Safe implementation of standard concentration 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 50 ml 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 (e.g. 0.1 ml/h of a morphine infusion usually equates to 5 mcg/kg per 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: (1) bespoke drug-to-diluent dose calculations based on patient weight (often aided by calculation tools),[4–6] (2) several manipulations during preparation and (3) 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 standardised 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 (e.g. sodium chloride 0.9% to a patient at high risk of hypoglycaemia). Following a risk appraisal in 2007, our paediatric 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 were thus twofold:

- To describe our process for introducing standard concentration IV infusions and
- 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 occurs 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 (e.g. 25% of our patients are neonates), age-appropriate diluents and the common clinical requirement for fluid restriction (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.

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

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
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<th>G</th>
<th>H</th>
<th>I</th>
<th>J</th>
<th>K</th>
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</thead>
<tbody>
<tr>
<td>4</td>
<td>MORPHINE STANDARD CONCENTRATIONS</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>36</td>
<td>37</td>
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</tbody>
</table>

Figure 2 Clinical design using a matrix weight/dose and concentration.

Guardrails for each patient per shift, and data were downloaded from was conducted via electronic forms filled by bedside nurses wastage, datasets and soft and hard alert limits by pumps. (Supplemental Digital Content: appendix S3).

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 were 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 hypoglycaemia (10% vs 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 programme >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 and 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 (2.5 mg in 50 ml), 7–19.9 kg (10 mg in 50 ml), 20–34.9 kg (30 mg in 50 ml) and >35 kg (50 mg in 50 ml). These were reduced to three after elimination of 30 mg in 50 ml, 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 >4 kg could now receive a higher dose of morphine infusion with less volume. The final weight bands are shown in Figure 3.

### 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.

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

<table>
<thead>
<tr>
<th>Error type</th>
<th>Mode of administration</th>
<th>NCA / PCA</th>
<th>Standard</th>
<th>Variable</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No signature</td>
<td></td>
<td>2 (25%)</td>
<td>2 (11.1%)</td>
<td>6 (8.3%)</td>
<td></td>
</tr>
<tr>
<td>Programming</td>
<td></td>
<td>2 (25%)</td>
<td>7 (15.2%)</td>
<td>4 (22.2%)</td>
<td>13 (18.1%)</td>
</tr>
<tr>
<td>Wrong syringe</td>
<td></td>
<td>1 (12.5%)</td>
<td>16 (34.8%)</td>
<td>0 (0%)</td>
<td>17 (23.6%)</td>
</tr>
<tr>
<td>Compatibility</td>
<td></td>
<td>0 (0%)</td>
<td>3 (6.5%)</td>
<td>1 (5.6%)</td>
<td>4 (5.6%)</td>
</tr>
<tr>
<td>Wrong mode</td>
<td></td>
<td>2 (25%)</td>
<td>9 (19.6%)</td>
<td>9 (50%)</td>
<td>20 (27.8%)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>1 (12.5%)</td>
<td>9 (19.6%)</td>
<td>2 (11.1%)</td>
<td>12 (16.7%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>8</td>
<td>46</td>
<td>18</td>
<td>72</td>
</tr>
</tbody>
</table>

PCA, patient-controlled analgesia; NCA, nurse-controlled analgesia.
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 (2007–2009). 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).

**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.\textsuperscript{[3–6]} Second, there was a need to identify a limited number of concentrations whilst 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 programme 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.\textsuperscript{[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\textsuperscript{[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 vs 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.\textsuperscript{[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,\textsuperscript{[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.,\textsuperscript{[20]} developed a paediatric mathematical algorithm in 2010, which derived two to four clinical standard concentrations for 39 continuous infusion medications, aided by a computerised 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 preset 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.\textsuperscript{[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 2013–2014. 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 latter 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 programme to patient/nurse-controlled analgesia, and rolling this out beyond PICU. 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 programme error (incorrect weight, 18\%). The effectiveness of bar coding is increasingly recognised. Poon\textsuperscript{[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,\textsuperscript{[24]} and the Joint Commission has highlighted the importance of introducing this technology with intravenous drugs.\textsuperscript{[25]} To our knowledge, this is still
under development in the United Kingdom 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 as preparation of individualised infusion manipulating small volumes is 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 optimising 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.

**Declarations**

**Acknowledgements**

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**Conflict of interest**

None.

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Supporting Information

Additional Supporting Information
may be found in the online version of
this article:
Appendix S1 Product development
and manufacturing.
Appendix S2 Ward protocol.
Appendix S3 Risk assessment.