ISSN 2277-2685

IJPSL/Jan . 2022/ Vol-12/Issue-1/1-5

Partitioning tablets: A risky business

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ABSTRACT

Background and Aims: Patients have a variety of reasons and tools at their disposal to divide tablets. There are two types of tablets: scored and unscored. Scoring allows for easier splitting of the tablets, but patients still run the danger of medication dosage variations, hazardous or subtherapeutic dose exposure, or both, even if there are recommendations to avoid this. The researchers set out to find out if there was a statistically significant variation in the weight of the tablet halves when divided between various demographics and measuring systems.Methods: The study used a 3-factor complete factorial design with three runs. The participants were patients, caregivers, nurses, medical professionals, and pharmacists. The tools used were scissors, pill cutters, knives, and the subjects' hands. The medications tested were warfarin, clonidine, metoprolol, and losartan. Each component and its interaction was examined for the likelihood of uneven tablet splitting using linearized generalized models. In average, the greatest weight fluctuations after splitting were seen in clonidine with patients employing scissors, and the results showed that the differences in weight were above 15% and 25% of the theoretical weight. For variations more than 15% and greater than 25%, the total chance of non-equal pill splitting was 22.5%.

The results show that dividing tablets is not a good idea since no pill was divided into equal weight halves in this research.

Keywords: Pill splitting, Patient risk, Equal weight, quantity

INTRODUCTION

Medications are often divided into smaller pieces using a variety of implements, including pill cutters, scissors, knives, scalpels, and even one's bare hands (Arnet & Hersberger, 2010; Verrue et al., 2011). A small number of patients have reported splitting the pill in half using their teeth. A line or bisect, often called a score, appears on certain tablets. This typically means that the tablets may be divided in half, with the assumption that this will ensure that the active ingredient content or weight of each half is the same. This is not always the case, however; some bisects serve purely cosmetic purposes (Rowley F, s. f., 2006; Thompson, 2012), causing individuals to mistakenly believe that they are dividing a tablet into two equal halves when in fact the drug content and weight are not equivalent. Guidelines for splitting a pill as "adequately" as feasible are even provided by state bodies such as the US Food and Drug Administration (FDA, 2013). Finding out whether individuals can successfully divide tablets into equal halves when given alternative instruments to do so is the goal of this research.

MATERIAL AND METHODS

A supermarket was shopped for knives and scissors, while a nearby pharmacy was stocked with pill cutters, brand-name warfarin and

metoprolol, and generic versions of clonidine and losartan. After completing the informed permission form, subjects were recruited in the research if they met the inclusion criteria (medical physicians, nurses, pharmacists, patients, and caregivers) and the exclusion criteria (mental illness, Parkinson's disease, and any neuromotor condition). Every occupation has its own set of three courses. There were a total of 45 caretakers, 2 female and 1 male; 75 patients, 2 male and 1 female; 50 medical physicians, 2 male and 1 female; 32 nurses, all female; and 30 pharmacists, 1 male and 2 female. Using a device and an active principle, each splitting was performed three times. Each tablet was spherical. To divide them in half, metoprolol and warfarin each had one

score line. No indication of the score's aesthetic or practical value was provided in the insert. There was just one flat metoprolol.

Clonidine (0.1 mg), losartan (50 mg), metoprolol (25 mg), and warfarin (5 mg) are the individual dosages. We chose these four medications because, in the past, we called many hospitals to find out which ones divided them the most often, and we found that they all split them between themselves.

Here is how the weight reduction and variation from the theoretical weight were determined for each tablet piece, or "half": according to Verrue et al. (2011), the theoretical weight is equal to half of the tablet's weight before splitting. The percentage departure from this weight is calculated as (weight of the tablet piece - theoretical weight)/theoretical weight x 100. The weight loss is equal to half of the tablet's weight before splitting minus the total of the two halves. Since these are the reference values in industry recommendations for content uniformity testing, the limitations for variation from theoretical weight were established at 15% and 25% (United States Pharmacopeial Convention Inc., 2018).

