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Practicality of dose prescriptions in a paediatric intensive care unit

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Background: **Appropriate paediatric formulations for many medicines are not available, resulting in the use of adult formulations within the paediatric setting. This increases the likelihood of medication errors during administration because of fixed officinal concentrations. We wished to document administration practicality for nursing staff of prescriptions in a paediatric intensive care unit (PICU).**

Methods: **We evaluated the suitability of the drug doses prescribed by medical staff for four commonly used drugs within a 16 bed PICU. A retrospective review was conducted of medication charts for 139 children discharged from the PICU over a three month period. The prescribed doses for paracetamol, pancuronium, diazepam and frusemide were recorded. These doses were assessed for suitability for administration by nursing staff. Suitability depended on formulation, officinal strength, dose measuring device and route of administration as well as predicted therapeutic effect.**

Results: **Dose was commonly prescribed as an exact measure based on an mg/kg calculation. The prescription of the dose could be improved to simplify volume calculation for administration by nursing staff in 17 of 63 diazepam doses, 24 of 42 pancuronium doses, four of 17 frusemide doses and 77 of 100 paracetamol doses.**

Conclusions: **The use of practical doses that are easily measured and administered by nursing staff, rather than exact dose based on an mg/kg calculation is suggested. The prescription of both dose weight and volume could improve awareness of the impractical nature of these prescriptions in the PICU. Greater dose flexibility can be afforded when calculating drug dosage than is currently presumed by medical staff.**

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Introduction

The challenges of paediatric prescribing have long been recognised. Size factors and physiological immaturity means adult data cannot be extrapolated to predict outcomes in children and infants[1,2]. There is anticipation that the current paucity of study of medicines in children that has resulted in physicians being forced to use many drugs off label[3] will be countered by European and North American legislation[4].

Unlike adult medicines, where a standard dose independent of size may be used[5], drug doses are calculated individually in children; the calculation often dependent upon age and weight or body surface area[6]. A common cause of medication errors in children is the calculation of the dose[6,7]. A substantial proportion of medical practitioners training in paediatrics make mistakes while calculating drug doses under optimal test conditions[8,9] and it is suggested that testing of calculations skills should be mandatory to prevent paediatric patients receiving wrong drug dosages[8,9].

Prescribed doses may be small in the very young. Despite accurate dose prescription, administration of this exact dose may be difficult. The need to split capsules or prepare dilutions increases the risk of administration errors[10]. Dose accuracy may be compromised, particularly in neonates[11]. Administration can be improved using small volume syringes (e.g. 1 ml, 3 ml and 5 ml) rather than larger syringes[11]. The difficulties of delivering small doses are further compounded by the lack of availability of suitable paediatric formulations[12,13]. This current study investigates the suitability of prescription of four drugs commonly used in a paediatric intensive care unit (PICU) for administration by nursing staff.

Methods

Observational data from children who were discharged from PICU from 1 September 2006 to 10 November 2006 were collected. The PICU is in a university affiliated children's hospital and provides intensive care services to a national paediatric population of 850,000 children less than 15 years old. The hospital has 350 beds and the PICU has 16 beds. Neonates were only included if admitted to the PICU from the community.

Four frequently used drugs were investigated. They were administered as an intermittent bolus either intravenously (diazepam, frusemide, pancuronium) or enterally (paracetamol). Drug dose was calculated using weight as a base for size. An Australasian formulary[14] specifically for children admitted to intensive care, was used as a reference guide by all staff. Formulary doses were diazepam 100–400 microg/kg, pancuronium 100–150 microg/kg, frusemide 0.5–1 mg/kg and paracetamol 15 mg/kg.

Drugs were prescribed on a dedicated medication chart by medical practitioners undergoing specialist training in paediatrics (registrars) working in the PICU who were within their 5th–7th year of postgraduate training. Medical staff were aware that an audit was being conducted, but were unaware of the nature or purpose of this audit. A paper medication order system was used in the PICU. Drug administration charts were reviewed daily during the study period. These paper records were saved electronically after hospital discharge.

A retrospective review of the patient's medication charts was undertaken using the hospital's computerised medical records system for those patients who were admitted and discharged outside of week day hours. Drug dose and patient weight were recorded. The prescribed dose (mg) was converted into the dose volume (ml) to be administered by the nursing staff.

A practical administration volume was defined as one that is easily measured and administered. The intravenous medications are supplied as 2 ml ampoules (diazepam 10 mg/2 ml, pancuronium 4 mg/2 ml, frusemide 20 mg/2 ml). An officinal volume that was prescribed with accuracy above one decimal point was considered impractical. That degree of accuracy cannot be easily accommodated with available syringe sizes[11]. Doses greater than diazepam 10 mg, pancuronium 8 mg and frusemide 20 mg were flagged. A dose less than half that recommended in the formulary was also flagged. Paracetamol elixir was available as 120 mg/5 ml. Multiples of 2.5 ml (60 mg) were considered as the smallest practical quantity. All paracetamol was administered as elixir through nasogastric or nasojejunal feeding tubes.

