 1: Physicochemical characteristics of the oral liquids. Results are shown as mean (SD) of triplicate measurements

	pH	Surface Tension (mN/m)	Viscosity (mPaS)
Deionized water	5.56 (± 0.19)	71.7 (± 0.3)	2.0 (± 0.1)
Aqueous Liquid			
Calcium Carbonate	7.09 (± 0.01)	79.1 (± 3.9)	82.3 (± 1.0)
Amoxicillin 125mg/5ml SF	4.70 (± 0.02)	86.7 (± 0.7)	68.7 (± 1.9)
Peppermint water BP 1973	6.36 (± 0.00)	64.4 (± 0.5)	87.0 (± 1.9)
Nifedipine	7.45 (± 0.18)	40.2 (± 1.2)	56.1 (± 1.7)
Hydroalcoholic Liquid			
Lanoxin-PG ELIX (Digoxin)	7.01 (± 0.01)	38.0 (± 0.8)	5.7 (± 0.5)
Sytron Elix	2.82 (± 0.01)	60.5 (± 0.3)	5.3 (± 0.2)
One-alpha (Alfacalcidol)	6.99 (± 0.01)	30.2 (± 2.3)	9.7 (± 0.7)
Epanutin (phenytoin)	5.07 (± 0.01)	78.8 (± 0.5)	299.1 (± 6.1)
Lipidic Liquid			
Neoral oral solution (cyclosporin)	7.20 (± 0.17)	33.7 (± 0.6)	144.1 (± 0.8)
Ciproxin suspension 250mg/5ml	5.15 (± 0.02)	30.5 (± 0.7)	82.6 (± 6.1)

In terms of overall volumetric accuracy, all 2- and 3-way interactions between brand, syringe size and formulation volume were significant (table 2S,

electronic supplement). This is shown by the ANOVA-estimated marginal means in figure 1, whereby the error is not consistent between all combinations of brand, syringe size and formulation volume.

Figure 1: Percentage volume error by syringe brand, syringe size and drug formulation volume. Data are marginal means with 95% confidence intervals, calculated from Analysis of Variance



Here, the Medicina syringes showed acceptable (i.e. <10%) average volume delivery errors across most combinations of syringe size and formulation volume, apart from an isolated, large under-provision of delivered volume (i.e. average negative error of 65% desired volume) when 0.1ml was used in a 2.5 ml syringe. Of note, the average syringe error for the 1ml Medicina was acceptable for all volumes, including the smallest volume of 0.05ml. In comparison, all Baxa syringes provided a trend towards unacceptable over-provision (positive error) of delivered volumes when smaller formulation volumes were used, Here the 5ml syringe over-delivered volume by

approximately 30% when 0.25ml was attempted, the 2.5ml syringe yielded a similar error when 0.1 ml was delivered, and the error for the 1ml syringe became borderline unacceptable (110%) when 0.1ml was used.

A limitation of figure 1 is that it provides only an estimation of bias (average error), but not precision. The latter was evaluated using box and whisker plots for each syringe size and formulation type, which revealed poorer overall precision for the Medicina brand. By inspecting the range of volume plots for each syringe size in a sequential manner, we were able to define the approximate limits of accuracy for each syringe. Figure 2 shows an example for the 1ml syringes. At formulation volumes of 0.05 ml and 0.1 ml, the precision for both syringe brands is inadequate, with many values lying outside of the 100% $\pm$ 10% limits (more so for Medicina). However at 0.25 ml, the majority of values were now acceptable.

Figure 3 shows the transition points for accuracy of the 2.5/3.0 ml syringes. Here, the limit of accuracy was likely to be at a formulation volume of 0.5 ml for both brands. Interestingly, the Baxa yielded a large, consistently positive error for cyclosporine, at all volumes up to and including 1.0 ml. For the 5 ml syringes, the Medicina demonstrated superior precision, being accurate at formulation volumes of 0.5 ml, compared to 1.0 ml for the Baxa (figure 2S online supplement).

The multiple regression models did not reveal a systematic pattern for error for any of the physicochemical properties (figure 3S, online supplement), with formulation volume again being the largest determinant of error.

Figure 2: Box and whisker plots showing precision for the two syringe brands using 1 mL syringes at three formulation volumes: 0.05 mL, 0.1 mL and 0.25 mL. Baxa are represented as grey boxes with outliers as crosses, Medicine are white boxes with outliers as open circles. Drug formulation abbreviations: Deion H2O, deionised water; Ca Carb, calcium carbonate; Amox, amoxicillin; Pepp H2O, peppermint water; Nifed, nifedipine; Digox, digoxin; Sytron, sodium iron edentate; One alpha, alfacalcidol; Phenyt, phenytoin; Cyclosp; cyclosporine; Ciproflox, ciprofloxacin.

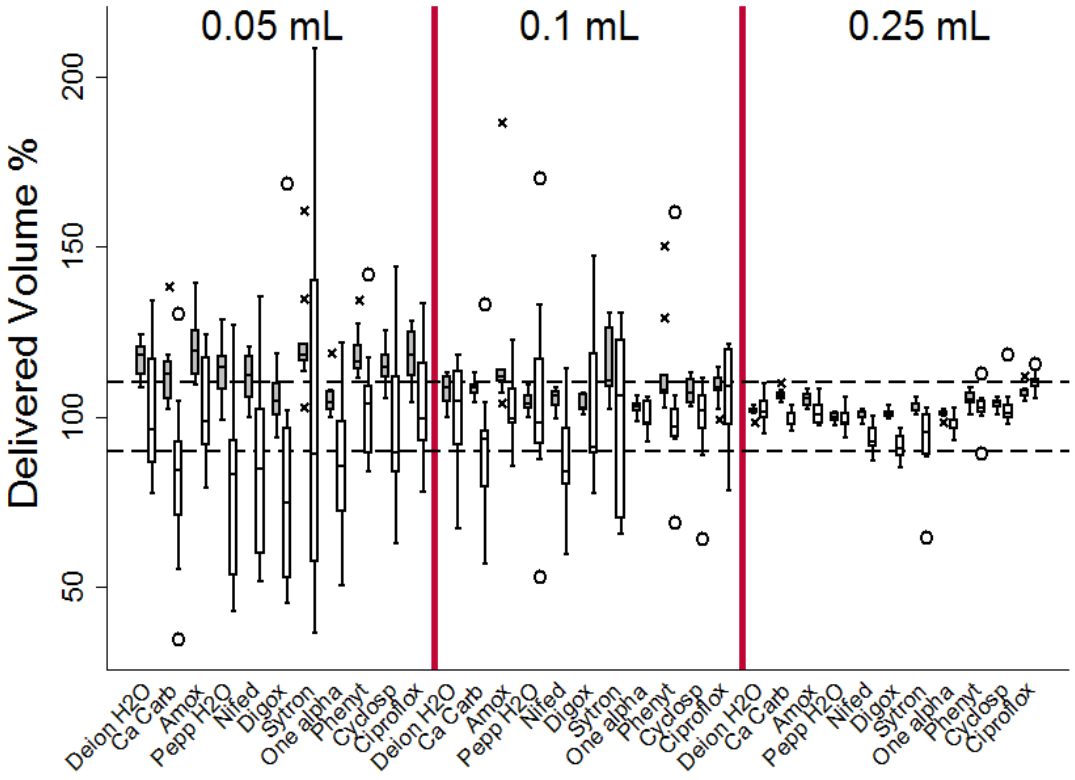
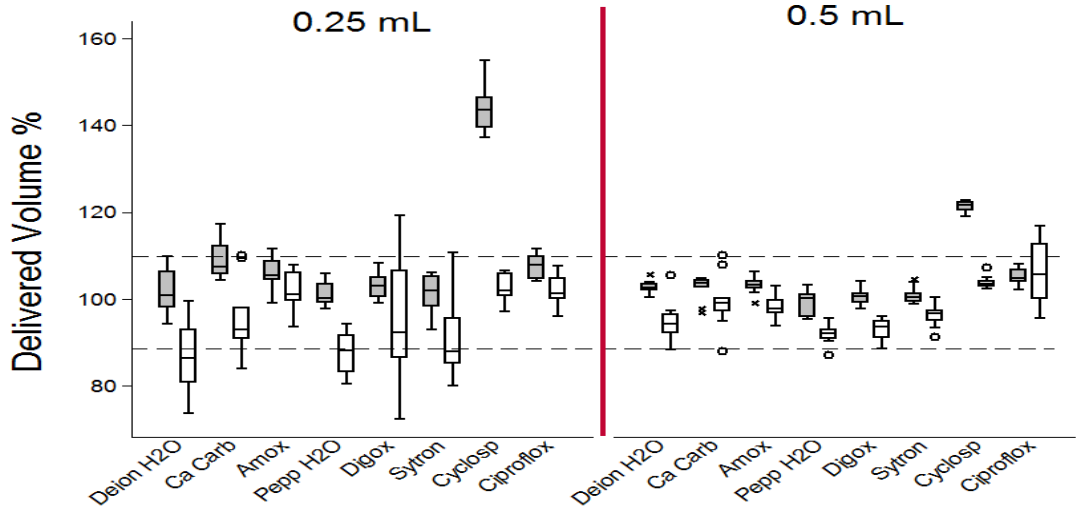


