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Original Article

Dividing the Tablets for Children–Good or Bad?

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ABSTRACT

Introduction: To investigate the dosing accuracy using split tablets in paediatric patients. **Methods:** Five brands of tablets (Alvedon® (paracetamol), Catapresan® (clonidine), Hydrocortone® (hydrocortisone), Prednisolon® (prednisolon) and Tavegyl® (clemastine) were split into halves and quarters by hand or by using a tablet splitter. The resulting halves and quarters were weighed. **Results:** Three out of the five tablet brands passed the test in the Ph. Eur. (European Pharmacopoeia) for subdivision of tablets when split once and when split twice to yield quarters only one of the tablets passed the test. When also applying the limit for relative standard deviation (RSD) from the US Pharmacopoeia only one of the tablet halves passed and the other two was just outside the limit. None of the tablet quarters passed the RSD limit. **Conclusion:** Our results indicate that tablets larger than 8 mm might be split once. Tablets should not be split more than once, due to uncertainty in dose accuracy. There is a need for more commercially available age-appropriate formulations. Extemporaneously prepared formulations should be considered as an alternative to the use of split tablets.

Key words: Dosing accuracy, Manipulation of drugs, Paediatric patients, Subdivision of tablets, Tablet splitting.

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INTRODUCTION

Medicines for paediatric patients are often prescribed as dose per kilo bodyweight or per meter square body surface area (BSA). Paediatric patients show a large variability in weight and BSA and hence there is a clinical need for a large variation of tablet strengths for proper drug treatment and also liquids or suspensions for oral or rectal use. Tablets are a practical solid dosage form with normally long shelf-life and a well defined dose. Even in children as young as two years of age, tablets can be used.[1] Small tablets have recently been shown to be preferred by parents to children as young as 6 months when compared to powder, suspension, and syrup.[2,3] Oro-dispersible mini-tablets is a recommended dosage form, either to be administered as they are or to be used for preparation of oral liquids.[4]

Only a few brands of tablets with strengths suitable for use in children are available and consequently split tablets are often used in the clinical practice to achieve the prescribed dose. In a nationwide study in Sweden at paediatric hospital wards, approximately 20% of all medication orders were for tablets and capsules. More than half of them (56%) were prescribed for adolescents, a little more than 30% for children, and even infants and neonates were prescribed tablets or capsules.[5]

Since 2002 the European Pharmacopoeia (Ph. Eur.) has guidelines how to measure the dosing accuracy of subdivided scored tablets[6,7] and since 2010 the European Commission has stated in their Guideline on Summary of Product Characteristics (SmPC) that for tablets designed with a score line, information on whether or not reproducible dividing of the tablets has been shown, according to the rules in Ph. Eur., one of the following phrases should be used in the SmPC:[8,9]

- "The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses"
- "The tablet can be divided into equal halves"
- "The tablet must not be divided at all"

This information is vital to both health professionals and patients, since many people believe that a score line is a sign that the tablet can be divided in two equal parts, although that is not always the case.[10,11] WHO amongst others have stated that non-functional breakmarks should be avoided.[12]

Reasons for splitting tablets other than achieving a smaller dose are to facilitate administration due to ease of swallowing and economical reasons, when tablets with high strength cost the same as tablets with low strength (mostly common for adults).[13]

The aim of the present study was to investigate the dosing accuracy for paediatric patients by weighing halves and quarters of tablets obtained from splitting intact tablets by hand or by the use of a tablet splitter. The brands of tablets investigated were chosen because they were commonly split into halves and quarters in clinical practice at Astrid Lindgren Children's Hospital (ALB), a large children's hospital in Stockholm.

MATERIALS AND METHODS

Splitting of the following tablets was studied: Alvedon® (paracetamol) GlaxoSmithKline, Consumer Healthcare A/S, Bröndby, Denmark, Catapresan® (clonidine) Boehringer Ingelheim, Stockholm, Sweden, Hydrocortone® (hydrocortisone) MSD, Sollentuna, Sweden, Prednisolon® (prednisolon) Pfizer, Sollentuna, Sweden and Tavegyl® (clemastine) Novartis, Täby, Sweden. All tablets studied had scores and one of them (Hydrocortone®) had a crossed score. All manufacturers stated that the active ingredient in their tablets is uniformly distributed. Earlier studies have shown that weight of a split tablet correlates to drug content, a statement we assume is correct.[14]

Three of the tablets studied, Alvedon, Prednisolon and Tavegyl, are licensed in Sweden. Catapresan and Hydrocortone are not licensed for use but can be prescribed as unlicensed drugs. Details regarding intact tablets are given in (Table 1).

