RESEARCH LETTER

Drug formulations that require less than 0.1 mL of stock solution to prepare doses for infants and children

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ABSTRACT

Intravenous doses of medications require formulations that permit accurate preparation and administration. Current equipment does not permit accurate measurement of volumes less than 0.1 mL. In a study of four hypothetical standard pediatric patients, we found that 28 common medications required less than 0.1 mL of available formulation to prepare the dose. In a clinical study of actual use in a pediatric intensive care unit (ICU), 5245 (7.4%) of 71 218 intravenous doses required preparation from less than 0.1 mL of stock solution. For 28.5% of the 1531 ICU admissions, at least one dose was prepared from a volume of less than 0.1 mL. Our findings identify a substantial source of dosing error. Correction will require revision of preparation methods, regulatory requirements and manufacturing practices.

Preparation of parenteral doses of medications from small volumes using commercially available syringes is imprecise and may result in serious dosing errors.[1–3] Previously, we showed that 60% of 116 doses prepared from 0.06 mL of stock solution had a dosing error of more than 10%, and 27% had a two-fold dosing error.[2] We hypothesized that small volumes of commercially available formulations are often required to prepare intravenous doses for infants and children.

Methods

We performed two studies: a theoretical study in which we evaluated the potential requirements for small volumes based on recommended use, and a clinical study in which we evaluated actual use. We included medications that had a commercially available parenteral or oral liquid formulation and were in our hospital's formulary.[4,5] We identified the least concentrated formulation in the product monograph in the 2006 edition of the *Canadian Compendium of Pharmaceuticals and Specialties*.[5] The primary outcome was the volume of the least concentrated commercially available formulation required to prepare the specified dose. Volumes of less than 0.1 mL were identified.

In the theoretical study of recommended use, we identified the listed clinical reason (indication) to prescribe each eligible drug in the hospital's formulary.[4] We then noted the lowest recommended dose for each of these indications for four hypothetical standard pediatric patients. The patients were a 3-kg term neonate (0.212 m^2), a 5-kg infant 6 months of age (0.303 m^2), a 10-kg infant 12 months of age (0.464 m^2) and a 20-kg child 3 years of age (0.464 m^2). All of the patients had normal renal and hepatic function.

In the clinical study of actual use, we identified single-injection intravenous medications ordered by physicians that had been administered to children in a university-affiliated pediatric intensive care unit (ICU) in 2006. The volume required to prepare the dose was calculated. If a dose could not be determined and the administered volume was documented, we included this volume in our analysis.

The study design was approved by the Research Ethics Board of the Hospital for Sick Children.

Results

In the theoretical study of the hypothetical patients, we evaluated 59 medications for the neonate and 121 medications for the other pediatric patients (Table 1). There were 982 indications listed in the formulary; for 79 (8.0%) of these indications, the recommended dose required less than 0.1 mL of stock solution. The number of medications with one or more indications that required less than 0.1 mL stock solution was 13 (22.0%) for the neonate, 20 (16.5%) for the 5-kg child, 12 (9.9%) for

the 10-kg child and 6 (5.0%) for the 20-kg child. These drugs included potent medications with direct effects on the circulation, brain and coagulation system (see Appendix 1, available at www.cmaj.ca/cgi/content/full/cmaj.100467/DC1).

In our evaluation of oral formulations, there were 845 indications in the formulary; for 9 (1.1%) of these indications, the recommended dose required preparation from less than 0.1 mL. There were seven medications with one or more indications that required preparation from less than 0.1 mL.

In the clinical study of actual use, there were 71 218 (81.8%) intravenous doses administered to 1531 patients admitted to the ICU in 2006. The median volume of stock solution was 1.0 (interquartile range [IQR] 0.3–3.48) mL. Of the doses, 5245 (7.4%) required preparation from less than 0.1 mL of stock solution; 12 439 (17.5%) required preparation from less than 0.2 mL.

For 437 (28.5%) of the ICU admissions, at least one dose was prepared from a volume of less than 0.1 mL. The median number of doses prepared from less than 0.1 mL per admission was 3 (IQR 1–11); in each of 19 admissions, more than 50 administered doses were prepared from less than 0.1 mL. The medications most commonly prepared from less than 0.1 mL were lorazepam, hydrocortisone, ranitidine, methylprednisolone, fentanyl and morphine (Table 2).