Results

Data were available from 109 patients. There were 27 children who had been discharged from the hospital whose notes were unavailable on the computerised medical records. A further three patients were excluded because no weight was recorded on the medication chart.

Examples of the results for the prescribed doses for diazepam, pancuronium, frusemide and paracetamol are shown in Table 1. Suggested improvements are also shown and when these differ from prescribed doses, they are marked

Table 1 Examples of data collected for each drug investigated

Drug	Patient weight (kg)	Prescribed dose (mg)	Prescribed dose (mg/kg)	Prescribed volume (ml)	Recommended dose (mg)	Recommended dose volume (ml)
Diazepam	4.2	0.8	0.19	0.16	1*	0.2
(10 mg/2 ml)	5.3	1.0	0.19	0.2	1	0.2
Pancuronium	4.9	0.5	0.1	0.25	0.6*	0.3
(4 mg/2 ml)	18	2.0	0.11	1.0	2	1.0
Frusemide	18	15	0.83	1.5	15	1.5
(20 mg/2 ml)	7.5	7.5	1.0	0.75	7*	0.7
Paracetamol	14	200	14.3	8.33	180*	7.5
(120 mg/5 ml)	3.9	40	10.3	1.67	60*	2.5
	8.6	120	14	5.0	120	5.0

*Improvements to facilitate accurate drug administration.

with an asterisk. The mean diazepam dose was 0.19 mg/kg (range 0.04–0.28 mg/kg); 17 of 63 (27%) prescriptions could be improved. There were two additional prescriptions flagged. One dose of diazepam 2.5 mg was administered appropriately to a 62 kg child with cardiovascular instability. Another 14 mg dose was given to an agitated 67 kg child. The mean pancuronium dose was 0.1 mg/kg (range 0.07–0.16 mg/kg); 24 of 42 (57%) prescriptions could be improved. The mean frusemide dose was 0.89 mg/kg (range 0.43–1.14 mg/kg) and only one dose greater than 20 mg was flagged; 8 of 26 (31%) prescriptions could be improved. The mean paracetamol dose was 15.22 mg/kg (range 9.82–30.30 mg/kg); 77 of 100 (77%) prescriptions could be improved.

Discussion

Junior doctors displayed a lack of awareness of actual prescribed volume. Prescribing volume as well as drug weight assists in the recognition of medication dosing errors. Current prescribing practice in our PICU is paper based and drug dose calculations determined using a local formulary[14]. The use of a pre-programmed computerised physician order entry system that showed resulting volume would be of assistance. Inappropriate dosing was unusual in this small sample study, however accuracy and appropriateness of dosing could be improved by the use of electronic prescribing systems in paediatrics. These systems eliminate illegible prescriptions, incorporate dose calculators and dose range checking can alert prescribers when doses are outside predetermined ranges[15].

This simple study is a retrospective "snap shot" of limited duration and numbers. Junior medical staff rotate through the PICU every 4–6 months. Findings may differ depending on PICU exposure and experience of junior medical staff. However, our data suggests improvements can be made, in particular for the paracetamol elixir. Small intravenous drug volumes can often be accommodated using a 1 ml syringe. Prescribed doses of the IV preparations can be converted into reasonable dose volumes for subsequent administration. Prescribing to a volume of two decimal point accuracy is inappropriate. The elixir preparation (paracetamol) that is prescribed as a larger volume than the IV formulations (diazepam, pancuronium, fusemide), had a wider range of inappropriate dose volumes that would need to be rounded up or down by nursing staff before administration. Dose calculation was commonly made using an mg/kg formula with little consideration for practicality of prescribed dose administration. Despite the potential for prescription dose improvement, there were no dose errors observed.

Weight, used to calculate dose, may not be accurate, further diminishing the requirement for precise dose prescription. Accurate weight measurement on admission may be difficult in the critically ill child. Weight may be an approximation, based on the average for the child's age. Measured weight, for example in an oedematous child, may be inappropriate.

