

Dose uniformity of samples prepared from dispersible aspirin tablets for paediatric use

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ABSTRACT

Background and study objectives: The practice of dispersing tablets in water and taking a proportional volume to give the required dose to children is widespread, although there is a lack of data to support the accuracy of dosing. This study was designed to analyse dose uniformity of samples prepared from dispersible aspirin tablets.

Method: The accuracy and reproducibility of doses sampled from dispersions of aspirin tablets were examined.

Results: Using dispersions of 75 mg dispersible aspirin tablets in 10 mL water, representative of one technique used in administering paediatric doses, the effects of varying dispersion time before sampling and the region of the dispersion sampled from an oral measure were assessed. Dose removal using 1 mL and 2 mL syringes was also compared. The doses withdrawn were less than required, varied according to the sampling method and never exceeded 76.5% of the intended dose.

The dispersion period before sampling significantly affected doses taken with a 1 mL oral syringe, with higher doses being obtained after five minutes than at three minutes. These differences with a 2 mL syringe were not significant. A concentration gradient within the dispersion in the measure was observed, doses taken from the base being higher. Individual doses larger than anticipated were sometimes withdrawn, especially with a 2 mL syringe; this was attributed to the volume of water (10 mL) not allowing complete dissolution of the drug and leaving a residue of undissolved aspirin.

Conclusion: It is suggested that tablets be dispersed for five minutes and stirred to reduce the under- or over-dosing, using withdrawal with a 1 mL syringe. These findings have serious implications for this method of dosing children from tablets.

KEYWORDS

Paediatric dosing, proportional dosing, dispersible tablets, aspirin

INTRODUCTION

Aspirin is no longer used as a routine antipyretic analgesic in children because of its association with the potentially fatal Reyes syndrome. However, because of its anti-platelet effect, it is administered to children with various cardiac pathologies, including Fontan circulation, and with pros-

thetic heart valves or modified Blalock-Taussig shunts. It is also used for its anti-inflammatory effect in both the acute and chronic phases of Kawasaki disease, which has a peak incidence at 12 to 18 months of age, and for managing pericardial effusion. However, typical doses for anti-platelet effect and Kawasaki disease are only 10 mg/kg and 25 mg/kg followed by 5 mg/kg respectively [1]. Since children usually present with Fontan circulation at or shortly after birth, and the mean weight of a patient with Kawasaki disease is 10 kg, doses as low as 18.75 mg may be required, and pharmacists need a means of delivering such low paediatric doses.

There is at present, a lack of paediatric dosage forms of drugs and of research into paediatric pharmacology and therapeutics. The creation in 2005 of the Medicines for Children Research Network [2] in the UK aims to address these issues and to facilitate the conduct of well-designed studies of medicines for children. However, the current scarcity of information on this subject causes frequent use of unlicensed medicines and off-label prescribing when certain therapies are required for children [3]. A recent study [4] concluded that a wide variety of unlicensed and untested

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captopril formulations were being used interchangeably in the treatment of children with heart failure, with some hospitals dispensing a range of liquid captopril formulations while others were dispensing captopril tablets for crushing and dissolving in water before administration. When drugs are unavailable as liquid preparations, sometimes tablets are crushed and added to food for ease of administration, but this approach is not feasible with coated tablets. Further consideration must be given when a child requires a dose smaller than that available in tablet form. Sometimes extemporaneous mixtures or suspensions are prepared from tablets using basic formulation principles, with conservative expiry dates applied from the limited stability data available. When a drug is manufactured in dispersible tablet form or if a tablet is known to disperse, fractional doses of tablets may be administered as appropriate volumes. The Neonatal Formulary [5] states that for paediatric use a 75 mg dispersible aspirin tablet may be added to 15 mL water to give a 5 mg per mL solution. A similar approach has also been recommended where the 75 mg aspirin tablet may be dissolved in 10 to 15 mL of water and a proportion used to achieve the correct dose [1]. Thus, for example, by routine use of 10 mL of freshly prepared dispersions in water, 7.5 mg aspirin can theoretically be attained as 1 mL of a 10 mL dispersion of a 75 mg aspirin dispersible tablet. None of these approaches provides an entirely satisfactory solution to the problem of paediatric dosing; although the principles applied to generate acceptable methods of administration are sound, the precise nature of the dosage forms thus produced has not been extensively studied.