The selection of tablets investigated in the present study was based on a short survey to ten clinically active paediatric nurses at ALB in Stockholm. The nurses stated which tablets they regularly split or even quartered

Table 1: Tablet characteristics

Trade name	Active ingredient	Mean weight (g)	SD	RSD (%)	Original size (mm) (ø * height)	Score/cross
Alvedon®	paracetamol 500 mg	0.548	0.007	1.11	16.2*7.7*5.8 (length*width* height)	Score
Hydrocortone®	hydrocortisone 10 mg	0.244	0.003	1.27	10.8*2.7	Cross score
Prednisolon®	prednisolon 5 mg	0.178	0.002	0.90	8.0*2.7	Score
Tavegyl®	clemastine 1 mg	0.131	0.001	0.93	7.0*2.4	Score
Catapresan®	clonidine 75 microg	0.096	0.001	1.08	6.0*2.3	Score

SD = standard deviation.
RSD = relative standard deviation.

Table 2: Results (Tablets are given in increasing size, see Table 1)

Trade name	Active ingredient	Mean weight (g)	Half or quarter	Splitting test as per the EUP (Total No. of tablets=30)			Adopted splitting test as per the USP	
				No. of tablets outside 85-115%	No. of tablets outside 75-125%	Test result	RSD%	Test result
Catapresan®	clonidine 75 microg	0.096	½	5	2	Failed	16.7	Failed
Catapresan®	clonidine 75 microg	-	¼	9	3	Failed	15.7	Failed
Tavegyl®	clemastine 1 mg	0.131	½	2	0	Failed	7.3	Failed
Tavegyl®	clemastine 1 mg	-	¼	1	0	Passed	8.2	Failed
Prednisolon®	prednisolon 5 mg	0.178	½	0	0	Passed	6.1	Failed
Prednisolon®	prednisolon 5 mg	-	¼	4	0	Failed	9.3	Failed
Hydrocortone®	hydrocortisone 10 mg	0.244	½	0	0	Passed	4.7	Passed
Hydrocortone®	hydrocortisone 10 mg	-	¼	5	0	Failed	9.4	Failed
Alvedon®	paracetamol 500 mg	0.548	½	1	0	Passed	6.5	Failed
Alvedon®	paracetamol 500 mg	-	¼	14	4	Failed	17.4	Failed

Figure 1: Tablet splitter from LGS Corp (USA).

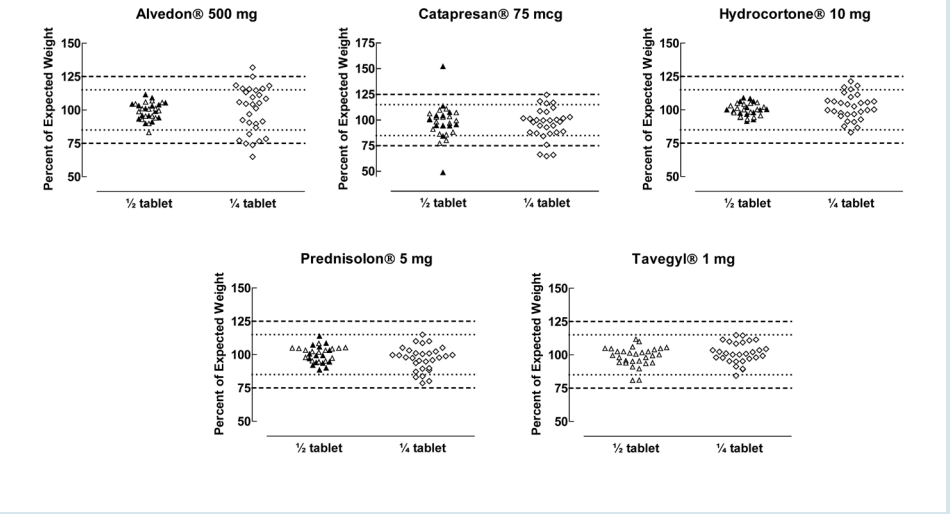

Figure 2: Results from splitting tablets
Filled figures=split manually
Non-filled figures=split by the use of a tablet splitter
The European Pharmacopoeia limits for uniformity of mass of subdivided scored tablets are presented with dotted lines:
..... =85 and 115%
------ =75 and 125%.

to paediatric patients. The tablets chosen also represent a wide variety of sizes. To avoid inter-individual variability the data presented in this report are the results of one paediatric pharmacist (ÅA) splitting the tablets using a tablet splitter in the pharmacy and using a pair of thumb forceps when lifting the halves or quarters onto the scale.

All tablets were weighed before splitting. All brands of tablets were split by the use of a tablet splitter (LGS Corp (USA)), (Figure 1). Four of the tablet brands were also halved manually. We were not able to split Tavegyl® manually probably due to a combination of size and hardness. The tablet halves split by the tablet splitter were further split into quarters.

