

Evaluation of the content of Atenolol tablets divided with a knife and homemade machine cutter*

Avaliação do teor de Atenolol em comprimidos divididos com faca caseira e aparelho cortador

Evaluación de la proporción de Atenolol en comprimidos divididos con cuchillo casero y con cortador

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ABSTRACT

Objective: To evaluate whether the content of Atenolol on fragments of tablets in dosages of 100 mg, 50 mg and 25 mg broken into four parts with the aid of homemade knife and cutter unit tablets is different, depending on how the division is performed. **Methods:** The intact tablets were divided with a knife and with a homemade pill cutter device, and the concentrations of Atenolol were determined in all fragments. **Results:** No significant difference existed between the levels of Atenolol obtained after splitting the tablets with the homemade knife or the pill cutter device, although the division led to severe levels of dispersal among fragments. When divided in half, the dispersion of results was between 7% and 12.1%, and when divided into four parts, it was between 9.2% and 21.1%, indicating the possibility of compromising the effectiveness of treating patients regardless of how the division was made. **Conclusion:** The results indicated a greater dispersion than would be acceptable to guarantee a uniform dose received at each drug administration, regardless of the way the division was performed, either by phone or homemade knife cutter pills.

Keywords: Atenolol/analysis; Tablets/administration & dosage; Equipment and supplies; Pharmaceutical care/ Technology, pharmaceutical/instrumentation

RESUMO

Objetivo: Avaliar se o teor de Atenolol em fragmentos de comprimidos nas dosagens de 100 mg, 50 mg e 25 mg partidos em duas e quatro partes com auxílio de faca caseira e de aparelho cortador de comprimidos é diferente em função do modo como a divisão é realizada. **Métodos:** Os comprimidos íntegros foram divididos com faca caseira e com aparelho cortador de comprimidos, e os teores de Atenolol foram determinados em todos os fragmentos. **Resultados:** Não houve diferença significativa entre os teores obtidos, após divisão dos comprimidos com faca caseira ou com aparelho cortador, apesar da divisão levar a acentuada dispersão dos teores entre os fragmentos, na divisão em metade, a dispersão dos resultados deu-se entre 7,8% e 12,1%, e quando divididos em quatro partes, foi entre 9,2% e 21,1%, indicando a possibilidade de comprometer a eficácia do tratamento dos pacientes independente de como a divisão foi feita. **Conclusão:** Os resultados indicaram a ocorrência de dispersão maior do que a estabelecida para garantir uniformidade da dose recebida a cada administração do medicamento independente da forma de realizar a divisão, seja por meio de faca caseira ou com aparelho cortador de comprimidos.

Descritores: Atenolol/análise; Comprimidos/administração & dosagem; Equipamentos e provisões; Atenção farmacêutica; Tecnologia farmacêutica/instrumentação

RESUMEN

Objetivo: Evaluar si la proporción de Atenolol en fragmentos de comprimidos en las dosis de 100 mg, 50 mg y 25 mg partidos en dos y cuatro partes con la ayuda de un cuchillo casero y de un cortador de comprimidos es diferente en función al modo cómo se realiza la división. **Métodos:** Los comprimidos enteros fueron divididos con un cuchillo casero y con un cortador de comprimidos, siendo determinadas las proporciones de Atenolol en todos los fragmentos. **Resultados:** No hubo diferencia significativa entre las proporciones obtenidas, después de la división de los comprimidos tanto con cuchillo casero como con el cortador. A pesar de que la división lleve una acentuada dispersión de las proporciones entre los fragmentos, en la división por la mitad, la dispersión de los resultados se dió entre 7,8% y 12,1%, y cuando fueron divididos en cuatro partes, fue entre 9,2% y 21,1%, indicando la posibilidad de comprometer la eficacia del tratamiento de los pacientes independiente de cómo haya sido realizada la división.

Conclusión: Los resultados indicaron la ocurrencia de mayor dispersión de la establecida para garantizar la uniformidad de la dosis recibida en cada administración del medicamento independiente de la forma de realizar la división, sea por medio de un cuchillo casero o un cortador de comprimidos.

Descriptores: Atenolol/análisis; Comprimidos/ administración & dosificación; Equipos y suministros; Atención farmacéutica; Tecnología farmacéutica/instrumentación

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INTRODUCTION

Tablet splitting has been used for many years, as early as 1984, authors⁽¹⁾ studied 100 pills of each of the 14 brands of anti-hypertensive drugs marketed at the time, and obtained appropriate splitting in only two brands. Initially, pill splitting was justified to adjust the dose to the patient, in cases where the required dosage was not commercially available⁽²⁾, or when patients needed a different dose, such as in cases of treatment start⁽³⁾. Currently, it has been widely used, especially in the United States and in Canada, as a strategy of health plans to decrease drug costs, making physicians prescribe the medicine in its higher dosage so that it is split and used by patients⁽⁴⁻¹⁰⁾.