Statistical analysis

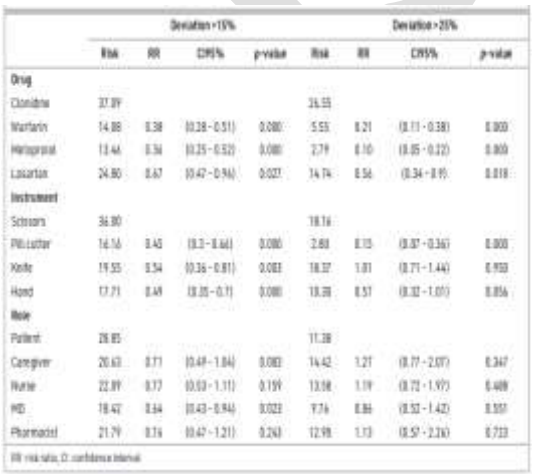
Using cluster robust estimate of variance for replications, statistical analyses were conducted using the generalized linear model, binomial family, and logarithmic link function. For deviations greater than 15% and 25%, the probability of improper pill splitting was determined using marginal estimates. Each component's impact on incorrect splitting was examined by calculating risk ratios (RR) with 95% confidence intervals (95%CI) for both the components alone and their interaction. Stata 16.1 (College Station, TX) was used to conduct the statistical analyses.

Concerns with ethics

This study was deemed to pose a minimal danger to participants in accordance with local standards, since the public was asked to handle sharp tools in order to break the tablets. Subjects were only included in the research once they completed an informed consent form, and the CES university ethics committee gave its approval (code 721).

RESULTS

For each given medicine and population, as well as any given instrument, Table 1 shows the danger of dividing pills into two equal halves. The same holds true for any given population, as well as any given drug and instrument. You may see a summary of the drugs, tools, and populations that are most likely to divide unevenly in Table 1. Aside from a nurse and patient who used the blade of the scissors as a knife, no one else who was asked about the process of dividing pills brought up the score line, which is supposed to make even splitting simpler. Tablet splitting according to Table 1 was the most challenging for both patients and nurses. Probability and risk ratio of uneven dosage distribution based on medication, device, and function.



hand, and on rare occasions they pounded the pill with the heel of the knife before slicing it in half with their bare hands; this happened with metoprolol and clonidine. Due to its diminutive size and lack of a score line, the clonidine pill proved to be the most difficult for all participants to divide.

After medical experts, nurses, and pharmacists, patients (who accounted for 28.85% of the population) had the most asymmetrical distribution of pills (with a departure of more than 15% of theoretical weight). The tool that produced the greatest uneven weights while breaking pills was the pill cutter, followed by the hand, knife, and scissors, with 36% of the total. Given its little size and absence of a score line, it should come as no surprise that clonidine exhibited the most fluctuation in the weight differential between the two halves after splitting. Losartan had the second-highest variance, after which warfarin and metoprolol came in. When the variation was more than 25%, the scissors and knives produced the most noticeable results. There was less chance of uneven splitting for the pill cutter. Caretakers, pharmacists, and patients all showed larger weight disparities for variations over 25% compared to the results for deviations over 15% described earlier. The scored pills could be divided more easily, albeit not evenly. The investigation found that halves did not always have the same weight.

Drugs and tools are contrasted in Table 2.

According to the results, these two variables are more likely to divide unequally, with larger weight deviation disparities. The reference used in this table was clonidine and scissors, which had the greatest chance of uneven splitting (55.56% for a deviation more than 15%). For deviations over 25%, the combination of clonidine and knife had the highest risk, although it was not statistically significant. The metoprolol and hand instance is the most severe. In addition, scissors had the greatest weight variation for losartan of any device. Due to the fact that cutting a tablet in half results in an uneven distribution of mass and sometimes even mass loss in one or both halves, Table 3 displays the average weight loss for the medication, instrument, and subject. It is clear that clonidine was the medication that resulted in the greatest weight loss upon splitting, irrespective of the instrument and patient. While some instances saw relatively small mass losses, others had losses of over half their mass. When this is factored in, the likelihood of patients not getting enough is too great. On average, 0.003 g of the 0.005 g warfarin was lost. Over half of the recommended dosage of the medicine has been consumed. When the drug's therapeutic index is taken into account, this weight loss becomes a major concern once again.

When using scissors or knives, the weight loss for any medicine was larger, averaging 0.010 g for scissors and 0.011 g for knives. Consideration of just clonidine or warfarin reveals that the quantity of medicine loss exceeds the drug amount. The pill cutter, on the other hand, dropped the least amount of weight overall, which is concerning since such large reductions might put patients at risk. Compared to patients, caregivers, and pharmacists, medical professionals and nurses lost more weight as a result of their subjects.

