The practice of dividing tablets: An uncertain act

David Galvis-Pareja¹, Clara Ines Manrique², Diego Rojas-Gualdron², Heidy Contreras¹

¹Universidad CES, Faculty of Pharmacy, Medellín, Colombia
²Universidad CES, Faculty of Medicine, Medellín, Colombia

ABSTRACT

Background and Aims: Tablets can be split by patients for a number of reasons, using various instruments. Tablets can be scored or unscored; if scored, they may be split into pieces, and in spite of guidelines to do so patients are still at risk of resultant drug dose fluctuations, or being exposed to toxic or subtherapeutic doses. The aim of this study was to investigate differences in weight between halves of tablets, split by different populations and with different devices.

Methods: A 3-factor full factorial design (3 runs) was used with participants: patients, caregivers, nurses, medical doctors, and pharmacists; instruments: scissors, tablet cutters, knives, hand; drugs: losartan, clonidine, metoprolol, and warfarin. The risk of unequal tablet splitting was estimated and analyzed for each factor and their interaction with linearized generalized models.

Results: Differences in weight were found to be above 15% and 25% of the theoretical weight as in general, the highest weight variations after splitting were found in clonidine with patients using scissors. The overall risk of non-equal tablet splitting was 22.5% for deviations > 15% and for > 25%.

Conclusion: In this study, no tablet was split into halves of equal weight; based on these findings, splitting tablets is a questionable practice.

Keywords: Splitting tablets, Equal weight, Amount, Patients, Risk

INTRODUCTION

The practice of splitting tablets is a widespread activity in hospitals, nursing homes and private homes, and is done with various tools, such as pill cutters, scissors, knives, scalpels, and hands (Arnet & Hersberger, 2010; Verrue et al., 2011). Some patients report using their teeth to break the tablet into two pieces. Some tablets come with a line or bisect, frequently referred to as a score; these scores are usually a sign that those tablets can be split, supposedly guaranteeing that each piece of the tablet will contain the same amount of active principle or just weigh exactly the same as the other half. However, not all scores are a sign of this; some of these bisects have an aesthetic purpose (Rowley F, s. f., 2006; Thompson, 2012), which can be misleading and people end up splitting a tablet that will not render two equal parts, with identical weight and amount of drug. State agencies, like the U.S. Food and Drug Administration (FDA, 2013), even give advice as to how to split a tablet as “adequately” as possible. The purpose of this study is to investigate whether people who split various medicines using different tools can effectively split tablets into equal halves.

MATERIAL AND METHODS

Knives and scissors were purchased in a supermarket while tablet cutters, brand warfarin and metoprolol, and generic clonidine and losartan were acquired from a local pharmacy. Subjects participated in this study after complying with inclusion criteria.
(medical doctors, nurses, pharmacists, patients, and caregivers) and exclusion criteria (mental illness, Parkinson’s, and any neuromotor disease), and were enrolled after signing the informed consent. There were three subjects for each profession. Caregivers’ mean age was 45 (two females and one male); patients’ mean age was 75 (two males and one female); medical doctors’ mean age was 50 (two males and one female); nurses’ mean age was 32 (all females); pharmacists’ mean age was 30 (one male and two females). All splitting was done in triplicate using an instrument and an active principle.

The tablets were all round. Metoprolol and warfarin were scored and had one score line each to split them into two halves. The insert had no information as to whether this score was aesthetical or functional. Only the metoprolol was flat. The amount for each drug is as follows: clonidine: 0.15 mg, losartan and metoprolol: 50 mg, and warfarin: 5 mg. These drugs were selected because previously, different hospitals were contacted by phone asking them which drugs they split more often and these four drugs were the most split in these institutions.

For each tablet piece or “half,” the deviation from the theoretical weight and the weight loss were calculated as follows: theoretical weight = weight of the tablet before splitting/2; deviation (%) from theoretical weight = (weight of the tablet piece - theoretical weight)/theoretical weight x 100; weight loss = weight of the tablet before splitting - sum of 2 tablet halves (Verrue et al., 2011). The limits for deviation from theoretical weight were set on 15% and 25%, as these are the reference values in industry guidelines when testing for content uniformity (United States Pharmacopeial Convention Inc., 2018).