Researchers⁽¹⁷⁻¹⁹⁾ have demonstrated that tablet splitting is also a habit in health clinics in Germany, determined both by the price of the medication and by the dose offered in the formula and it occurs regardless being a scored tablet and of manufacturers recommendation for splitting or not; authors⁽²⁰⁾ reported that 30% of the pills provided in five community pharmacies in Holland were used split, by patients' initiative, either to have a lower dose or to make swallowing easier and 11% of the pills divided were not scored.

The economic aspect has always been an issue when access to drugs is mentioned, so much so, that health plans in the United States have refused to pay for medicines in smaller doses, when they are also sold in higher doses. However, many authors claim that the reduction of cost based on pill splitting strategy is not very effective and should not be the main focus of the issue⁽²¹⁻²⁴⁾ because when all patients are seen indiscriminately, we are no longer taking into account the natural limitations of certain groups, such as the elderly that often present visual and motor impairments that hinder their abilities to split tablets. Authors⁽¹¹⁾ have demonstrated in a study with 94 healthy volunteers splitting tablets of 25 mg of hydrochlorothiazide, that 41.3% of the split tablet portions deviated by more than 10% from the ideal weight, and that 12.4% of the volunteers deviated by more than 20%. The aspects connected with the characteristics of the different medicines have also been assessed by researchers, indicating that tablets that are not scored those with modified or extended release, enteric coated tablets, those with narrow therapeutic index, film-coated tablets and the association of pills and tablets should not be split⁽²⁵⁻²⁸⁾.

When the tablet is split, the possibility of moist incorporation and exposure to light become real, and these factors speed up degradation and oxidation of the formula components and may change the solubility of the drug, increase friability (loss of dust) and fragmentation of the halves and because of that they are considered extemporaneous⁽²⁴⁾, since manufacturers perform stability

tests in intact tablets. In some cases, the halves that are not taken should not be used, such as dipyron in which the process of degradation starts right after tablet splitting. Studies carried out to assess the "breakability" of scored tables to produce halves or fragments with greater uniformity of content⁽²⁹⁻³¹⁾, demonstrated that in the manufacturing validation processes, the hardness of the pills was a discriminating factor in the control of compression to increase uniformity both of the intact tablets and in the fragments.

The drug Atenolol is a selective B1 adrenergic receptor antagonist, used in the treatment of hypertension in a daily dose of 50 milligrams at the start of treatment, it has incomplete absorption, even though the greatest part of the absorbed portion reaches the systemic circulation, it is almost completely excreted, in the non-modified form, by the urine, and its half life is from five to eight hours. When the therapeutic response obtained is not satisfactory, the dose is increased to 100 milligrams⁽³²⁾. In Brazil, the forms of presentation recorded are 25 mg, 50 mg and 100 mg doses, traded as reference medications, generics and similar, and it is also made available to patients by the National Health System.

The objective of the present study was to assess the individual contents of the active substance (Atenolol) in the fragments obtained, after splitting tablets of Atenolol, in the 100 mg, 50 mg and 25 mg doses, in a material supplied by one of the many manufacturers from the Brazilian drug market, employing a kitchen knife and a tablet splitter available in drugstores. We have adopted for the assessment the acceptance criteria established by the Brazilian Pharmacopeia⁽³³⁾ to determine Dosage Uniformity of units as for the relative standard-deviation between the measurements.

METHODS

Sample

In the present study, round white scored tablets have been used in the 25 mg, 50 mg and 100 mg doses of Atenolol. The samples were from one of the manufacturers available in the Brazilian market.

Tablet splitting

We have used a kitchen knife to simulate the conditions in which this procedure is more commonly carried out by patients or their care takers, and we have also used a tablet splitter purchased in drugstores.

The tablets of each dose (100 mg, 50 mg and 25mg) have been split in half with the help of the kitchen knife, obtaining 20 fragments for each dose. The same action was taken in another 10 pills of each dose, using a tablet splitter, therefore, obtaining 20 fragments for each dose.

Next, 10 pills in the 100 mg and 50 mg doses were

divided into 4 parts with the help of the kitchen knife, obtaining 40 fragments for each dose. The same action was carried out in another 10 pills in the 100 mg and 50 mg doses with a tablet splitter, obtaining 40 fragments for each dose.

All tablet-splitting procedures were carried out by a lab technician with the supervision of a pharmacist.