Interpretation

Our findings indicate a substantial source of dosing error that involved potent medications and affected more than a quarter of the children studied. Small volumes of stock solution are required because of the relatively low doses needed for infants and young children and the relatively high concentrations of commercially available stock solutions. The clinical sequelae of errors occurring as a result of preparing doses from small volumes will be compounded by incomplete safety data,[6–10] errors in medication orders,[11] and errors in preparation[2,12–14] or administration.[15,16]

Preparation-associated errors could be prevented if more accurate equipment were available to measure small volumes. They could also be avoided with predilution of commercially available solutions, either by means of a double-dilution technique for single doses or the creation of local "stock solutions" for multiple patients. However, additional manipulation of stock solutions may result in further dose-volume inaccuracies.

Our evaluation has four main limitations. First, we assumed that the least concentrated formulation was used. Twenty-five medications had two or more formulations. If the most concentrated formulation of these medications were used, 8715 (12.2%) doses would have been prepared from less than 0.1 mL. Second, we assumed that there was no intermediate dilution. This may have permitted larger volumes of commercially available solution to be used.

Table 1: Volumes of commercially available formulations required to prepare recommended doses of parenteral medications for four hypothetical standard pediatric patients*

Patient	Volume of stock solution required, mL		
	< 0.1	0.1 to < 1.0	≥ 1.0
	No. (%) of medications		
3-kg neonate	13 (22.0)	27 (46.8)	19 (32.2)
5-kg infant	20 (16.5)	56 (46.2)	45 (37.2)
10-kg infant	12 (9.9)	46 (38.0)	63 (52.1)
20-kg child	6 (5.0)	39 (32.2)	76 (62.8)
	No. (%) of indications		
3-kg neonate	24 (21.8)	50 (45.5)	36 (32.7)
5-kg infant	30 (10.3)	107 (36.9)	153 (52.8)
10-kg infant	17 (5.8)	77 (26.5)	197 (67.7)
20-kg child	8 (2.7)	65 (22.3)	218 (74.9)

*The upper portion of the table reports the volume of stock solution required to prepare the lowest recommended dose for 180 medications (59 medications for the neonate and 121 for the other pediatric patients) listed in the hospital formulary. The formulary included 982 indications of these medications. The volumes of stock solution required to prepare the dose corresponding to each indication are represented in the lower portion of the table.

Table 2: Medications requiring less than 0.1 mL of stock solution for preparation of intravenous doses administered to 1531 patients in a pediatric intensive care unit

Medication	Total no. of doses	No. (%) of doses requiring preparation from < 0.1 mL
Lorazepam	10 167	2 497 (24.6)
Hydrocortisone	2 415	951 (39.4)
Ranitidine	5 097	370 (7.3)
Methylprednisolone	1 431	259 (18.1)
Fentanyl	2 873	245 (8.5)
Morphine	1 201	141 (11.7)
Tacrolimus	135	99 (73.3)
Midazolam	316	98 (31.0)
Metoclopramide	503	94 (18.7)
Phenoxybenzamine	143	90 (62.9)
Vitamin K	339	76 (22.4)
Other*	46 598	325 (0.7)
Total	71 218	5 245 (7.4)

*Includes adenosine (20 [17.7%] of 113 doses were prepared from less than 0.1 mL), digoxin (16 [94.1%] of 17 doses), propranolol (9 [47.4%] of 19 doses) and meperidine (33 [100%] of 33 doses).

Third, we assumed that the electronically signed documentation correctly reported the administered dose, which may not have been the case.[14] Fourth, adverse events are challenging to study retrospectively and were not evaluated in our study.[17]

The potential clinical implications of errors associated with medications prepared from small volumes are substantial and in excess of the errors in medication orders previously described.[11,18] The medications most commonly prepared from small volumes in our study included potent narcotics, sedatives and immunosupressants. Re-evaluation of preparation methods, regulatory requirements and manufacturing practices is warranted.

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