Accuracy of enteral syringes with commonly prescribed paediatric oral liquid medicines

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ABSTRACT (273 Words)

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 $\pm$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. These volumes reflect those used in clinical practice; thus error could potentially be reduced by manufacturers revising formulation concentrations for certain drugs.

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:

$$\text{density (g/ml)} = \text{mass(g)}/\text{volume(ml)}$$

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.

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.

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.

Brand	Syringe Size	Formulation Volume (mL)					
		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 viscosity, 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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Figure Legend

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

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, Medicina 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, Medicina are white boxes with outliers as open circles. Drug formulation abbreviations are as for figure 2.

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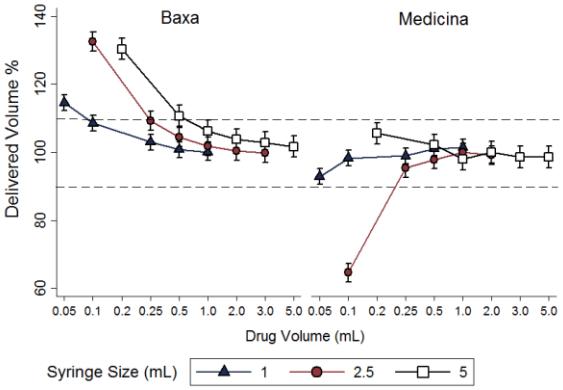

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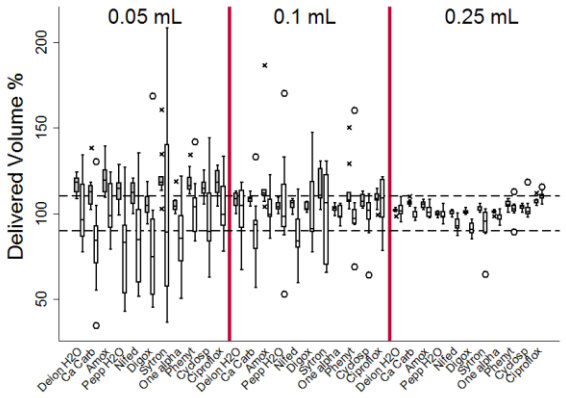

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