Determining Atenolol content

Atenolol dosage was determined by ultraviolet absorption spectrophotometry, according to the Brazilian Pharmacopeia, 4th edition⁽³⁴⁾, freely using the acceptance criterion for intact tablets, of the Dosage Uniformity essay in which the highest value of Relative Standard Deviation (RSD) between the measures should not exceed 7.8%.

Sample preparation

Each fragment of the pill was dissolved in Methanol grade UV/HPLC-Spectroscopy VETEC® and heated at 60°C for 10 minutes, with occasional stirring. After the heating period, mechanical stirring was carried out for 15 minutes and then a solution was prepared in a 0.01% (p/v) methanol concentration.

The same procedure was carried out with ten intact pills of each dose (100 mg, 50 mg and 25mg), to ensure they match the content declared for each of the dosages indicated in the label.

Atenolol Analytical Curve

From the Reference Chemical Substance Atenolol FB, of the Brazilian Pharmacopeia (batch 1,028) the solution in the 0.2 mg/mL Methanol concentration was prepared. From this solution, methanolic solutions with concentrations of 40 µg/mL, 60 µg/mL, 80 µg/mL, 100 µg/mL, 120 µg/mL, 140 µg/mL and 160 µg/mL were prepared.

Spectrophotometry Analysis

Absorbance measurements have been obtained for each one of the standard solutions of Atenolol and of the sample solutions, using HP spectrophotometer® -

model UV8453 coupled to a computer and printer in a 275 nm wave length, using the quartz cuvette with 1 cm optical path. From these readings, the amount of Atenolol was calculated (C₁₄H₂₂N₂O₃) in the intact pills and fragments.

RESULTS

The results were summarized in Pictures (1 and 2) and Table (1). Picture 1 refers to analytical data of the contents, demonstrating that the analytical methodology employed met the criteria of good practices of the laboratory, obtained based on the methanolic solutions of the standard Atenolol through linear regression, carried out with the use of data analysis tools from Excell®, finding a 0.9993 ($p < 0.01$) correlation coefficient.

In picture 2 we can see the effects observed in the set of tablets studied regarding the band of accepted content loss in the fragments and the values obtained in the curve.

Table 1 shows the standard deviation of the dosage of Atenolol in intact pills and in the fragments of the pill according to the way splitting was obtained (kitchen knife or tablet splitter) in different dosages of the drug, showing that there are deviations above the limits that are considered safe to maintain the constancy of the received dose at each use.

DISCUSSION

The present study has not found significant differences between splitting the tablets with a kitchen knife or a tablet splitter for the 100 mg ($p = 0.123$), 50 mg ($p = 0.194$) and 25 mg ($p = 1.17$) doses, split into halves. When the 100 mg and 50 mg pills were split into four parts, there were no significant differences either ($p = 0.164$ and 0.39, respectively) between the split with kitchen knife and tablet splitter.

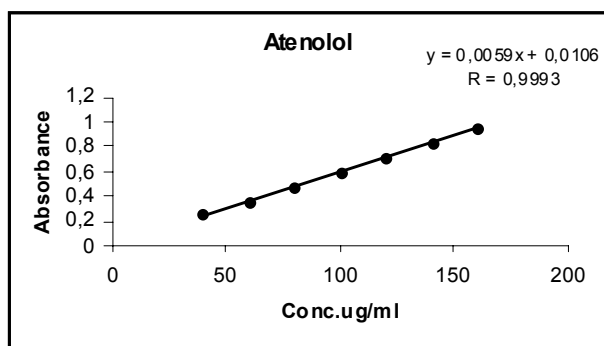
Although in these pills we have not found significant differences between the amount of active principles in the fragments obtained after splitting in half with the kitchen knife and the tablet splitter in the conditions used in the

Table 1 – Distribution of Relative Standard Deviation (RSD) for Dosage Uniformity, according to the number of splits and the form pills have been split in the 100 mg, 50 mg and 25 mg dose of Atenolol. Instituto Adolfo Lutz, São Paulo, 2008.

Pill dosage	Relative standard-deviation (%)				
	Intact	Kitchen knife		Pill-splitter	
		Two parts	Four parts	Two parts	Four parts
100 mg	2.27	7.55	12.98*	7.81	9.01*
50 mg	2.30	11.97*	20.71*	9.15*	12.02*
25 mg	2.87	12.70*	---	9.48*	--

—: not carried out

*: outside the acceptable band, up to 7.8%, according to F.Bras, 4th ed.



