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Original Article

STATISTIC ESTIMATION OF BREAKING TABLETS OF ENALAPRIL 20 MG

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ABSTRACT

Objective: The aim of this study was to evaluate the accuracy of breaking into half and quarter-tablets Enalapril 20 mg sold in the Albanian market, in dosages suitable for use in children.

Methods: 100 whole tablets of Enalapril 20 mg were chosen at random from each of three different manufacturers based on scoring characteristic: scored on one side, scored on both sides and not scored. Whole tablets from each of the three product types were weighed and the mean weight calculated. The pills were then split in half and quarter by using a pill-splitter. The resulting half-tablets and quarter-tablets were weighed and the mean weights were calculated.

Results: All the whole tablets were found to conform to the set criteria. Only halves from those tablets scored on both sides passed the weight uniformity test, with no individual half outside the 85-115 % range. Quarter-tablets failed the weight uniformity test. A higher relative standard deviation was observed for half and quarter-tablets of the not-scored tablet.

Conclusion: The study shows that deviations in weight were observed in half tablets and quarter tablets of Enalapril 20 mg. These deviations were related to the presence or not of the score line. Such inadequate breaking of the tablets may result in dose variability and complicate therapeutic outcome.

Keywords: Enalapril, Breaking tablets, Pediatric formulations, Score line

INTRODUCTION

Many drugs administered to children are not available in formulations for pediatric use. Most marketed oral medicines are intended for adults and are solid dosage forms. Solid dosage forms present problems as children have difficulty swallowing whole tablets or capsules. Therefore, tablets are sometimes cut into smaller parts to obtain appropriate dosage units for children [1-3]. Physicians also prescribe half and quarter tablet doses of higher strength tablets in order to reduce costs because parity pricing is common. A study conducted in the US in 2002 estimated potential cost savings of $1.7 billion nationally if tablet splitting was performed for 7 antidepressant medical products [4].

Tablet breaking is a frequent method used to obtain the desired dose. Pediatric doses depend on the child's weight and the drugs are not always available in the desired dose. Several studies have been conducted to assess the accuracy of tablet breaking [5-10]. One study analyzed drug weight uniformity of cyclobenzaprine tablets split in half using either a pill-splitter or a kitchen knife.

The results showed that both methods resulted in a wide variation in fragment weight between 49.9 % to 149.5 % of the theoretical weight using a kitchen knife and 69.4 % to 130.2 % using the pill-splitter [11]. These studies concluded that tablet breaking resulted in an unacceptable weight variation which may produce clinically important outcomes or risks of adverse effects, depending on the indication and product used. The above studies did not clearly define the level at which the reported mass unconformity compromised the therapeutic efficacy of the drug.

There are no established criteria for evaluation of dosage uniformity in tablet fractions obtained by patients [12, 13]. Most studies on split tablets adopted the United States Pharmacopeia and European Pharmacopoeia Standard. That allows a 15 % deviation in weight from the label claim and a Standard Deviation (SD) of not greater than 6 % [14, 15]. This standard has been applied to other studies examining the accuracy of tablet breaking [10, 12, 16].

Enalapril Maleate is widely used in pediatric cardiology in the treatment of essential and renovascular hypertension and in congestive heart failure. The daily dose of Enalapril Maleate in children is in the range of 0.2-1.0 mg/kg [17, 18]. In the absence of liquid formulations for oral administration, it is common practice to split available medicines intended for adults. We chose Enalapril 20 mg tablets that are commonly split and used for long-term therapy. The aim of this study was to evaluate the accuracy of breaking into half and quarter-tablets Enalapril 20 mg sold in the Albanian market, in dosages suitable for use in children.

MATERIALS AND METHODS

Three drugs available in the Albanian market were studied: Enalapril 20 mg tablets (Kwizda Pharma GmbH); Enalapril 20 mg tablets (1A Pharma GmbH); Enalapril 20 mg tablets (Merck Sharp & Dohme). They have been chosen based on the presence of a single-sided score line, a double-sided score line, and no score line. The basic characteristics (active substance, strength, form, manufacturer, and tablet description) of the three products studied are listed in table 1. For simplicity, the different types will be referred to as S (score line on one side of the tablet), NS (Not scored) and BS (score line on both sides of the tablet).

Table 1: Characteristics of enalapril tablets tested

Active substance/Strength	Manufacturer	Tablet description
Enalapril 20 mg tablets	Kwizda Pharma GmbH	Scored on one side
Enalapril 20 mg tablets	1A Pharma GmbH	Scored on both sides
Enalapril 20 mg tablets	Merck Sharp & Dohme	Not scored

A total of 100 whole tablets was randomly selected from each of the three drugs. The whole tablets were weighed and the mean weights were calculated. Randomly selected tablets were split in half by a single investigator, using a pill-splitter (MEDA Pharma GmbH & Co. KG) and weighed. The mean weight of the halves was calculated. The same person was asked to split the halves again into quarters. One-quarter per tablet was weighed and the mean weight of the quarter of a tablet was calculated.

The criteria for assessing weight uniformity were adapted from European Pharmacopoeia Standard mass uniformity requirements and other studies examining the accuracy of tablet breaking [15, 16, 19]. The criteria are as follows:

- The ideal split tablets are half-tablets and quarter-tablets within the 85 % to 115 % range of weight.
- The tablets pass the weight uniformity test if not more than one-half and one-quarter were outside the 85 % to 115 % range and within the 75 % to 125 %, and if the RSD was less or equal 10 %.
- The half-tablets and quarter-tablets fail the weight uniformity test if more than one of the 100 half-tablets and quarter-tablets were outside the 85 % to 115 % range, or if any half-tablets and quarter-tablets were outside 75 % to 125 % range.