Risk and risk ratio of unequal pill splitting with respect to medication and instrument are shown in Table 2.

Drug	Instrument	Deviation >15%				Deviation >25%			
		Risk	RR	95%CI	p- value	Risk	RR	95%CI	p- value
Clonidine	Scissors	55.56	1.00			35.56			
	Pill cutter	35.56	0.64	(0.43 - 0.96)	0.032	8.89	0.25	(0.1 - 0.63)	0.003
	Knife	28.89	0.52	(0.28 - 0.98)	0.044	37.78	1.06	(0.69 - 1.63)	0.783
	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
Metoprolol	Pill cutter	4.44	0.08	(0.02 - 0.3)	0.000	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	62.22	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

Table 3. Mean and mean difference of weight loss.

	Mean (g)	Diff.	95%CI		p-value
Drug					
Clonidine	0.014	0.000			
Warfarin	0.003	-0.009	-0.020	0.002	0.105
Metoprolol	0.004	-0.008	-0.018	0.003	0.174
Losartan	0.009	-0.003	-0.016	0.009	0.599
Instrument					
Scissors	0.010	0.000			
Pill cutter	0.002	-0.004	-0.007	-0.002	0.003
Knife	0.011	0.002	-0.002	0.005	0.358
Hand	0.007	-0.002	-0.009	0.004	0.497
Role					
Patient	0.004	0.000			
Care giver	0.004	0.000	-0.001	0.001	0.497
Nurse	0.011	0.006	-0.003	0.016	0.198
MD	0.015	0.010	-0.004	0.025	0.167
Pharmacist	0.003	0.000	-0.001	0.001	0.638

CI: confidence interval

DISCUSSION

There was a discrepancy of more than 15% in the distribution of one pill out of five. Since this is more than the 15% suggested by USP Pharmacopeia's quality control, it warrants close examination (United States Pharmacopeial Convention Inc., 2018).

In addition, the weight loss was uniform throughout the pill halves and not equal to each other. Departures greater than 25% were further detected in this investigation. No matter how you slice it, the theoretical weight of the tablet was not achieved by any of the tablet halves. The quantity of medication or excipients was lost. This is significant because therapeutic failure or toxic consequences may result from the amount lost if half the dose is too much, as is the case with clonidine in Table 2. Cook et al. (2004) and Elliott et al. (2014) are among the few publications that have neglected to discuss how the active ingredient is distributed throughout the tablet. It should be remembered that the formulation includes both the medication and excipients (Haywood & Glass, 2011; Palcsó & Zelkó, 2018), and that the active component distribution in the tablet is difficult to determine due to their mixing (Shah et al., 2010). It is worth considering whether the patients are primarily consuming the medication or the excipients in light of this. The therapeutic objectives and patient safety might be jeopardized if, while dividing a losartan tablet, one half is larger and heavier than the other. Splitting the tablet increases the danger of the active component not dispersing evenly throughout the tablet, as previously noted (Shah et al., 2010; Veronin & Youan, 2004).

Also take into account the therapeutic index. Two medications with limited therapeutic windows were examined in this study: warfarin and clonidine (Johnson, 2012; Spiller et al., 2005). There may be as little as half of the entire quantity of these active substances, which means the adverse consequences might be fatal. We utilized clonidine pills with a weight of around 0.12 g in our experiment, even though the dosage was 0.00015 g. The presence of 0.11985 g of excipients is definitely shown. These levels suggest that the active component may be dispersed over the tablet or contained in just one area. Taking warfarin into account, the weight of the active component is 0.005g, whereas the whole tablet is around 0.2g. The pill contains excipients at a concentration of 97.5%. The patient is more likely to not get the prescribed dosage, and there is a larger chance of uneven distribution of the active component.

CONCLUSION

When it comes to dividing pills, there are a few unknowns. To begin, the tablet itself determines a number of variables, including the therapeutic index, the distribution of active ingredients, and whether the tablet is scored or unscored (the latter being more difficult to split and having a greater chance of splitting unequally). Second, some are context dependent; for example, how one splits a pill can change depending on their age or health. Third, the tool for splitting the tablet affects the effectiveness of certain of them. Given all of these factors, telling a patient to divide a pill seems like a ridiculous request. They run the danger of experiencing adverse effects or having their therapy fail if they do not get the correct dosage for their treatment. Since both are

problematic, it would be foolish to risk breaking up. Different formulations or extended-release tablets are other options that should be thought about.

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