### Statistical analysis
Statistical analyses were performed with the generalized linear model, binomial family, and logarithmic link function using cluster robust estimation of variance for replications. The risk of inappropriate tablet splitting was obtained from marginal estimations for deviation over 15% and 25%. To analyze the influence of each factor in inappropriate splitting, risk ratios (RR) with 95% confidence intervals (95%CI) were calculated for each factor independently and for their interaction. Statistical analyses were performed using the Stata 16.1 software (College Station, TX).

### Ethical considerations
As the population manipulated sharp objects in order to split the tablets, this research was labeled with a minimum risk to participants according to local regulations. This investigation was approved by CES university ethical committee, code 721 and only the subjects that signed an informed consent were enrolled in the study.

### RESULTS
Table 1 displays the risk of splitting tablets into two unequal halves for the drug regardless of instrument and population, and the same applies for instrument (regardless of drug and population) and population (regardless of drug and instrument). Table 1 provides an overview of which drug, tool, and population are most prone to splitting unevenly. When splitting tablets, none of the subjects except one mentioned the score line, stating that its purpose is to make an even split easier; also, a nurse and a patient split tablets using the scissors’ blade as a knife. The nurses and patients had the most difficulty when splitting tablets by

---

**Table 1. Risk and risk ratio of nonequal pill splitting according to drug, instrument, and role.**

| Drug   | Deviation >15% | Deviation >25% |
|--------|----------------|----------------|
|        | Risk RR CI95%  | Risk RR CI95%  |
|        | p-value        | p-value        |
| Clonidine | 37.09 0.36 (0.25 - 0.52) 0.000 | 26.55 0.21 (0.11 - 0.38) 0.000 |
| Warfarin | 14.08 0.36 (0.25 - 0.52) 0.000 | 14.42 0.36 (0.14 - 0.71) 0.056 |
| Metoprolol | 24.80 0.67 (0.47 - 0.96) 0.027 | 14.74 0.56 (0.34 - 0.9) 0.018 |

| Instrument | Deviation >15% | Deviation >25% |
|------------|----------------|----------------|
| Scissors | 36.00 0.45 (0.3 - 0.66) 0.000 | 18.16 0.15 (0.07 - 0.36) 0.000 |
| Pill cutter | 16.16 0.54 (0.36 - 0.81) 0.003 | 18.37 0.10 (0.71 - 1.44) 0.950 |
| Knife | 19.55 0.49 (0.35 - 0.7) 0.000 | 10.30 0.57 (0.32 - 1.01) 0.056 |
| Hand | 22.09 0.71 (0.49 - 1.04) 0.083 | 14.42 1.27 (0.77 - 2.07) 0.347 |

| Role | Deviation >15% | Deviation >25% |
|------|----------------|----------------|
| Patient | 28.85 0.64 (0.43 - 0.94) 0.023 | 12.90 1.13 (0.57 - 2.26) 0.723 |
| Caregiver | 20.63 0.71 (0.49 - 1.04) 0.083 | 14.42 1.27 (0.77 - 2.07) 0.347 |
| Nurse | 22.09 0.77 (0.53 - 1.11) 0.159 | 13.58 1.19 (0.72 - 1.97) 0.488 |
| MD | 18.42 0.64 (0.43 - 0.94) 0.023 | 9.76 0.86 (0.52 - 1.42) 0.551 |
| Pharmacist | 21.79 0.76 (0.47 - 1.21) 0.243 | 12.90 1.13 (0.57 - 2.26) 0.723 |