Figure 3: Box and whisker plots showing precision for the two syringe brands using 2.5 / 3 mL syringes at two formulation volumes: 0.25 mL, and 0.5 mL. Baxa are represented as grey boxes with outliers as crosses, Medicine are white boxes with outliers as open circles. Drug formulation abbreviations are as for figure 2.



DISCUSSION

We have evaluated *in vitro* limits of volume accuracy for two brands of oral syringe, when dispensing common paediatric drug formulations. The largest source of error appeared to be related to the chosen dispensing volume relative to syringe size, rather than the physicochemical properties of the drug formulation itself. Also, the type of error varied between the two syringe brands. Medicina exhibited less bias, but poorer precision (i.e. repeatability)

overall; the latter may have been influenced by the larger dead space for this brand. In comparison, Baxa tended to provide a slight positive bias when smaller volumes were administered relative to each syringe size; however this was generally small and the precision (repeatability) was better. Of the two errors, we would suggest that precision is the more important, as this provides less variability with repeated dosing in individual patients.

For each syringe size and brand, there appeared to be a transition point whereby error became unacceptable, which has allowed us to make recommendations for the minimum volume to dispense at each syringe size for both syringe brands (table 2).

Table 2: Volumetric accuracy of formulation volumes when tested across brands and syringe sizes.

		Formulation Volume (mL)					
Brand	**Syringe Size**	**0.05**	**0.1**	**0.20**	**0.25**	**0.5**	**1.0**
Baxa	1 mL	–	– / +		+	+	+
Medicina	1 mL	–	–		+	+	+
Baxa	3 mL	–	–		– / +*	+*	+
Medicina	2.5 mL	–	–		–	+	+
Baxa	5 mL	–	–	–		–	+
Medicina	5 mL	–	–	–		– / +	+

Legend: – inaccurate; – /+ borderline accurate; + accurate; * inaccurate for cyclosporine only. Blank, grey cells occur when the formulation volume was not tested for a given syringe size.

However, these recommendations should be interpreted with some caution for three reasons. First, we did not test small volume increments close to the transition point. Thus, for example, we can see that when dispensing formulations via the 1 mL syringe (figure 2), volumes of 0.25 mL are acceptable, whereas volumes of 0.1 mL are not: however, we do not know if

any volumes of administration between these two values (e.g. 0.15mL, 0.2 mL) are acceptable. Second, one drug, cyclosporine, appeared to exhibit a consistent error (over-administration) for one syringe brand (Baxa) at volumes where other drugs were accurate for this syringe brand (see figure 3). It is unclear whether this is due to the combination of physicochemical properties not seen with other drugs, or an interaction between a chemical compound in the Baxa syringe not seen in the Medicina brand. Thus, we do not know whether an error of similar magnitude exists for drugs not evaluated in the current study. Third, other factors may influence *in vivo* error: for example, when administered orally, small children may suck on the syringe, thereby increasing drug delivery. Similarly, the effect on volume error of administering these drugs via an enteral feeding tube is unknown.

We chose drugs and volumes to reflect those used in clinical practice. For example, a 5kg baby prescribed nifedipine at doses of 200 mcg/kg would receive volumes of 0.05 mL (UK nifedipine formulation strength 20mg/mL). From figure 2, this could result in a relative under-dosing in >50% of administrations using a Medicina syringe, and an over-dosing in a similar proportion (albeit by a smaller amount) using a Baxa syringe. It is unlikely that a similar dosing inaccuracy for an adult formulation would be acceptable in clinical practice.

To our knowledge, there are very few other studies in the public domain comparing accuracy of oral syringes for different small dose volumes and characteristics of oral liquids. Padden Elliott et al conducted a study looking at the influence of viscosity in three different oral devices: oral syringes, cups and droppers. They found that syringes were the most accurate device *in vitro* for more highly viscous liquids at a 5mL volume, and also in an *in vivo* sample of 320 volunteers from community pharmacies. However, this team did not look into doses smaller than 5mL, they did not examine physicochemical properties other then density and they only used one brand of syringe[21]. Other studies examining volumes less than 5 mL have concluded that oral syringes are more accurate than other devices; however these have tended to

concentrate on a limited range of volumes, typically 1.25, 2.5 and 5 mL (equating to one-quarter, one-half and one teaspoon).[22, 23]

One further potential source of error not examined in our study was the effect of rounding when a dose prescription requires a number of decimal places beyond what is available on the syringe. For example, a drug dose of 1.26 mL cannot be delivered adequately when the smallest graduation on a syringe is 0.1 mL. This is common in clinical practice. Morecroft and colleagues audited 1599 inpatient prescriptions of oral liquid medicines, and discovered that 12.5% could not be given accurately, requiring the use of more than one syringe of different volumes[24].

Thus we would encourage the pharmaceutical industry, medicines regulators and licensing bodies to mandate the provision of paediatric drug formulations in concentrations that provide adequate dosing volumes to minimise error across the entire spectrum of paediatric practice.

CONCLUSION

Dosing accuracy with enteral syringes commonly found in the HealthCare systems was heterogenous for different brands, sizes and liquid characteristics especially for small volumes (0.25ml and less) which are not uncommon doses in paediatrics.

To improve medication safety in paediatrics, carers should choose the right syringe size for the dose (for small volumes <0.5ml use 1ml size syringes or less if available) and keep to the same brand if properly tested syringes for the intended dose are not available.

Manufacturers need to include as part of the pharmaceutical development plan the validation of the syringes to use with their products especially if dosing volumes are envisaged to be <0.5ml, and possibly take into account the national guidelines available to reduce the risk of using these devices.

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Online Supplementary Material

Table 1S: Formulation volumes measured for each syringe size

Table 1: Volumes measured per syringe size

Syringe size	Volumes Measured Per Syringe Size (each n=10)							
1ml	0.05ml	0.1ml	0.25ml	0.5ml	1ml			
2.5ml/3ml		0.1ml	0.25ml	0.5ml	1ml	2ml		
5ml			0.2ml	0.5ml	1ml	2ml	3ml	5ml