The mean prescribed diazepam dose of 0.19 mg/kg suggests that prescribing physicians used an intentional dose of 0.2 mg/kg. This dose appeared to be prescribed with little regard to intended duration of effect, concurrent pathology, clearance changes with age, ontogeny of CYP3A or side effect profile. A single bolus of diazepam 14 mg dose for an agitated 67 kg child may be an accurate dose, but it may also cause cardiovascular compromise in a critically ill child. Gamma-aminobutyric acid (GABA) is the neurotransmitter at most inhibitory synapses in the human central nervous system and the $GABA_A$ receptor complex is the site of action for benzodiazepines. $GABA_A$ receptors undergo major changes in receptor binding and subunit expression occurs during postnatal development[16-18]. These changes possibly contribute to different benzodiazepine doses required at different ages for sedation[17]. Adherence to a strict 0.2 mg/kg is unreasonable

if the dose to be administered is impractical. Dose would be better titrated to a measure of effect, e.g. a COMFORT score[19].

Approximately half (57%) of pancuronium prescriptions could be improved to facilitate accurate drug administration. Neuromuscular blocking drug (NMBD) use in the operating room is dictated by duration of effect. The anaesthetist must choose the NMBD drug, dose and subsequent doses depending on when the return of spontaneous breathing is required. However, the situation in PICU is not so precise. NMBDs may be given to establish artificial positive pressure ventilation, decrease work of breathing or for surgical interventions. The requirement and timing of the return of spontaneous ventilation is not imperative. Larger doses can be administered than in the operating room. It is possible to ignore inter-individual variability of NMBDs by giving a large dose, but inter-individual variability remains and can be observed in the duration of neuromuscular blockade. Larger doses have a more rapid onset of action, but have longer duration of effect. Concomitant disease processes (e.g. renal failure) will also affect duration of effect for pancuronium. As the dose of pancuronium prescribed was commonly 0.1 mg/kg, there seemed to be little allowance for other disease processes influencing clearance or expected duration of effect. Dose volumes of 0.25 ml, that are difficult to accurately measure with a 1 ml syringe, could be rounded up with no alteration in clinical measures. Indeed, nursing staff sometimes complained that the NMBD wears off too quickly and that the frequency of dosing is onerous.

Frusemide formulation strength (20 mg/2 ml) and dose of 1 mg/kg render dose accuracy relatively easy for intravenous administration. Nevertheless, eight (31%) prescriptions were difficult to administer. Frusemide administered after cardiac surgery is often accompanied by a potassium sparing diuretic (spironolactone, amiloride) and dose accuracy down to two decimal points is unnecessary because of the additive effect from the second diuretic. Furthermore, this accuracy of dosing is impractical when the route of administration is changed from intravenous to nasogastric. In general terms, factors such as delayed gastric emptying, absorption to plastic or first pass effects will all affect the drug amount that reaches the systemic circulation.

There are other factors to consider when administering oral preparations. Due to the viscous nature of paracetamol formulations, volume may be lost through coating of the syringes and the nasogastric tubes through which they are usually administered. Between individual pharmacokinetic parameter variability is large for paracetamol (CL 44%, V 20%)[20] making it difficult to predict concentration in any one individual after a prescribed dose. In addition, the variability on absorption half-time has been reported as high as 120%[20]. Gastric emptying is frequently reduced in critically ill children and is also reduced in neonates. This variability in bioavailability, clearance, volume of distribution and absorption renders the prediction of concentration and consequent effect difficult.

An understanding of paracetamol analgesic effect contributes to this reduced necessity of dose accuracy compared with the intravenous formulations. Pharmacodynamic estimates for an Emax model, in which the greatest possible pain relief (VAS 0-10) equates to an Emax of 10, were Emax 5.17 (64%) and EC_{50} 9.98 (107%) mg/l. The equilibration half-time (Teq) of the analgesic effect compartment was 53 (217%) min[21]. These estimates confirm paracetamol as a mild analgesic and that there is a delay after peak serum concentration before maximal pain relief becomes apparent. An effect site concentration of 10 mg/l resulted in pain reduction of 2.6 pain units[21]. Higher concentrations are associated with a decrease in the incremental pain relief and the maximum pain reduction can only be 5.17 pain units[21]. Increasing dose will not maximise benefit but will increase propensity to side effects such as hepatotoxicity. Consequently, achieving dose precision for paracetamol is unnecessary. Doses can be prescribed dependent on formulation strength. For example, a formulation strength of 120 mg/5ml can be rounded to a dose such as 60 mg, 120 mg, 180 mg. Reduced clearance and slower absorption in the very young can be accommodated by increasing the dosing interval instead of administering a small impractical dose more frequently. The dosing interval was almost always 4–6 hours in our study group suggesting medical staff did not consider these factors when prescribing the drug.

Medication errors are common and ensuring practical doses are prescribed will help reduce the risk of drug administration errors. Improvements could be made to some of the prescribed doses, most notably those of paracetamol. Medical staff appeared to adhere rigidly to recommended dosing regimes rather than considering inter-patient variability in pharmacokinetics and pharmacodynamics. More flexibility can be afforded than is presumed by medical staff when calculating drug doses.

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