In particular, a method using proportional doses of dispersible tablets assumes uniform dispersion of the tablet. The British Pharmacopoeia (2007) [6] requirements for dispersible tablets consist solely of uniformity of content and mass, disintegration testing and a fineness of dispersion such that the suspension will pass through a 710 µm aperture sieve. The disintegration test merely ensures that disintegration occurs under the conditions of the test within three minutes, and the fineness of dispersion assessment guarantees only that the resultant particles are within the stated size range; neither test determines whether or not a uniform dispersion is produced. During dissolution testing, single time-point testing is usually sufficient for immediate-release tablets [7]. Because the total dispersion of a tablet is not always used to administer a dose to a child, multiple-point testing would provide more appropriate information to assess the accuracy of administering fractional doses to children.

This study investigates the homogeneity of dispersions produced from aspirin dispersible tablets that were prepared

by a method that carers are advised to use. The influence of the time interval from dispersion to taking the dose, the region sampled and the size of the syringe used to take the sample were assessed in relation to the accuracy of proportional doses taken from the dispersion.

MATERIALS AND METHODS

Materials

Acetylsalicylic acid (aspirin) (Merck Pharmaceuticals, Middlesex, UK), 96% ethanol and water purified by reverse osmosis were used. Additionally, aspirin 75 mg dispersible tablets (Alpharma Ltd, Devon, UK), 30 mL graduated plastic medicine measures (Henleys Medical Supplies Ltd, Hertfordshire, UK), 1 mL and 2 mL oral syringes (Baxa Ltd, Berkshire, UK) were used to obtain aspirin dispersions in a manner analogous to that recommended to carers. The same syringes and measures were used for all measurements, to exclude the possibility of variations in volume caused by changing syringe or measure.

Methods

Dispersions of aspirin tablets in water

For each test, an aspirin 75 mg dispersible tablet was added to 10 mL purified water in a 30 mL graduated plastic medicine measure at a room temperature of about 20°C.

Only one sample of the resultant solution was taken for each tablet. Samples were taken by holding the oral syringe perpendicular to the beaker so that the tip of the syringe remained at the 2 mL, 4 mL, 6 mL or 8 mL mark of the measure (zones 2, 3, 4 and 5 respectively) with the syringe inserted centrally as viewed from above. Samples were similarly taken from the base of the measuring beaker (zone 1). Syringes with a volume of 1 mL or 2 mL were used to remove 1 mL and 2 mL samples respectively, after a dispersion time of three or five minutes. The former time was selected because the tablet looked fully dispersed at this interval. Carers are not given a precise sampling time.

Following removal, samples were made up to 1 L in volumetric flasks. After manually inverting the flask vertically 30 times, the solution was left to stand for 10 minutes and the UV absorbance was measured at 230 nm (Hewlett Packard, model 8452A diode-array spectrophotometer). The mean of three absorbance readings taken from the 1 L dilution was used to determine the aspirin content. For each set of data, the mean dose measured was determined and expressed as a percentage of the intended dose.

Calibration of standards

Aspirin standards were prepared by dissolving 0.15 g acetylsalicylic acid (Sigma-Aldrich, Leeds, UK), accurately

weighed, in 96% ethanol in a 10 mL volumetric flask. From this solution, 1 mL was diluted to 100 mL and 1, 2, 3, 4 or 5 mL samples were taken and diluted to 25 mL with water to generate solutions of the standards that were assayed at 230 nm. The solutions obeyed Beer-Lambert's Law and the presence of small amounts of ethanol during these dilutions did not affect the assay.

Statistical analysis

Two-factor analysis of variance (ANOVA) with replication was applied to all results obtained for doses measured with each syringe; this was to detect whether any relationship existed between the length of time that a tablet was left to disperse before a dose was taken and the subsequent dose derived, or if certain zones were associated with a particularly high or low dose.

RESULTS

It is clear from the percentage of intended dose column in Tables 1 and 2 that, irrespective of the length of time that the tablet was dispersed before a sample was withdrawn and the zone of dispersion sampled, the mean doses measured were less than the intended doses. Because no set of conditions was identified as consistently providing the required amount of drug, statistical analysis was performed to establish the significance of the effect of each parameter on the dose measured and whether any particular combination of factors lead to a more favourable outcome in terms of dosing.