Table 2S: Analysis of Variance table for the interaction between brand, syringe size and formulation volume

```
                           Number of obs =    2693    R-squared     =  0.4177
                           Root MSE      = 12.3015    Adj R-squared =  0.4107

                  Source |  Partial SS    df       MS           F     Prob > F
  ---------------------+------------------------------------------------------
                 Model |  288800.554    32  9025.01732      59.64      0.0000
                       |
                 brand |  84252.4058     1  84252.4058     556.76      0.0000
              size_cat |  2971.77868     2  1485.88934       9.82      0.0001
       brand#size_cat |  38137.2635     2  19068.6318     126.01      0.0000
              vol_cat |   31361.479     8  3920.18488      25.91      0.0000
        brand#vol_cat |  125801.918     8  15725.2398     103.92      0.0000
     size_cat#vol_cat |  3406.25573     6  567.709288       3.75      0.0010
brand#size_cat#vol_cat|  47619.2302     5  9523.84604      62.94      0.0000
                       |
                Residual |  402526.666  2660  151.325814
  ---------------------+------------------------------------------------------
                   Total |   691327.22  2692  256.808031
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Figure 1S: Different syringes and sizes used as part of the study

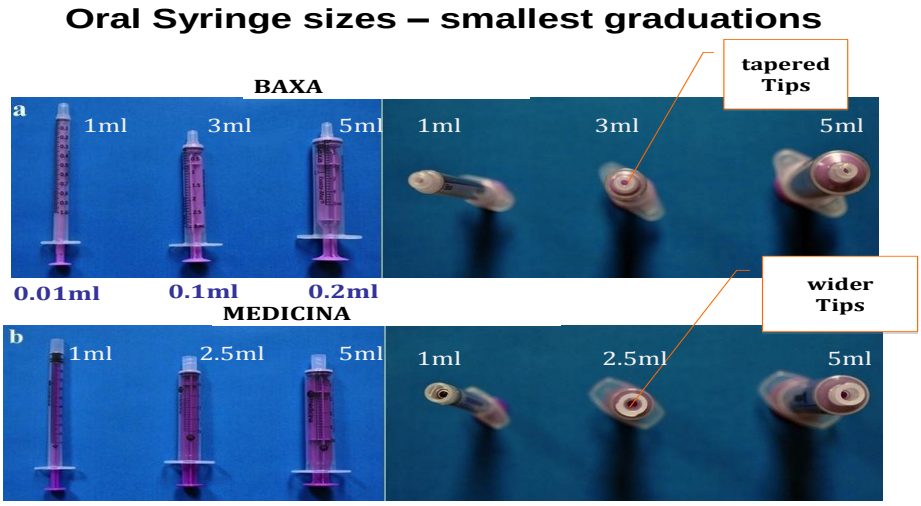


Figure 2S: Box and whisker plots showing precision for the two syringe brands using 5 mL syringes at two formulation volumes: 0.1 mL and 0.25 mL. Baxa are represented as grey boxes with outliers as crosses, Medicine are white boxes with outliers as open circles. Drug formulation abbreviations are as for figure 2 of main manuscript

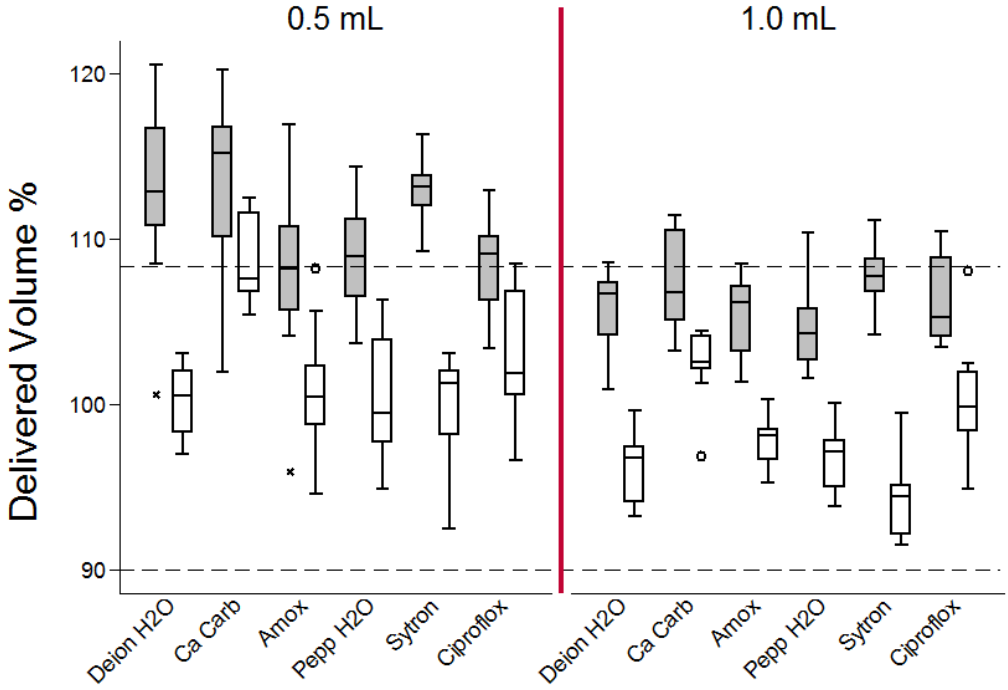
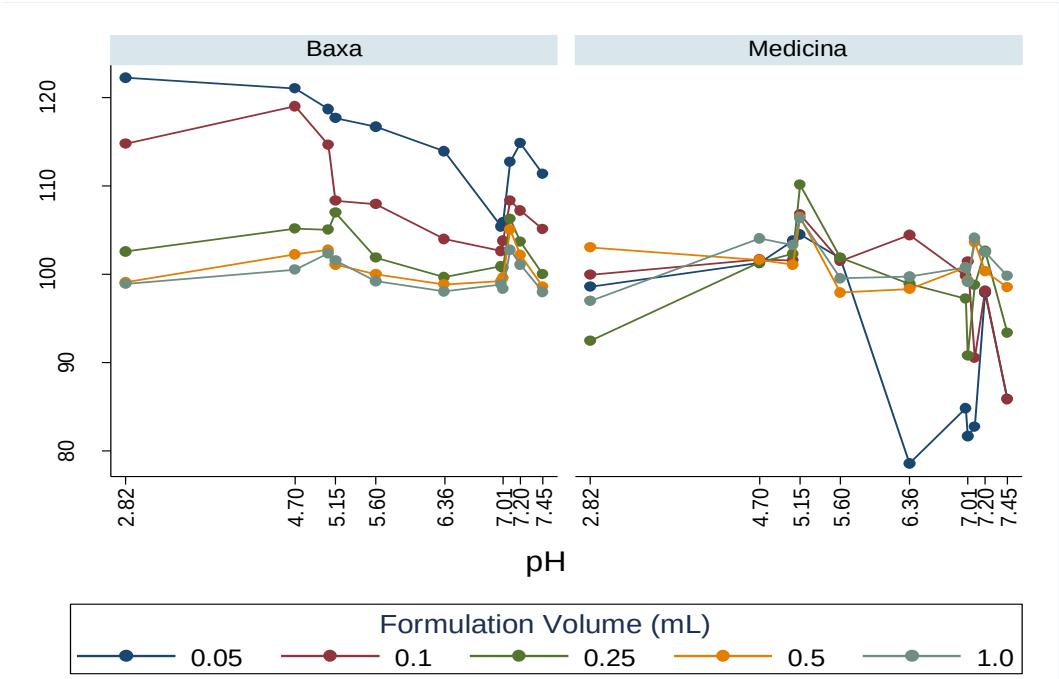
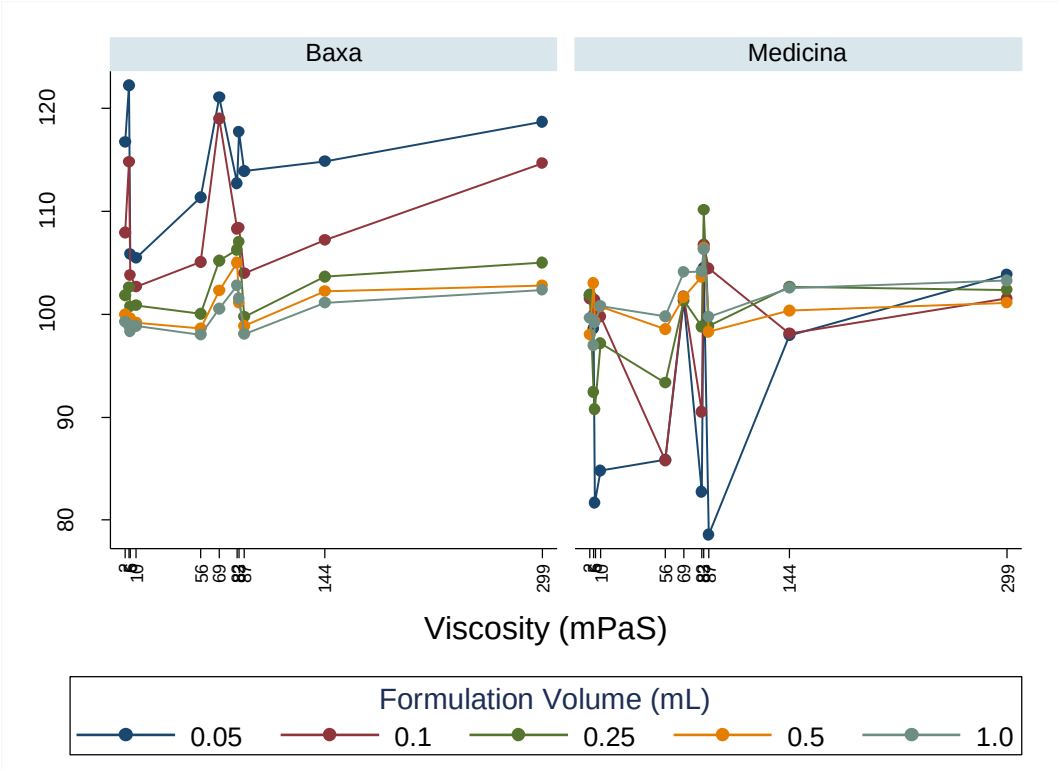
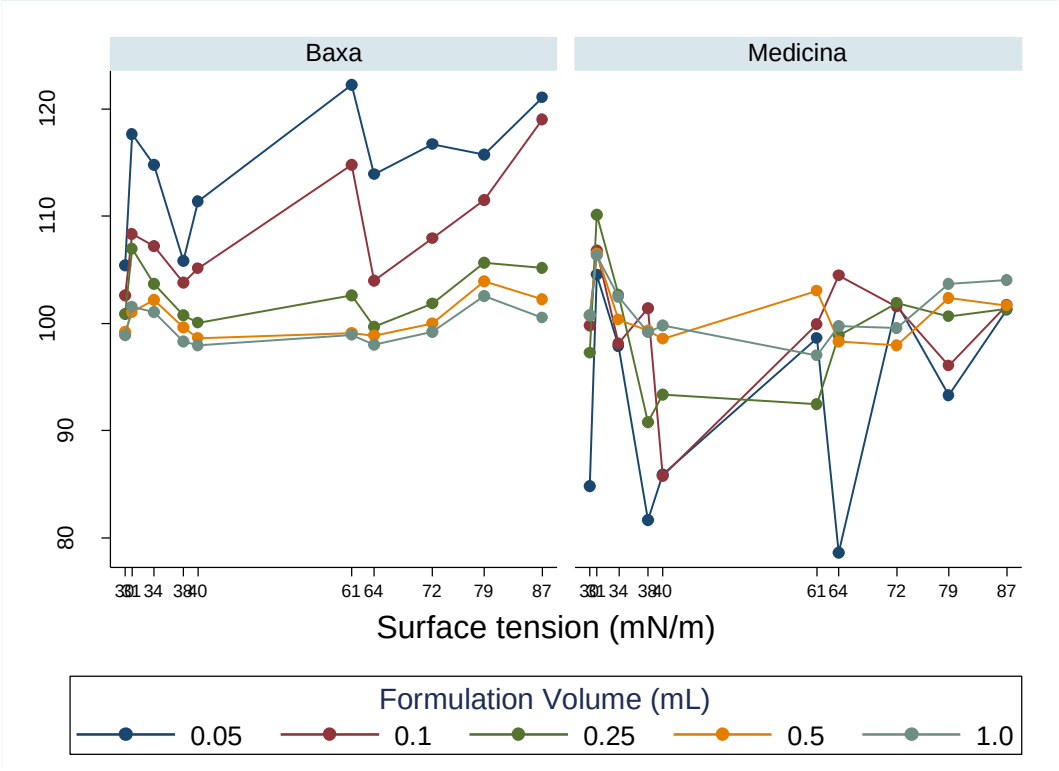


Figure 3S: Multiple linear regression-derived marginal means (+ 95% confidence intervals) for the three physicochemical properties (pH, surface tension, viscosity), when tested using a 1mL syringe.






Baxa
Medicina
120
110
100
90
80
61 64 72 79 87
Surface tension (mN/m)
Formulation Volume (mL)
0.05
0.1
0.25
0.5
1.0

CHAPTER 5:

GENERAL DISCUSSION ON THE PhD THESIS AND CONCLUSIONS

GENERAL DISCUSSION

This thesis provides an understanding of efficacy and safety aspects in paediatric intensive care sedation treatments as well as an insight on the challenge of accuracy of drug administration. Each chapter addresses the different objectives identified on the thesis proposal.

First, we began this work examining the safety and efficacy of clonidine as a sedative agent for the PICU population. For this purpose two studies were conducted and are detailed in chapter 2 of this manuscript. The first one is a foundation study supporting the clinical decision for PICUs choosing this agent as an alternative to benzodiazepines, the initial part of this work was the basis of the Masters in Science degree of the PhD Student in 2002. The article has been cited in over 50 publications related to sedation in paediatric critical children. As such, it remains an important publication regarding the use of clonidine for sedation in paediatric critical care, as we addressed the haemodynamic safety aspects and the decreased requirements of opioids and benzodiazepines. As such, it has been used recently to inform a Randomized Controlled Trial (RCT) with premature neonates by Hünseler et al [66]. The authors studied as the primary endpoint, the requirements of fentanyl and midazolam in the neonatal and paediatric ICU population up to the age of 2 years following 72h from onset of clonidine administration (1microgram/kg/hr). They enrolled 219 infants and 212 received the study medication. In the overall population there was no difference in the requirements of fentanyl and midazolam, however when the results were analysed in age groups, in the first group (n=112, age 0-28 days) the clonidine group had a significantly lower requirement for fentanyl (clonidine group: 2.1 ± 1.8 microgram/kg/hr, placebo: 3.2 ± 3.1 microgram/kg/hr; p= 0.03) and midazolam (clonidine group: 113.0 ± 100.1 microgram/kg/hr, placebo: 180.2 ± 204.0 microgram/kg/hr; p= 0.03). Groups 2 (n= 43, age 29-120 days) and 3 (n= 46, age 121 days-2 years) showed no statistical difference. Sedation and withdrawal-scores (COMFORT Score) were significantly lower in the clonidine arm of Group 1 (p< 0.001). Frequency of severe adverse events did not differ between groups.

Clonidine, at 1microgram/kg/hr in ventilated newborns, reduced fentanyl and midazolam demand with deeper levels of analgesia and sedation without substantial side effects. This was not shown in older infants, possibly due to lower clonidine plasma concentrations with a median value of 4.92 ng/mL (IQR, 3.36–5.62) in group 1 versus groups 2 (median concentration= 2.81 ng/mL (IQR, 2.06–3.51)) and group 3 (median concentration= 3.21 ng/mL (IQR, 2.15–4.59)). These findings differ from our initial study, where we demonstrated an overall decrease in the average hourly requirements for both morphine and lorazepam when clonidine plasma concentrations reached 1.4ng/mL. it is possible that this may be explained by differences in casemix between the two studies; however in order to provide more insight on this issue, a larger study with similar patients needs to be conducted.

Duffett et al [68], conducted a pilot randomized control trial in mechanically ventilated children enrolling 50 children. Patients were randomised to 5microgram/kg of enteral clonidine every 6h or placebo every 6h, other sedatives were administered at the discretion of physicians if required. The median interquartile range (IQR) age was 2.5 (0.7-5.2) years, and Pediatric Risk of Mortality score on pediatric intensive care unit admission was 12 (8-15). In terms of feasibility outcomes, 90 (87%) of 104 eligible patients were approached for consent, and on average, 1.7 children were enrolled per month. Thereafter, 94% of doses were administered by protocol. Clinical outcomes and adverse effects were not significantly different between the groups. The authors conducted this study to ascertain if a larger RCT was feasible and their conclusion was positive; however the protocol required amendments, which they described in their manuscript and they could not provide conclusive results on the efficacy and safety of clonidine.

In 2014, a very important and highly awaited RCT was published from the UK. The SLEEPS trial[69] was a prospective multicenter randomised, double blind study involving 10 PICU's. It was designed as an equivalence study comparing IV clonidine to IV Midazolam for sedation in PICU with the intention of recruitment of n=1000 subjects. The inclusion criteria were children from 30 days to 15 years old (<50kg) requiring ventilation for more than 12-h.

Study participants were randomised to clonidine (3microgrammes/kg bolus followed by an infusion of 0-3microgramme/kg/hour) versus midazolam (200microgram/kg bolus followed by infusion 0-200microgram/kg/hr). Doses were adjusted according to the sedation scores and both groups also received morphine. The primary endpoint was sedation measured using the validated COMFORT score (>80% of time in between 17-26 with a +/-0.15 margin of equivalence). As secondary endpoints, percentage of time spent adequately sedated, increase in sedation/analgesia, recovery after sedation and safety data were measured.