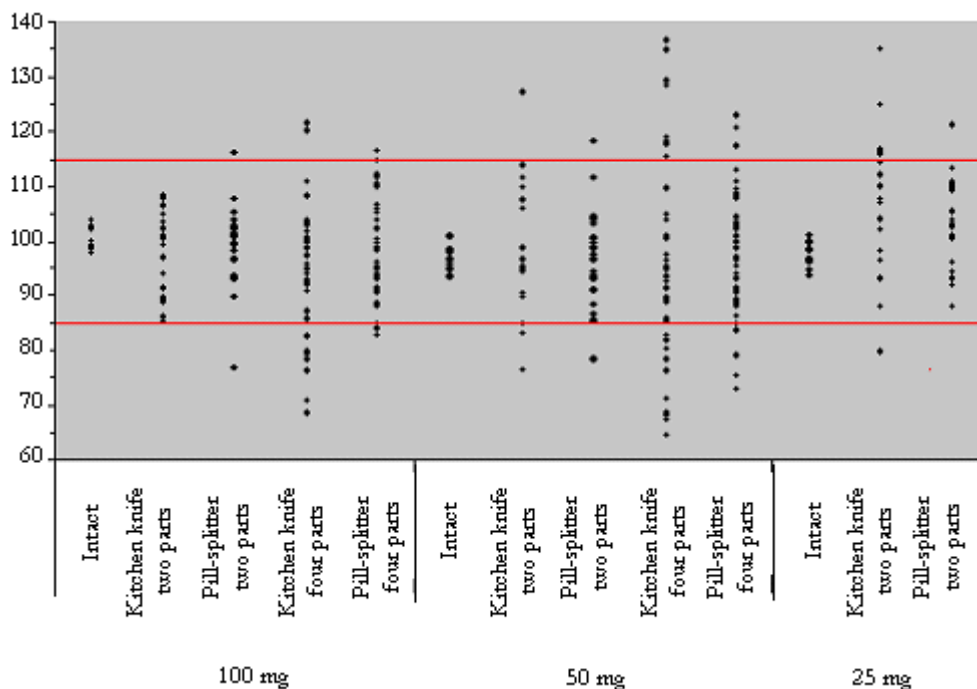
Picture 1 – Atenolol analytical curve in methanolic solution and spectrophotometry reading in the UV region, in $\lambda=275\text{nm}$. Instituto Adolfo Lutz, São Paulo, 2008.

laboratory, according to the data of Table 1, splitting in half showed less loss of the content in the fragments compared to the splitting into four parts. Both the use of the kitchen knife and the tablet splitter provided fragments with amount of active principles above the variation limit (7.8%) recommended by the Brazilian Pharmacopeia, to ensure that the dose received is not affected after each use of the medication, when compared to the contents obtained from the intact pills. In the graphic representation of the outcomes obtained by the present study (Picture 2), we can observe that a great deal of the contents remain in the critical zone of variation of $\pm 15\%$ (85 to 115%), which corresponds to an acceptable dose variation. However, there are points outside this acceptance band in which the patient will receive a dose of the medicine

outside the acceptable limit and therefore, there is the risk of hindering treatment efficacy.

In the present study, the remaining fragments have not been assessed for later use, however, the concern should be greater with these fragments rather than those that are used right after splitting because those are subject to exposure of their content to factors that affect stability /degradation of the drug, such as light, humidity, heat and also mass loss resulting from the splitting itself that can be exacerbated by the friction of fragments to a greater or lesser degree, according to the conditions in which they are stored until the next use.

Another aspect that could not be assessed by the present study, but that is essential to the success of splitting and should be taken into account, is patients' ability to split medicine properly, especially for elderly patients with motor and/or visual impairment, as already reported by several studies assessed here. We should keep in mind that the elderly may take many drugs together and, because of that, the correct understanding about which pill should be split is essential so that there are no errors regarding their use, with adverse results to patients. In the present study, we have seen that although the splitting occurred in controlled conditions within the laboratory, when the pill splitter is used there was a risk for injury to the operator, indicating that handling it requires attention and ability in the operation of inserting the pill and /or cleaning the device, since the blade is very sharp, and for that reason, choosing this device for splitting the pills should be carefully assessed.



Picture 2 – Dispersion of the DPR outcomes of the halves and quarters of pills, comparatively to the acceptance criteria established in the Brazilian Pharmacopeia. Instituto Adolfo Lutz, São Paulo, 2008.

CONCLUSION

We do not know the extension of the recommendation and use of split tablets in Brazil because studies in this area are still limited when we search the data base. The outcomes obtained in the present study indicate the occurrence of content loss higher than that established to ensure the uniformity of the received dose at each administration of the drug, regardless of the form splitting was performed, either with a kitchen knife or a tablet-splitter.

However, whenever this practice is recommended by prescribers, the patient should understand completely the splitting process, which is an important task of the Pharmaceutical Action, so that the treatment is not hindered.

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