RR: risk ratio, CI: confidence interval
hand, and in some cases they used the butt of the knife to hit the tablet and then proceeded to break the tablet into two pieces with their hands; this was seen with clonidine and metoprolol. All subjects agreed that the clonidine tablet was the most challenging to split since it has no score line and it has a small size. With a deviation of more than 15% of theoretical weight, patients were 28.85% of the population, which tended to split all tablets more unevenly, followed by nurses, pharmacists, caregivers, and medical doctors. The instrument for splitting tablets that rendered the most unequal weights was scissors, with a rate of 36%, followed by knife, hand, and pill cutter. It was no surprise to find that clonidine was the tablet with the highest variations in the halves' weight differences after splitting due to its smaller size and lack of a score line. The second highest variation was that of losartan, followed by warfarin and metoprolol. In deviations greater than 25%, the higher differences were seen with the scissors and knife. The pill cutter had a lower risk of splitting unequally. Also, for deviations greater than 25%, caregivers had greater differences in weight followed closely by pharmacists and patients, as opposed to the findings for deviations greater than 15% mentioned above. The scored tablets were easier to split but not equally. Halves were not the same weight in all cases in this study.

Table 2 focuses on the differences between drugs and instruments. The findings show that these two variables have the highest probability of splitting unequally, exhibiting greater differences in weight deviation. In this table, the reference taken was clonidine and scissors; this combination has the highest risk of splitting unequally (55.56% for a deviation greater than 15%) and for deviations beyond 25%, the clonidine and knife combination was the highest but not statistically significant. The case of metoprolol and hand is the lowest. Scissors was the instrument with the highest weight variations for losartan, as well.

Table 3 shows the mean weight loss for drug, instrument, and subject because it has been seen that after splitting a tablet not only do the two halves have an unequal weight but also one or both halves lose mass. It can be seen that after splitting (regardless of instrument and subject), clonidine was the drug that lost more weight. In some cases, the mass lost was not big, but in some others (almost one half) the majority of their mass was lost. Taking this into consideration, the risk of patients not receiving the needed amount is too high. Warfarin lost an average of 0.003 g out of 0.005 g. That is more than half of the drug's intended dose. Once again, this weight loss becomes a serious risk if the therapeutic index of the drug is considered.

Weight loss for any drug was higher when scissors or knives were used (a mean of 0.010 g for scissors and 0.011 g for knives). If we consider just clonidine or warfarin, the amount of drug lost surpasses that of the drug amount. In contrast, the pill cutter lost an average weight lower than any other instrument; these losses are very high and might endanger patients' safety. As for weight loss related to subjects, this was higher for medical doctors and nurses, and lower for pharmacists, caregivers, and patients.

Table 2. Risk and risk ratio of nonequal pill splitting regarding drug and instrument.

| Drug      | Instrument | Deviation >15% | Deviation >25% |
|-----------|------------|----------------|---------------|
|           | Risk       | RR 95%CI p-value | Risk       | RR 95%CI p-value |
| Clonidine | Scissors   | 55.56 1.00 (0.43 - 0.96) 0.032 | 35.56 0.25 (0.1 - 0.63) 0.003 |
|           | Pill cutter | 35.56 0.64 (0.28 - 0.98) 0.044 | 8.89 37.78 (0.69 - 1.63) 0.783 |
|           | Knife      | 28.89 0.52 (0.38 - 0.95) 0.030 | 26.67 0.75 (0.36 - 1.57) 0.444 |
|           | Hand       | 33.33 0.60 (0.38 - 0.95) 0.030 | 26.67 0.75 (0.36 - 1.57) 0.444 |
| Warfarin  | Pill cutter | 0.00 NE | 0.00 NE |
|           | Scissors   | 24.44 0.44 (0.25 - 0.78) 0.005 | 11.11 0.31 (0.12 - 0.82) 0.019 |
|           | Knife      | 13.33 0.24 (0.12 - 0.46) 0.000 | 4.44 0.13 (0.03 - 0.48) 0.002 |
|           | Hand       | 17.78 0.32 (0.17 - 0.6) 0.000 | 6.67 0.19 (0.06 - 0.55) 0.002 |
| Metoprol  | Pill cutter | 4.44 0.08 (0.02 - 0.3) | 0.00 NE |
|           | Scissors   | 24.44 0.44 (0.26 - 0.74) 0.002 | 6.67 0.19 (0.06 - 0.55) 0.002 |
|           | Knife      | 13.33 0.24 (0.11 - 0.54) 0.001 | 2.22 0.06 (0.01 - 0.43) 0.005 |
|           | Hand       | 11.11 0.20 (0.09 - 0.42) 0.000 | 2.22 0.06 (0.01 - 0.43) 0.005 |
| Losartan  | Pill cutter | 22.22 0.40 (0.19 - 0.85) 0.017 | 2.22 0.06 (0.01 - 0.43) 0.005 |
|           | Scissors   | 42.22 0.76 (0.55 - 1.04) 0.088 | 22.22 0.63 (0.33 - 1.17) 0.141 |
|           | Knife      | 24.44 0.44 (0.2 - 0.95) 0.037 | 28.89 0.81 (0.46 - 1.44) 0.479 |
|           | Hand       | 8.89 0.16 (0.07 - 0.38) 0.000 | 4.44 0.125 (0.03 - 0.48) 0.002 |