The trial did not recruit to target (129 of 1000 planned children) and was thus substantially underpowered in its objective to demonstrate equivalence[69]. From 129 subjects only 120 (93%) contributed data for the primary endpoint, namely the proportion of patients receiving adequate sedation (as judged by the COMFORT score) for ≥80% of their PICU time. This occurred in 34.4% of the clonidine group and 30.5% of the midazolam group (absolute difference 3.9%, 95% CI -13% to +21%); thus equivalence could not be demonstrated. Time to reach maximum sedation and duration of the effect was similar in both groups and withdrawal symptoms requiring interventions occurred in a greater proportion of the midazolam group (27.6% versus 18.3%).

Although equivalence could not be demonstrated; non-inferiority of clonidine to midazolam was suggested, with the only values outside the equivalence range favouring clonidine. The investigators concluded the study stating that clonidine was similar to midazolam and likely to be a cost effective sedative agent. This was planned as a large multicentre trial and had expectations among the PICU community to demonstrate the beneficial effects of clonidine for the sedation indication, however, the recruitment process was more difficult than expected this was likely due to several factors such as: conflicting recruitment with other large, multicentre studies conducted at the same time such as CATCH and CHIP trials, timing of consent, reluctance of clinicians on the floor for studying sedation in some critically ill children and others such as delays in study start with the manufacture of the investigational

medicinal product (IMP). Building on from the SLEEP trial, the EC funded in 2013, as part of the 7th Framework Programme, an international project named CloSed, aimed at evaluating the sedative efficacy of clonidine compared to midazolam, with a view to filing an application of Marketing Authorisation for clonidine ready-to-use age appropriate infusions[70]. Hopefully this project will provide a definitive answer on the efficacy of clonidine as a sedative for paediatric critical care children and neonates.

The work from our first study was extended via a second clonidine study conducted in post cardiac surgery children. This work provides an answer for the use of enteral clonidine in this specific patient group, where gastrointestinal perfusion may be impaired due to the low cardiac output state seen post cardiac bypass surgery and concomitant drugs administered, with the resultant negative effect on the absorption profile. The study showed that decreased total absorption did not occur, but the rate of absorption was impaired, leading to a delay in the clinical effect. Haemodynamic parameters were not perturbed, reassuring us that clonidine is a safe drug in this population. However if urgent sedation is required, IV clonidine may be preferable.

One cohort study in the neonatal cardiac surgery population has come to light recently with similar findings to our two studies. *Kleiber et al* [71] looked at the haemodynamic effects of clonidine post cardiac surgery in infants younger than 2 months of age. This study included 23 neonates that received clonidine as IV infusion (0.5-2microgram/kg/hr) for a median duration of 30h (Q1-Q3 12-54) at a median of 12h post surgery (Q1-Q3 5-23). The heart rate decreased by 12% (149 beats/min (SD 17) to 131 beats/min (SD 17 $p<0.0001$) and they found a transient drop in the diastolic blood pressure of 13% (maximal mean decrease from 42.8 mm Hg (SD5.9) to 37.1mmHg (SD4.0) $p=0.018$). The remainder of the cardiovascular variables were stable. The investigators concluded that the observed decreased in blood pressure and heart rate was of minimal clinical importance, not requiring intervention

To our knowledge, since our recent publication no other work on clonidine for oral sedation has been published in the PICU setting apart from the *Duffet et al* RCT feasibility study which does not address pharmacokinetic parameters and neither does it establish conclusive pharmacodynamic effects[68].

We then proceeded to examine aspects of how sedatives were administered in PICU, finding that the most common route of administration was the intravenous continuous infusion, although some drugs, such as clonidine, were also commonly administered via the enteral route.

Chapter 3 explores safety of continuous IV drug administration. Firstly we evaluated current practice by nursing staff and pharmacy and focused on measuring the accuracy of the syringes prepared following normal practice of calculating the dose and concentration with the weight of the child. This showed that 27% of syringes made using this practice were outside of British Pharmacopeia recommendations. There is evidence to show that administration of intravenous medicines in PICU and NICU is a very high risk practice [72,73] . In the last year, two new reports conducted in Spanish NICU's reinforced these findings [59,74]. Current literature such as these studies reinforces the use of standard concentrations to avoid these inaccuracies and other risks.

Standard concentrations of infusions is an important topic in the United Kingdom Department of Health's Agenda [64] and even for the WHO as published in their High 5s document[62].

It was therefore decided to implement standard concentrations of infusions using morphine as the pilot. Our second study of this section evaluates the implementation of this change in practice and finally the results of this experience are applied to all infusions administered in PICU and this is described on our third study of chapter 3.

In order to improve safety, the main way forward is to prescribe and administer IV medicines, especially infusions, as standard concentrations. The technology is evolving towards bar-coding which will likely reduce the main error, mis-selection of the concentrations that occurs with standard concentrations, especially if the products are manufactured in pharmacy and barcoding is connected to electronic prescribing systems. Nevertheless this is the way forward for children's IV therapy, it ensures minimal to none manipulation of small volumes, high quality products which follow quality assurance testing and usage of technology which diminishes the programming errors and infusion of the wrong dose.

Despite the published work from several units and the interest from Governments and International Organisations, to our knowledge, there is no international consensus on how to administer IV drugs as standard concentrations to neonates and children in intensive care, only local national references with very general information [75-77]. However, increasing evidence indicates that the use of standard concentration of IV medication and standard protocols[74] improve safety in the paediatric population, especially if technology such as Smart pumps with "Dose Error Reduction Software" (DERS)[78] and barcoding[79] to identify products and doses is used. The FDA lately emphasized this in their August 2016 safety communication regarding the administration of low infusion rates using syringe pumps [80].

The complexity of the current situation and benefits of standardisation is reflected in some EU Guidelines for the Pharmaceutical Development of Medicines for Neonatal and Paediatric Use [81,82] and in the overall EU Paediatric Regulation [15].