All intact tablets as well as all halves and quarters were weighed on a Mettler HK 160 scale (Mettler Instrumente AG, Zürich, Switzerland). The precision measured by controlled standard weights and expressed as relative standard deviation (RSD) at 20 mg, 200 mg, and 500 mg were 0.67, 0.042, and 0.019%, respectively. We applied the European Pharmacopoeia Test for subdivided scored tablets (European Pharmacopoeia 8.0) which states that thirty tablets are randomly selected from each batch of the chosen products. These thirty tablets were split and the tablets of a certain product were judged to have passed the test if no more than one individual mass was outside the range of 85-115% of the predicted average mass and if no individual mass was outside the range of 75-125% of the predicted average mass.[7]

We also applied the limit for RSD from the United States Pharmacopoeia (USP), stating that the product passed the test if the RSD is less than 6%.[15] The USP has a somewhat different method for deciding what halves to weigh and all of the weighed tablet parts must be within the 85-115% range of the target tablet weight, so in our study we used the criteria in the European Ph guideline with the addition of the RSD limit from the USP.

Statistics

The statistical software used for statistical analysis is Graph PAD Instat version 3.10 (LaJolla, CA, USA). The variance ratio test was used for the comparison of the variability of data in two populations.[16] The Fisher's exact test was used for the comparison of classified data from two independent populations. Two-tailed p-value less than 0.05 was considered statistically significant.

RESULTS

All intact tablets fulfilled the criteria for uniformity of mass according to Ph. Eur.[17] The variability in weight, expressed as relative standard deviation (RSD), was very low (0.90-1.27%), (Table 1).

Due to the design of the tablet splitter oval tablets must be placed in the cutter so that the blade would cut along the scoring line. Round tablets can be put in the splitter either way.

The variability of weight, expressed as relative standard deviation (RSD) of the halved tablets was within the range 4.7 to 16.7% RSD with a tendency to a higher variability for smaller tablets, (Table 2). The variability of the weight of the tablet halves resulting from splitting by hand were higher for Catapresan® and Prednisolon® than after splitting by the tablet splitter (p=0.002 and 0.057, respectively). The accuracy of the tablet splitter was independent of whether the tablets were split within or apart from the score (data not shown).

The variability in weight (RSD%) was within the range 8.2 to 17.4% for tablet quarters, (Table 2). The loss of tablet weight caused by splitting was less than 1.2% for all tablet parts.

After splitting into halves three of the tablet brands fulfilled the criteria for subdivision of scored tablets according to the Ph. Eur., Hydrocortone® (hydrocortisone) and Prednisolon® had no tablet halves outside the 85-115% range and Alvedon® (paracetamol) only had one tablet halve outside the 85-115% range. When we also applied the limit of 6% RSD from the USP, Hydrocortone® still passed the test (4.7%) and Prednisolon® and Alvedon® were just outside the test limit (6.1 and 6.4% respectively). One of the tablet brands, Tavegyl® passed the Ph. Eur. guideline, but did not pass the USP limit for standard deviation (8.2%), (Table 2).

Our data demonstrate that splitting of tablets generally results in a very low dosing accuracy, (Figure 2), most pronounced for the tablet quarters.

DISCUSSION

The results in the present study confirm previous findings that tablets split more than once generally fail to meet expectations for uniformity of weight. We do not recommend the general practice of splitting tablets more than once for paediatric use. The fact that the dose administered may differ from the one prescribed when using subdivided tablets, must be taken into account when evaluating the effect of drug therapy.

Paediatric patients are at a higher risk of medication errors since a high proportion of paediatric drug orders are off-label[5] and alteration of available dosage forms is often required.[18] Uncertainty in dose administered, enhances the possible uncertainty from off-label prescribing, and must be considered when evaluating drug therapy in paediatric patients. The use of subdivision of tablets in paediatric drug treatment to ensure lower dosing is often necessary due to the fact that only a few brands of tablets with strengths suitable for use in children are available. It might be harder to swallow a broken tablet both because it normally has sharp ends and there is also a possible exposure of bitter taste not masked by a coating. In our study we found that larger tablets split more correctly than the smaller tablets. The results from our study also indicates that splitting can be made once if the tablet is larger than 8 mm in diameter/length to achieve halves, but splitting twice to get quarter of tablets results in too high an uncertainty in dose administered. This finding is supported in earlier studies.[19,20]

Only splitting of scored tablets were investigated in the present study. The splitting of our tablets caused an almost negligible loss of weight (less than 1.2%).