RR: risk ratio, CI: confidence interval
DISCUSSION

One out of five tablets was unequally split with a deviation >15%. This should be looked at carefully because it is higher than the 15% recommended by quality control in USP Pharmacopeia (United States Pharmacopeial Convention Inc., 2018). Furthermore, all tablets’ halves lost weight and none of them weighed the same as the other half. In this study, deviations higher than 25% were also seen. Regardless of statistics, all tablets’ halves did not weigh the same and did not weigh the theoretical weight. They lost either excipients or drug amount. This is relevant because the quantity lost might lead to therapeutic failure or, if one half weighs more, as it is the case of clonidine in Table 2, this could end up having toxic effects. Other papers have paid little attention to the distribution of the active ingredient in the tablet (Cook et al., 2004; Elliott et al., 2014). It is relevant to recall that in addition to the drug, excipients are also added to the formulation (Haywood & Glass, 2011; Palscő & Zelkó, 2018), and as they are mixed together it makes it difficult to know the active ingredient distribution in the tablet (Shah et al., 2010). This raises the question of whether the patients are taking mostly the drug or the excipients. When splitting a losartan tablet, if one half of the tablet is bigger and weighs more, this might pose a threat to the therapeutic goals and to the safety of the patient. As was mentioned above, the active ingredient does not distribute homogenously in the tablet, making the splitting practice riskier (Shah et al., 2010; Veronin & Youan, 2004).

The therapeutic index is something to consider, too. In this study, two narrow-range drugs (clonidine and warfarin) (Johnson, 2012; Spiller et al., 2005) were studied. The toxic effects could even be lethal given that a very high amount or the total amount of these active ingredients might be present in just one half. The clonidine tablets used in our assay came in 0.00015g amounts, however the tablets weighed around 0.12 g. This clearly shows that 0.11985 g are excipients. Given these amounts, the active ingredient may be in just one part of the tablet or unevenly distributed. Now, if warfarin is considered, the active ingredient weight is 0.005g and the whole tablet is around 0.2g. The content of the tablet is 97.5% excipients. The probability of active ingredient uneven distribution is higher, as is the risk of the patient not receiving the required dose.

CONCLUSION

There are some uncertainty factors regarding the practice of splitting tablets. First, some factors are dependent on the tablet itself, such as if they are scored or unscored (the latter being more difficult to split and with a higher risk of splitting unevenly), active ingredient heterogeneous distribution, and therapeutic index. Second, some are dependent on the subject doing the splitting (age and disease have an impact on the practice of tablet splitting). Third, some are dependent on the instrument used to split the tablet. These many variables make it seem unreasonable to instruct a patient to split a tablet. The risk of not getting the right amount for their therapy is too high, and this means that toxic effects or therapy failure might happen. Both pose a problem, therefore it is not worthwhile to run the risk of splitting. Other alternatives, such as different formulations or extended release tablets, should be considered.

Ethics Committee Approval: This investigation was approved by CES university ethical committee, code 721 and only the subjects that signed an informed consent were enrolled in the study.