The articles in this thesis could act as a foundation to inform Authorities and individual hospitals or paediatric organisations to aid the safe implementation of the use of standard concentrations. Hopefully, this will also inform pharmaceutical manufacturers, guided by clinicians working together as a community, on standard concentrations products that can be made by industry.

To conclude our research for this thesis we explored the enteral administration practice since it is an important route of administration in critically ill children and used to administer sedatives (chapter 4). This last project idea emerged from clinical practice and from the work that the PhD student currently conducts for the European Medicines Agency Paediatric Committee. Many nurses commented on the use of different oral liquids and the accuracy of the syringes. Some of the liquids used in paediatric intensive care are very water soluble and easy to administer (i.e such as clonidine oral solution) and others are viscous (i.e such as oral morphine sulphate solution). Nurses had the impression that not all the dose volume was expelled out of the syringe on administration and they were unsure whether the dose administered was accurate.

The Centre for Paediatric Medicines Research, at the University College London (UCL) School of Pharmacy, has extensive expertise on paediatric formulations and devices therefore collaboration was established to investigate this phenomenon.

At the time of planning the study a selection of the most common liquids used in the unit was made, however, we faced some challenges with the two main drugs involved in this thesis, clonidine and morphine. Regarding clonidine, this product is manufactured as an unlicensed medicine and we had restrictions on its supply for research purposes outside the clinical environment. In relation to oral Morphine, this is classified as a controlled drug and we could not use samples of bottles for the study as it is against the legislation. Therefore, we had to choose other liquids of similar characteristics to clonidine (aqueous) and oral morphine (viscous aqueous).

The main findings from this study can be applied to clinical practice. First of all, its been shown that the syringe brands are not interchangeable for small volumes since there is great variability on accuracy of volumes for different oral liquids specially with dose volumes < 0.25mL. Furthermore the correct

size of syringe has to be used to administer a specific dose, the smaller the dose the smaller the syringe size.

This study conveys an important message to manufacturers and regulators. There is a need to perform validation studies of the oral administration device for the specific liquid under marketing authorisation, especially if small dose volume requirements are envisaged which reflect those used in clinical practice. The commonly commercially available syringes are not accurate for small volumes for all types of oral liquid medicines. In addition, it would be ideal if Healthcare Authorities, manufacturers and regulators incorporate current national practice guidelines on the manufacturing of the syringes. In hospital settings, enteral administration of drugs needs to be differentiated from parenteral to prevent fatal errors of wrong route of administration, this implies that syringes that come as part of the packaging in the majority of cases cannot be used in the clinical setting as they do not comply with this safety guidelines despite of being the syringes licensed in the Marketing Authorisation.

The dosing error could also potentially be reduced by manufacturers revising formulation concentrations for certain drugs in order to avoid small dosing volumes.

Finally, the message to patients and healthcare professionals in community is to always use the same brand and size of syringe for the doses with the same drug and if the syringe comes in the packaging of a licensed medicine, they should use it.

From completion of this study we are not aware of any other publication related to this work.

The Role of the Pharmacist in a Paediatric Intensive Care Unit: Direct Pharmaceutical Care, Education & Training and Research

Hepler and Strand introduced in 1990 the concept of pharmaceutical care as *"the process through which a pharmacist cooperates with a patient and other professionals in designing, implementing and monitoring a therapeutic plan that will produce specific therapeutic outcomes for the patient and that it involves three major functions: 1- Identifying potential and actual drug-related problems, 2- resolving actual drug-related problems, and 3- preventing potential drug-related problems"* [83].

This definition implies the direct responsibility by the pharmacist to the patient for effectiveness and quality of care, via pharmaceutical care as the component of pharmacy practice leading to the direct benefit of the patient

In 1994, *Barber et al* [84] in the United Kingdom already described the changes that the pharmacy profession was undergoing. They referred to a major shift in practice already from the 60's when numerous amount of drug errors in hospitals were found and the Government's report, *Gillie Report*, as a consequence where it was stated that services that had pharmacists visiting wards were shown to be effective and were subsequently recommended for implementation in all hospitals [85].

These recommendations led to pharmacists being clinically involved and having more direct patient contact. The next advancement occurred in the 1970's when many medicines information centers were introduced in hospitals and the pharmacists knowledge contribution to the direct benefit of the patient and became known as clinical pharmacy. Towards the end of the 80's a Health circular was released[86] on the future for hospital pharmacy services setting out the roles of pharmacy in the hospitals and specified some specialist services such as drug history taking, pain control management, therapeutic drug monitoring, side effect reporting and contributions to the economic aspects of drug use. Directorate managers started to see the

benefits of having a pharmacist allocated to their service and paid for this service.

Over these years the pharmacist has made substantial contributions to the overall quality of healthcare by ensuring that the use of medicines is safe, effective and economic, and by providing the necessary information to prescribers to make prescribing decisions and to patients so they can optimize treatment benefit.

Since these changes for the pharmacy profession took place the areas where clinical pharmacy developed are as many as medical specialties and its future is intimately linked with the future of medicines. The more drug complexity the more need of a pharmacist input.

The majority of the publications available in the literature report clinical pharmacy services in areas of high complexity such as oncology, intensive care, anticoagulant services but mostly describing the daily contributions of the pharmacist like ward rounds attending, interventions, prevention of medication errors.

Small evidence was found for the specific role of a pharmacist in Paediatric Intensive Care. A combined literature search on EMBASE and MEDLINE was conducted using the terms: Pharmacist AND Intensive Care AND/OR Paediatrics showing 181 articles in the English language where these terms were reflected as main terms, however only 26 articles had a link to the topic under discussion and 9 were discussing pharmacy services to either Neonatal or Paediatric Intensive Care (3 of them conference abstracts).