RESULTS AND DISCUSSION

All the tested tablet types (S, BS, and NS) were found to conform to the set criteria as all the individual whole tablet weights were between 85 % and 115 % of the respective average weights.

The respective mean weights for S, BS, and NS tablets are presented in table 2.

Table 2: Mean weight of the evaluated tablets

Tablet type	Mean weight of whole tablets (mg±SD)	Mean weight of halves (mg±SD)	Mean weight of quarters (mg±SD)
S	170.47±7.25	85.14±13.27	41.96±6.36
BS	162.6±7.5	80.3±7.90	38.71±4.78
NS	182.7±6.11	87.7±13.91	44.49±10.03

S: Line score on one side of the tablet, BS: Line score on both sides of the tablet, NS: No line score, SD: Standard deviation, n = 100.

The results of the weight uniformity test performed on half-tablets and quarter-tablets of the S, BS, and NS products are found in table 3 and table 4. The half-tablets of the BS drug passed the weight uniformity test, with no individual outside the 85 % to 115 % range and an RSD less than 10 %. The half-tablets of the S and NS products failed a weight uniformity test; the halves were outside the 75 %-125 % and had an RSD more than 10 %.

Table 3: Results of weight uniformity test of half-tablets

Tablet type	Number of halves within 85–115 %	Number of halves within 75–125 %	Number of halves outside 75–125 %	Relative standard deviation (%)	Result
S	74	21	5	15.58	Fail
BS	100	0	0	9.82	Pass
NS	63	30	7	15.86	Fail

S: Line score on one side of the tablet, BS: Line score on both sides of the tablet, NS: No line score, n= 100

The quarter-tablets failed the weight uniformity test. All three tablets types had an RSD more than 10 % and quarter-tablets were outside the 75 % to 125 % range. The highest RDS (22.54 %) were found in NS tablets.

Table 4: Results of weight uniformity test of quarter-tablets

Tablet type	Number of quarters within 85–115 %	Number of quarters within 75–125 %	Number of quarters outside 75–125 %	Relative standard deviation (%)	Result
S	67	24	9	15.16	Fail
BS	72	22	6	12.34	Fail
NS	52	30	18	22.54	Fail

S: Line score on one side of the tablet, BS: Line score on both sides of the tablet, NS: No line score, n= 100

The practice of tablet splitting is frequently pursued in the treatment of the pediatric population to obtain appropriately-sized dosage units. Recent articles that question tablet splitting safety illustrate why splitting accuracy is important [20].

In this study, the good performance of BS tablets in the splitting test of half-tablets may have been due to the presence of the score line on both sides of the tablets and the oblong shape of the tablets. This combination of the characteristics seems to provide an ideal tablet for accurate splitting. On the other hand, NS tablets were reported to have the highest number of failing units, of both half and quarter-tablets tested, outside the 85 % to 115 % and 75 % to 125 % range.

Other studies found an association between tablet characteristics and splitting accuracy. In a study similar to ours, Polli *et al.* found that of the 12 products evaluated, all scored tablets passed the uniformity test while most of not scored tablets failed [21]. Zaid *et al.* found that scored tablets of Angiopril 20 (Enalapril) had the highest number of failing units, with 9 tablets out of 30 weighing outside the 85–115 % range and 6 tablets outside the 75–125 % range. This was attributed to the lower level of hardness, and not appropriate scoring.

The shape of the product was reported as round, which may have further reduced the ease of splitting [22]. Hill *et al.* found that 11.1 % of half-tablets of scored medications failed the weight uniformity test compared to 14.4% of half-tablets of not scored medications [23]. None of these studies have evaluated the accuracy of splitting tablets into quarters.

Results from the weight uniformity test (table 3 and table 4) suggest greater variability in half and quarter-tablet, drug weight for NS medications than for scored medications. Assuming that the enalapril content was uniformly distributed throughout each tablet, this variability in splitting could result in considerable variation in drug content. The estimated range of active substance content in not scored tablets is 5.89 mg–13.51 mg for halves and 2.68 mg–7.52 mg for quarters. This lack of dosing predictability will be compounded if several unevenly split tablets are taken consecutively. Administration of dosages lower than those intended can compromise the therapeutic effect. In contrast, intake of a dose higher than intended may increase dose-related adverse effects.

Such results can be of clinical significance for drugs which have a narrow therapeutic range. If the half-life of the drug is long or the therapeutic range is wide, dosage fluctuations are less likely to be clinically significant. Enalapril is available in two strengths in the Albanian market (10 mg and 20 mg). This requires tablet splitting for use in a pediatric population. Enalapril 20 mg was selected as the drug of choice because it is frequently used in the treatment of essential and renovascular hypertension and in congestive heart failure, and dosage in children is achieved by breaking the tablets into smaller authorized strengths. The recommended initial dose of Enalapril is 2.5 mg for patients with a body weight of 20 kg up to<50 kg and 5 mg for patients with a body weight 50 kg. This study suggests that splitting tablets that are not scored results in significant irregularities of dosage, which can be clinically unacceptable for patients who split these tablets on a regular basis. The desired results were achieved only by splitting drugs scored on both sides (BS) into half-tablets.

CONCLUSION

Wide weight deviations have been observed when the tablets are split into subdivisions. Those deviations have been found to be related to the presence of the score line. Such inadequate breaking of the tablets may result in dose variability and complicate the therapeutic outcome. We conclude that the presence of a score line in medicinal products fulfills a very important role for the physician to prescribe the correct dose.

In small markets where the introduction of lower doses may not have a commercial interest and there is a lack of pediatric formulations, appropriately scored tablets can ensure more flexible dosage.

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CONFLICT OF INTERESTS

No conflict of interest to declare

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