Peer-review: Externally peer-reviewed.
Author Contributions: Conception/Design of Study- D.G.P., C.I.M.; Data Acquisition- D.G.P., C.I.M., M.N.; Data Analysis/Interpretation- D.G.P., C.I.M., D.R.G., H.C.; Drafting Manuscript- D.G.P.; Critical Revision of Manuscript- C.I.M., D.R.G., H.C.; Final Approval and Accountability- D.G.P., C.I.M., D.R.G., H.C.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: Authors declared no financial support.

REFERENCES

- Arnet, I., & Hersberger, K. E. (2010). Misleading score-lines on tablets: Facilitated intake or fractional dosing? Swiss Medical Weekly, 140(7-8), 105-110. https://doi.org/smw-12953
- Cook, T. J., Edwards, S., Gyemah, C., Shah, M., Shah, I., & Fox, T. (2004). Variability in tablet fragment weights when splitting unscored cyclobenzaprine 10 mg tablets. Journal of the American Pharmacists Association: JAPhA, 44(5), 583-586. https://doi.org/10.1331/1544-3191.44.5.583.cook
- Elliott, I., Mayxay, M., Yeuchaixong, S., Lee, S. J., & Newton, P. N. (2014). The practice and clinical implications of tablet splitting in international health. Tropical Medicine & International Health, 19(7), 754-760. https://doi.org/10.1111/tmi.12309
- FDA. (2013). Best Practices for Tablet Splitting. https://www.fda.gov/drugs/ensuring-safe-use-medicine/best-practices-tablet-splitting
- Haywood, A., & Glass, B. D. (2011). Pharmaceutical excipients – where do we begin? Australian Prescriber, 34(4), 112-114. https://doi.org/10.18773/austprescr.2011.060
- Johnson, J. A. (2012). Warfarin pharmacogenetics: A rising tide for its clinical value. Circulation, 125(16), 1964-1966. https://doi.org/10.1161/CIRCULATIONAHA.112.100628
- Palcsó, B., & Zelkó, R. (2018). Different types, applications and limits of enabling excipients of pharmaceutical dosage forms. Drug Discovery Today: Technologies, 27, 21-39. https://doi.org/10.1016/j.ddtec.2018.04.002
- Rowley F. (s. f.). Minimize Bisect Risk: Part I. Oct 06, 2006. https://www.pharmamanufacturing.com/articles/2006/188/
- Shah, R. B., Collier, J. S., Sayeed, V. A., Bryant, A., Habib, M. J., & Khan, M. A. (2010). Tablet splitting of a narrow therapeutic index drug: A case with levothyroxine sodium. AAPS PharmSciTech, 11(3), 1359-1367. https://doi.org/10.1208/s12249-010-9515-8
- Spiller, H. A., Klein-Schwartz, W., Colvin, J. M., Villalobos, D., Johnson, P. B., & Anderson, D. L. (2005). Toxic clonidine ingestion in children. The Journal of Pediatrics, 146(2), 263-266. https://doi.org/10.1016/j.jpeds.2004.09.027
- Thompson, C. A. (2012). New term will distinguish tablets known to split in half. American Journal of Health-System Pharmacy: AJHP: Official Journal of the American Society of Health-System Pharmacists, 69(19), 1619-1621. https://doi.org/10.2146/news120071
- United States Pharmacopeial Convention Inc. (2018). USP 41-NF 36. En United States Pharmacopeia and National Formulary. https://www.deutscher-apotheke-verlag.de/shop/produkt/9783769270228/usp-41-nf-36-the-united-states-pharmacopeia-and-national-formulary-2018
- Veronin, M. A., & Youan, B.-B. C. (2004). Medicine. Magic bullet gone astray: Medications and the Internet. Science (New York, N.Y.), 305(5683), 481. https://doi.org/10.1126/science.1097355
- Verrue, C., Mehys, E., Boussery, K., Remon, J.-P., & Petrovic, M. (2011). Tablet-splitting: A common yet not so innocent practice. Journal of Advanced Nursing, 67(1), 26-32. https://doi.org/10.1111/j.1365-2648.2010.05477.x