Only two articles talked specifically on the overall impact of a pharmacist in the paediatric intensive care unit, *Krupicka et al*[87] focused on studying the type and quantity of patient care interventions by the clinical pharmacist and examine the cost of these interventions concluding that the regular input of the paediatric pharmacist during hourly daily visits and twice a week attendance to multidisciplinary rounds resulted in 35 recommendations per

100 patient days generating direct cost savings per year of $9,135. In the second article, *LaRochelle et al*[88] describes also the clinical pharmacy interventions made in a tertiary care pediatric intensive care unit over a period of 7 months, the average of interventions were 13 interventions per day and 5.3 per patient. Analgo-sedation and antimicrobials were the most common drug classes in which interventions were made (34.4% and 20.6% respectively) and 98% of the interventions were accepted by the medical team.

A third study[89] looked at the impact of a clinical pharmacist in several paediatric specialties with regards to a reduction on the rate of serious medication errors. The authors of this study reported that the incidence of errors in a PICU was of 29 per 1000 patient days as opposed to 8 in the general medical unit or 7 in the general surgical unit per 1000 patient days. The introduction of the pharmacist dropped the ICU rate to 6 per 1000 patient days whereas in the other areas this rate was not reduced and the difference was that for ICU the pharmacist was full time based in the unit and for the other wards the pharmacist was part-time and the impact was not as effective. *Cies J et al* reported two conference abstracts looking at the impact of the pharmacist on antimicrobial prescribing with regards to improvement of achievement of therapeutic target levels by pharmacokinetic modelling and protocols compliance. One discussed the management of vancomycin serum level monitoring[90] and the second one aminoglycosides[91].

Isaac R et al at another conference discussed the types of parenteral nutrition in PICU patients, individually tailored versus standard concluding that due to the fluid restriction that these patients are normally subjected to, a standard parenteral nutrition bag will provide more calories than a tailored one leading to financial and productivity savings for PICU[92].

Two articles reported the role of a pharmacist in the neonatal intensive care unit with regards to Parenteral nutrition prescribing support[93] and interventions made[94]. The latter reports 5.4 interventions per 100 patient days and 9.1 interventions per 100 prescriptions reviewed. Over 69% of these interventions

were considered significant and 11.1 % very significant and clinicians accepted 91.8% of the suggestions made by the pharmacist. These findings supported the permanent position of a clinical pharmacist to the neonatal unit. Similar studies have been conducted in broader paediatric areas[95].

The value of the pharmacist to this medical specialty has been better documented in adult critical care although some reports are conference supplements too and the majority of them are based in North America as this is where the specialty emerged and has further developed. Several studies have demonstrated that critical care pharmacists reduce medication errors [96,97], reduce drug interactions[98], improve patient outcomes by decreasing among others the number of days of sedation[99] and therefore having an impact on duration of mechanical ventilation[100], improve treatment protocol compliance for example with regards sepsis antimicrobial therapy[101], stress ulcer prophylaxis[102] and sedation[103], reduce waste, optimise use of drugs and even decrease mortality rates among patients with thromboembolic diseases or infections[104]. Many studies have focused on the number and financial impact of interventions to justify the service to the unit [105,106].

The majority of the reports above describe the pharmacists' input reviewing patients, providing drug information and following pre-established guidelines and protocols, including performing pharmacokinetic reviews based on pre-existing information on antibiotics for example. Most of the work assessing the impact of the pharmacists in the area of paediatric intensive care has been in a quantitative way evaluating the number of interventions and performing a cost analysis of short-term interventions.

Conducting research by the pharmacist working in Paediatric Intensive Care can be very challenging if research time is not allotted and then protected by the department. Planning research studies, obtaining funding and approvals from Ethics Committees and Research and Development departments is becoming even more complex and requires dedicated time outside the normal workload of usually extremely busy and intense units. However, the pharmacist is in a very good position to advance the knowledge of this

specialty as once he/she becomes familiar with the clinical aspects of the intensive care specialty we have a very broad understanding of the pharmacology and pharmaceutics of the medicines and we can easily identify problems with drug use and help finding a solution. The important aspect is to document these interventions as they will enlighten other colleagues and build the scientific information. Basically the role of the PICU pharmacist is very privileged for translational medicine, identification of research gaps, answering these questions via conducting planned research and translating the results into clinical practice again.

Interestingly, *Paciullo et al* [107] explored in 2011 the research contributions from pharmacists to the scientific literature as the figure and number of adult ICU pharmacists had increased over 10 years. From 3265 manuscripts in intensive care journals (1999-2009) pharmacists were first authors in 42 of them and all of them were written on disease states, patient safety, pharmacoeconomics or pharmacotherapy. The manuscripts were a result of a multidisciplinary collaboration but pharmacists were poorly represented and this has not increased over time, the authors concluded that pharmacists had a high clinical demand and little time or support for clinical research.

Furthermore, in 2012 *Perreault et al* [108] conducted a survey among critical care pharmacists in Canada to explore the pharmacists' involvement in research. From the results 58% of pharmacists were not involved at all in the research activities of their Intensive Care Units and 15.7% highly involved (33/215), these pharmacists were trained in research, had higher academic degrees and received support from the ICU and pharmacy teams. However, the overall desire to be involved in clinical research was 80.2% but 80.8% felt they had insufficient protected time to conduct research. There is no specific information on involvement or input on publications by the Paediatric Intensive Care Pharmacist.

TRANSFERABILITY OF SKILLS

The results of the studies presented in this manuscript have had an impact on different aspects of patient care, directly or indirectly.

At local level, within our Institution, the studies exploring the efficacy and safety of clonidine for sedation in our paediatric population influenced the change of the Pain and Sedation guidelines in PICU (Appendix 6.2)[109]. At the time of initiating the studies children were exposed to regular and high doses of benzodiazepines for sedation, however, for the past 12 years children only received morphine and clonidine as primary agents, this led to a decreased requirement of opioids and facilitated in the long run the planning for extubation and shortening the length of stay in the PICU.