Approximately half of all tablets licensed for use in Sweden are made with a score or a crossed score[21] and this may falsely lead the nurse and/or patient/parent to believe that they are designed to be split safely and accurately.[22] It has to be noticed that also tablets containing antibiotic, anti-neoplastic or antiviral substances in some cases are scored. Such tablets must not be split to avoid exposure of harmful compounds. Despite the fact that these tablets are scored their summary of product characteristics clearly states that they should not be split or crushed.[21] At least two anti-neoplastic drugs licensed for use in Sweden have a score line, Puri-Nethol (mercaptopurine) 50 mg, and Metotrexathe Teva 2.5 mg. Even slow release tablets can be found with a score and with contradictory information in the SmPC, where the information in one section states that the tablet can be split, generating two equal parts and in another section it is stated that the tablet must not be chewed, crushed or otherwise modified.[21]

In the Guideline on Summary of Product Characteristics (SmPC) it is clearly stated that for scored tablets the SmPC must contain information regarding whether reproducible splitting of the tablet has been shown or not.[8]

Studies, including this, have shown that it is more difficult to split smaller sized tablets and our results are in line with earlier findings stating that scored tablets should be at least 8 mm in diameter to be easier to handle.[13] In the Guideline on Pharmaceutical Development of Medicines for Paediatric Use, it is stated that "the tablet size is fundamental to the ability of a child to swallow a tablet".[23] Different sizes of tablets are considered acceptable for different age groups, although there are inter-individual differences in ability to swallow tablets of course, and also different illnesses and/or conditions may interfere with the ability to swallow solid dosage forms. To improve dosing accuracy and administration of medicines to children the production and use of oro-dispersible mini-tablets should be encouraged. Mini-tablets enable varied dosing because children in different age groups can take one or several small tablets.[23] Mini-tablets are a valuable, or in some cases even superior, alternative to syrup in children as young as six months.[3]

From an earlier Swedish study we know that tablets and capsules are a common dosage form for paediatric patients. Approximately 20% of all medication orders were oral solid dosage forms. Unfortunately we do not have any information/numbers regarding how many of these medication orders that needed some drug manipulation to enable administration.[5]

The use of a tablet splitter is, in our experience, an advantage, since splitting by hand results in a higher, albeit not statistically significant, percentage of accepted parts, also found by[24] but not by.[19]

The European Pharmacopoeia 7.0 section 2.9.5 Uniformity of mass of single-dose preparations is stricter than the Ph. Eur. test for subdivision of scored tablets.[17] It could be argued that when a tablet is split to give a smaller dose the tablet half represents a new dosage form and therefore the stricter guideline should be applied, but since there are rules for subdivided tablets we applied them in this study. If we had applied the stricter rules only Hydrocortone would have fulfilled the criteria. It is also important to remember that the conditions in this study with one pharmacist splitting the tablets and lifting the halves and quarters with a thumb forceps, were optimized and probably giving better results than reality.

Extemporaneously prepared formulations for paediatric use may have advantages over the use of split tablets. There is, however, still a lack of information regarding the pharmacokinetics and bioequivalence of extemporaneous products, reformulated from the original products or compounded from active substances.

Splitting tablets may also result in altered pharmacokinetics, since the surface of the tablet in relation to its weight becomes larger and it may dissolve more rapidly further promoted by a not intact coating.

CONCLUSION

Our results indicate that tablets larger than 8 mm could be split once to achieve an approximate half dose for paediatric use. We do not recommend tablets to be split more than once since the resulting parts deviate too much to fulfil the Ph. Eur. test for weight uniformity of tablet parts after splitting.

Since paediatric patients are at higher risk for medication errors due to a number of reasons there is a great need for more age-appropriate dosage forms including small tablets which enables safe administration of medicines to children.

We also agree totally with WHO that non-functional score lines should be avoided since most patients and health professionals falsely believe that a score line indicates the possibility to divide the tablet in two equal parts.

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CONFLICT OF INTEREST

The author declare no conflict of interst.

ABBREVIATIONS USED

Ph. Eur: European Pharmacopoeia, **RSD:** Relative Standard Deviation, **USP:** United States Pharmacopoeia, **BSA:** Body Surface Area, **SmPC:** Summary of Product Characteristics, **WHO:** World Health Organization, **ALB:** Astrid Lindgren Children´s Hospital ("Barnsjukhus" in Swedish).

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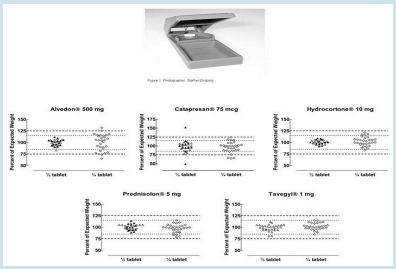
PICTORIAL ABSTRACT



SUMMARY

- Tablets larger than 8 mm could be split once to achieve an approximate half dose for paediatric use.
- There is a great need for more age-appropriate dosage forms including small tablets which enables safe administration of medicines to children.
- Non-functional score lines should be avoided since they falsely lead people to believe that the tablet can be divided in two equal parts.

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