The ANOVA of samples taken with the 1 mL syringe (Table 3) identified that both the time since initiation of dispersion

and the choice of zone that a dose is taken from affected the dose that was measured. There was no statistically significant evidence of interaction between the factors. The model indicates that it is not possible to suggest a combination of a time for dispersion and a zone to be sampled that would generate a dose fully equivalent to the intended dose, but samples from the lower zones contained doses closest to that required.

There was also found to be a relationship between the 2 mL dose measured and the zone sampled (Table 4), but unlike the results for the 1 mL syringe, the data for the length of time for which a tablet is dispersed did not achieve statistical significance.

No visual difference in the appearance of the dispersions of tablets dispersed after three or five minutes was apparent. Both dispersions had white sediment from the base of the measure to the 2 mL mark, which probably consisted of undissolved aspirin and excipients. The dispersible tablets used in the study contained aspirin as the active ingredient (and not one of the more soluble salt forms) which is soluble 1 in 300 of water [8]. This is equivalent to a solubility of about 33 mg in 10 mL. Therefore the dispersion of a 75 mg tablet in 10 mL water must have generated a solution of aspirin, possibly saturated, and a suspension of undissolved aspirin and tablet excipients. Consequently, with a sample taken from the base of the measure, there is a risk of obtaining a dose much higher than would be anticipated from calculations using solely the concept of proportionality, which assumes a uniform dispersion, because of the undissolved aspirin particles.

Table 1: Doses measured from different zones with 1 mL oral syringes

Dispersion time	Zone	Mean dose (mg)	% of intended dose	Range (mg)	Range (% of intended dose)
Three minutes	1	5.2	68.9	4.5-6.0	60-80%
	2	4.4	58.5	3.2-5.3	43-71%
	3	2.8	37.5	1.8-3.3	24-44%
	4	3.5	46.5	2.5-4.2	33-56%
	5	3.7	49.8	2.6-5.0	35-67%
Five minutes	1	5.7	76.5	4.6-6.9	61-92%
	2	5.1	67.5	4.3-6.6	57-88%
	3	4.5	59.4	3.0-6.0	40-80%
	4	4.4	58.3	3.3-7.1	44-95%
	5	3.8	50.4	3.0-6.0	40-80%

The intended dose was 7.5 mg and the number of samples for each zone was 10.

The range of doses measured with the syringes is given in Tables 1 and 2. They show that although the mean doses were less than the intended dose, some individual doses measured with the 2 mL syringe contained almost double the required dose of aspirin. The samples derived from zone 1 were consistently closest to the intended dose, with doses larger than intended notably arising from zone 2, irrespective of dispersion time. It is also apparent that the general trend is for aspirin dose to decrease with ascending zones, suggesting the existence of a concentration gradient within the dispersion. In addition to the danger of overdose from uneven distribution within the dispersion, the

in the distribution of the drug in the beaker, which would be further exacerbated by different hydrodynamic conditions produced by using two syringes of different size. Additionally, 75 mg aspirin cannot dissolve in 10 mL water; instead, there would be a near-saturated solution that would not permit complete dissolution and which would raise the risk of taking a sample containing a dose larger than intended because of undissolved aspirin. When fluid restriction is necessary, the risk of sampling doses higher than intended can be exacerbated by the use of smaller volumes of water to disperse the tablet. When fluid restriction is not necessary, dispersing the tablet in a larger volume of medium possibly increases the

Table 2: Doses measured from different zones with 2 mL oral syringes

Dispersion time	Zone	Mean dose (mg)	% of intended dose	Range (mg)	Range (% of intended dose)
Three minutes	1	9.7	64.4	7.6-14.2	51-95%
	2	9.2	61.5	5.5-22.0	37-147%
	3	7.7	51.1	6.3-9.2	42-61%
	4	6.1	40.9	4.2-8.9	28-59%
	5	5.4	35.9	3.4-6.9	23-46%
Five minutes	1	9.4	62.8	7.9-12.2	53-81%
	2	9.5	63.6	6.5-28.2	43-188%
	3	7.5	49.7	6.0-9.8	40-65%
	4	7.9	52.3	6.0-25.1	40-167%
	5	6.9	46.2	5.3-9.5	35-63%

The intended dose was 15 mg and the number of samples for each zone was 20.

sampling of doses less than that intended may also cause adverse effects in the patient. There was also a general trend towards higher concentrations of aspirin towards the bottom of the measure when 1 mL samples were taken.