The studies looking at administration practices have also led to a total change on administration of IV continuous infusions across the entire children's hospital. Other areas are now using morphine as standard concentration such as our Neonatal Unit or theatres. Milrinone standard concentration was implemented in 2010 and also used across several areas like cardiac theatres and the cardiology ward. Finally, we have now rolled out dinoprostone (Prostaglandin E1) infusions in NICU, PICU and cardiology.

An extensive piece of work has been undertaken calculating the appropriate clinical concentrations for all the other drugs that are administered as IV continuous infusions in different clinical areas as part of this thesis (chapter 3.3) and we are working through the practicalities of getting the products made in pharmacy and rolling this out. In 2016-2017 the majority of IV continuous infusions in PICU and NICU will be administered as standard concentrations.

At national level, many PICU's in the country are now using clonidine as a sedative in intensive care. The results from our studies were used to inform the U.K. SLEEP trial[110]

In addition, the PhD student is leading through the Neonatal and Paediatric Pharmacist Group (NPPG)[111] on a national working group to facilitate the implementation of standard concentrations of infusions across the country.

At international level, the knowledge acquired and the research conducted as a clinical pharmacist are very valuable for regulators such as the European Medicines Agency (EMA) in their evaluation of clinical trials for the paediatric population. Pharmaceutical industries apply to get licenses on medicines for paediatric use supplying quality data of the products but sometimes they lack the knowledge on how drugs are used in clinical settings and the specific needs of intensive care children and neonates as opposed to other children. The PhD applicant was appointed to work for the EMA as a National Expert on Secondment in view of the unique clinical pharmacy expertise gained in the field of Paediatric Intensive Care to support the work of the Paediatric Committee[112] and to help the wider paediatric global community on the conduct of paediatric clinical trials [113].

The pharmacist was able to contribute to the clinical assessment of products to be used in the PICU in areas such as sedation, analgesia, sepsis and cardiology. In addition to this, the pharmacist made contributions on the formulation of the products, applicability for paediatric use and safety of administration. This input is still provided to the Paediatric Committee via the Formulation Working Group (FWG) on a monthly basis.

More recently the work included in this thesis regarding administration of IV infusions is serving as the basis for an international COST Action proposal [114] at the European Commission, the application involves 31 partners globally to harmonise the definitions and practice on standard concentrations for neonates and children in paediatric intensive care.

Dissemination of knowledge and skills

The PhD applicant has been involved in the organisation of Education and Training programmes in the U.K. and internationally to share the clinical pharmacy expertise with other colleagues around the world that may not have

had the chance of exposing themselves to this specialty in their own country. The courses empowered students to gain the foundation knowledge and skills to provide a clinical service to the Paediatrics and PICU /NICU specialties. In addition, in the U.K. work is in progress for the development of the subspecialisation of pharmacists including Paediatric Intensive Care, perhaps following steps already taken by colleagues in North America in the specialty of adult intensive care[115,116]. Some of the materials produced by the PhD student were part of the development of a training programme for the Paediatric Intensive Care Pharmacists specialty.

Lately the PhD applicant works part time as a Consultant for the European Commission Project GRIP-Global Research in Paediatrics[117]. The role of the clinical pharmacist in the wider clinical Paediatric Pharmacology agenda has been recognised at a European Level and there is a Work Package (5) fully dedicated to Paediatric Formulations. This Working Group produced a Masters Module (compulsory) on the Global Masters programme. The role of the PhD student on this project is to co-lead on the design of the Masters Degree and research projects on the topic of paediatric formulations, especially around neonatal and paediatric intensive care using the knowledge acquired during her PhD studies.

CONCLUSIONS

Sedation is one of the main therapeutic fields for the management of children in paediatric critical care. Undersedation and oversedation may both lead to negative effects possibly resulting in prolonged hospitalisation; therefore sedatives administered to critically ill children should be titrated to effect.

Clonidine is frequently used as a sedative in this setting, however, as many other drugs used in the neonatal and paediatric critical care areas, it is used in an unlicensed manner lacking safety and efficacy data. This thesis identified important pharmacological aspects of this drug in this paediatric population that have been informative to the design of further clinical trial studies internationally.

In order to plan and conduct pharmacology studies and to administer drugs to children in an effective manner it is paramount to know exactly the exact dose that the patient receives. At present this is subject to many variables in clinical practice. This thesis addressed, partially, this problem for two sedative drugs, clonidine and morphine, proposing measures to improve the situation in clinical practice.

Administration of medicines as continuous IV infusion is not harmonised in between countries or even within individual institutions. In order to provide the most appropriate pharmaceutical products, an international consensus is needed between institutions and regulatory bodies, this will enable the drug and devices manufacturers to produce accurate medicinal products that can be accurately delivered to children and that will lead to consistent effects.

The articles in this thesis could act as a foundation to inform Authorities and individual hospitals or paediatric organisations to aid the safe implementation of the use of standard concentrations and to manufacturers of drugs and devices to produce age appropriate formulations and accurate devices.

Similar findings arose from studying accuracy with enteral administration of drugs. Commonly found syringes in healthcare settings are not designed to accurately administer very small doses, and these are common doses used in neonatal and paediatric critical care. Addressing this problem requires joint institutional efforts.

Finally, the work presented in this thesis demonstrates a more in depth dimension of a pharmacist's pharmaceutical care contribution to the advancement of a highly complex specialty such as Paediatric Intensive Care. The role of the PICU pharmacist is very privileged for translational medicine, identification of therapeutic research gaps and pharmaceutical aspects of medicines use, answering these questions via conducting planned research and translating the results into clinical practice again.

CHAPTER 6: APPENDICES

APPENDIX 6.1: References used for manuscript

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APPENDIX 6.2: Pain and Sedation Guidelines in PICU

Guy's and St Thomas' NHS
NHS Foundation Trust

Clinical Guideline

PICU Pain and Sedation

Document Detail	
Document Type	Guidelines
Document name	PICU Pain and Sedation
Document location	GTi Clinical Guidance Database
Version	2.0
Effective from	*02 September 2015*
Review date	*02 September 2018*
Owner	Children's Services
Author	Andrew Durward, Consultant in Paediatric Intensive Care Joanne Perkins, Paediatric Consultant
Approved by, date	Drug & Therapeutics Committee, *September 2015*
Superseded documents	1.0
Related documents	**References : 1.** Lynn AM. Anesth Analg. 1993.:695-701, **2.** Parke TJ BMJ 1992;305(6854):613-6. **3.** Fonsmark. Critical Care Medicine 1999 27(1):196-199
Keywords	Sedation, analagesia, morphine, clonidine, withdrawal
Relevant external law, regulation, standards	

Change History		
Date	Change details, since approval	Approved by
DTC Ref	15095n	Drugs & Therapeutics Committee Sep 2015 Review Sep 2018

PICU PAIN AND SEDATION GUIDELINES

Drugs should be titrated using the algorithm below to optimise comfort and sedation

1st Line:

- **Morphine** intravenous infusion: **10 to 40** micrograms/kg/hour. Rates of up to 60 microcgram/kg/hour are RARELY needed. Neonates usually ≤ 20 microgram/kg/hour[1]
- **Clonidine** enterally (well absorbed gastrically): **3 to 5** micrograms/kg **8 hourly** (maximum initial dose **50 microgram**) for morphine sparing. Recommended dose if weight >25kg is **3** micrograms/kg up to max 300microgram/day. Above this dose only if directed by consultant.
- **Paracetamol** regularly (4 to 6 hourly) via enteral route. **15 mg/kg.** IV paracetamol only if directed by consultant.
- **Lorazepam (adjunct if needed)** intravenous bolus: **0.1 microgram/kg**, whilst morphine/clonidine optimised. Lorazepam may cause hypotension. Use diazepam if lorazepam not available

2nd line:

- **Clonidine** intravenous infusion**: 0.5 to 2** microgram/kg/hour to replace oral clonidine Increment by 0.5 microgram/kg/hour. Do not bolus.
- Recommended dose if >25kg is 1 microgram/kg/hour. May be used concurrently with inotropes

3rd Line:

- **Discuss with PICU consultant to initiate**
- **Propofol** infusion: **1 to 4 mg/kg/hour** short term use only. High lipid content.
- Avoid in sepsis or croup (propofol syndrome risk). DO NOT bolus for sedation

Morphine bolus
FIRST bolus (50-100 microgram/kg), then optimise baseline rate. SUBSEQUENT boluses 20 – 40 microgram/kg
Avoid repeated boluses

CLONIDINE
Plasma half life 8-16 hrs. Prolonged in renal failure. Does nor depress respiratory drive.
Sinus bradycardia common during sleep (no need to discontinue). High dose can cause hypertension

Propofol Syndrome
Irreversible lactic acidosis. Risk if prolonged (>48 hour) infusion or high dose infusion (>4mg/kg/hour).

Gabapentin
Discuss with Consultant

- Used in neuropathic and chronic pain
- Day 1: 5mg/kg (max 300mg) OD. Day 2: 5mg/kg BD. Day 3: 5mg/kg TDS
- Increase to 10mg/kg TDS. The max dose is 3.6g/day.

In rare circumstances (Autism, ADHD) Consultant decision only
Levomepromazine (Methotrimeprazine) enterally 0.5 mg/kg 8 hrly. Double dose every 8 hrs until target sedation achieved. Potent sedative. Side effects include dry mouth, urinary retention, inhibition sweating and hypotension (alpha 1 blockade).
Risk of neuroleptic malignant syndrome (idiosyncratic) & agranulocytosis.

Other issues

- Avoid non-steroidal anti-inflammatory agents (NSAIDs) in PICU patients: risk of renal impairment if associated hypotension except in specific indications eg spinal surgery
- Avoid codeine, chloral hydrate, buccal midazolam and other sedative anti-histamines
- Avoid fentanyl and midazolam infusions as associated with highest incidence of drug withdrawal[3]
- Immediate release oral morphine (Oramorph) should only be used as part of morphine weaning plan; not as an analgesic

Weaning sedation. Wean morphine 1st then Clonidine

Weaning IV Morphine (5 day wean plan)
< 2 weeks: No weaning needed
> 2 week infusion:

- Consider **oral morphine** when IV rate 10 microgram/kg/hour : Use **250microgram/kg** PO **6 hourly***
- **Wean over 5 days** by 50microgram/kg per day i.e. Day1 250 microgram/kg PO 6

Weaning IV Clonidine (5 day wean plan)
< 2 weeks: No weaning needed
> 2 week infusion or oral clonidine:

- **Wean over 5 days** by 1microgram/kg per day i.e.: 5 microgram/kg PO 8 hourly, 4 microgram/kg 8 hourly, 3 microgram/kg 8 hourly, 2 microgram/kg 8 hourly, 1 microgram/kg 8 hourly then stop.

*** Morphine wean:**
Dose of 250microgram/kg oral morphine is **fixed** regardless of current IV infusion rate
Please adhere to 6 hourly dosage (not 4 hourly) as this is a weaning plan to prevent withdrawal (not pain control)

Post operative pain relief for PICU patients discharged to wards

- If IV infusion of morphine necessary (e.g. surgery within last 24 hrs), transfer to wards on PCA (patient controlled anaesthesia) or NCA (nurse controlled anaesthesia) according to Pain Team prescription
  Contact Pain Team Sister Bleep 1684 or on-call anaesthetist outside of normal working hours
- Do not use pre-filled morphine syringes for PCA/NCA. These must be setup by Pain Team / Anaesthesia
- Ensure regular oral paracetamol is prescribed and where relevant oral clonidine (as analgesic agent)
- Codeine phoshate and NSAIDs should NOT be prescribed by PICU for ward patients with exception of specific patients (orthopaedic spinal surgery patients). These should be prescribed by Ward team if needed

APPENDIX 6.3: Tables and Figures

Chapter 1: Introduction

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2) Timelines of studies (Table), Page 28

Chapter 2: Oral Clonidine studies

Chapter 2.1

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Chapter 2.2

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APPENDIX 6.4: Abbreviations

ADHD: Attention Deficit Hyperactivity Disorder

ANOVA: Analysis of Variance

BP: British Pharmacopeia

CD: Controlled Drug

CIVAS: Centralised Intravenous Admixture Service

CNS: Central Nervous System

COMFORT: Behavioural scale

COST: European Cooperation in Science and Technology

DERS: Dose Error Reduction System

ELCH: Evelina London Children's Hospital

EMA: European Medicines Agency

FWG: Formulation Working Group at EMA

GABA: Gamma Aminobutyric Acid

GRIP: Global Research in Paediatrics project approved under European Union Seventh Framework Programme (FP7/2007-2013) grant agreement n° 261060

ICU: Intensive Care Unit

IV: Intravenous

MHRA: Medicines and Healthcare Regulatory Agency

NICU: Neonatal Intensive Care Unit

PD: Pharmacodynamics

PDCO: Paediatric Committee

PICS: Paediatric Intensive Care Society

PICU: Paediatric Intensive Care Unit

PIM score: Paediatric Index of Mortality

PK: Pharmacokinetics

PKA: Proteinkinase A

RCT: Randomised Control Trial

UCIN: Unidad de Cuidados Intensivos Neonatal

UCIP: Unidad de Cuidados Intensivos Pediátricos

USA: United States of America

UK: United Kingdom

WHO: World Health Organisation

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APPENDIX 6.6:

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APPENDIX 6.7: Publications from this author

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