DISCUSSION

A number of factors could have contributed to the results. The effect of dispersion time, noted particularly with 1 mL doses, could have been because of the mechanisms of disintegration and dissolution of tablets. Dissolution from any tablet includes four phases: disintegration to particles of <2 mm diameter, followed by de-aggregation that generates smaller particles (typically <0.25 mm diameter), then dissolution and finally diffusion of the dissolved drug into the dissolution medium [9]. Even for dispersible tablets, it is possible that complete disintegration did not occur within five minutes; this could have led to intrinsic variation

extent and rate of disintegration and permits more accurate doses to be measured from the dispersion. (75 mg dispersed in 25 mL water should produce a solution of aspirin with, for example, 18.75 mg in 6.25 mL). However, lack of co-operation in young children, especially if poor taste of medication is also a factor, means that in practice, volumes used are as small as possible.

Although the preparation of aspirin dispersions was by the same method recommended to carers, other variables can also alter the dissolution of aspirin in water and hence the dose sampled. Such factors could include the presence of air bubbles in water. Air bubbles can attach to aggregates resulting in changes to the solid-liquid interface (so that the surface area exposed to the solvent is reduced) and changing the specific gravity of the particle so that the motion of the particle within the medium is altered. The

Table 3: Two-factor analysis of variance (with replication) of data described in Table 1 obtained for the withdrawal of 7.5 mg doses using 1 mL oral syringes

Source of variation	Df	F	P-value
Dispersion time	1	9.3	0.003
Zone sampled	4	10.2	<0.001
Interaction	4	1.7	0.15

Key: Df: degrees of freedom, F: Test statistic, P-value: the probability that these results could have arisen if the null hypothesis had been true

Table 4: Two-factor analysis of variance (with replication) of data described in Table 2 obtained for the withdrawal of 15 mg doses using 2 mL oral syringes

Source of variation	Df	F	P-value
Dispersion time	1	3.25	0.07
Zone sampled	4	14.83	<0.001
Interaction	4	1.48	0.21

Key: Df: degrees of freedom, F: Test statistic, P-value: the probability that these results could have arisen if the null hypothesis had been true

effect can be to increase or decrease the disintegration rate depending on the formulation assessed; this can be very significant for some drugs, exemplified by changes as high as a 30% increase in the disintegration/dissolution rate of prednisolone observed by some researchers [10]. Dissolution testing of tablets by pharmacopoeial methods requires air removal from the dissolution medium. Variations in environmental temperature are likely to exist during day-to-day use of the tablets. Raising the temperature of the medium usually increases the solubility of a drug, but the effect of temperature on disintegration and dissolution varies for different formulations; a 5% difference per °C has been observed [9]. It would be impractical to recommend control of temperature or de-aeration to users in the hospital ward or home environment. However, such simple factors will contribute to the variation in the amount of aspirin a volume contains when measured by a carer.

Variability in measuring the dose of aspirin from dispersions can mean that aspirin therapy is inconsistent in clinical effect. Significant under-dosing could lead to platelet aggregation and clotting, with a possible failure of prostheses. Delivering higher doses than required can be associated with adverse effects such as gastric irritation or bleeding. Many other drugs are dispersed in water and fraction doses taken, including diclofenac, omeprazole, amlodipine, olan-

zapine and lamotrigine. Their solubility characteristics and dispersion properties are not generally considered when recommending volumes for dispersion or the method of preparation.

CONCLUSION

The preparation of proportional doses does not generate the anticipated dose. The existence of samples with doses larger than those intended is undoubtedly of concern for a drug such as aspirin. However, the apparent under-dosing when medication is administered via this method is also of significance if anti-platelet effect is reduced clinically. Our study suggests that the heterogeneity of the saturated solution thus produced is great enough to demand the stirring of all dispersions immediately before doses are taken, to attempt the prevention of dose failure; this can be concluded even before further studies are undertaken to characterise the dose profile of samples after stirring. At present, the most accurate way of dosing, by taking proportional volumes from dispersible tablets, would appear to be to disperse the tablet for five minutes, stir the dispersion and sample the dose, but this requires further study. However, the potential for inaccurate dosing when using this method must be stressed and should be investigated for other drugs and formulations with different solubility and formulation characteristics.

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