Meta-analysis for bioequivalence studies: interchangeability of generic drugs and similar containing Hydrochlorothiazide is possible but not for those with Enalapril Maleate

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Abstract

Introduction: The generic drugs program provided a better population's access to medicines. To ensure interchangeability between a brand-name and generic or similar drugs is necessary that they are bioequivalent. With the growing number of generic drugs, it is common for patients to replace a generic to another or one similar. However, this exchange can not guarantee the maintenance of bioequivalence. To evaluate the safety interchangeability between different generic and similar drugs with Hydrochlorothiazide and Enalapril Maleate, a meta-analysis was carried out with several bioequivalence studies with these drugs. **Methods:** Data from bioequivalence of generic and similar drugs approved by the National Health Surveillance Agency (Anvisa) (drug regulatory agency in Brazil) were used. The compatibility of data from each study was analyzed and the determination of a confidence interval for the differences between the means of pharmacokinetic parameters, area under the curve (ASC0-t) and maximum plasma concentration (C_{max}), was made for each study by meta-analysis. **Results:** The interchangeability between the combinations of the three products with Hydrochlorothiazide was confirmed based on the obtained confidence intervals. For the drugs studied with Enalapril Maleate interchangeability has not been confirmed for 50% of the product comparisons. **Conclusion:** The exchange was established between the three products with hydrochlorothiazide. However, for the Enalapril Maleate half of the products studied are not interchangeable, considering they do not match the established intervals for bioequivalence tests, so the pharmacokinetics behavior and thus the effectiveness of the product may be changed.

Keywords: therapeutic equivalency, meta-analysis, antihypertensive agents, drugs generic, interchange of drugs.

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Introduction

When a reference drug loses its patent, the pharmaceutical companies that manufacture generic drugs submit processes requesting permission to produce copies of those reference drugs. No generic drug can be marketed before the regulatory agency – Food and Drug Administration (FDA) in the United States and the National Health Surveillance Agency (Agência Nacional de Vigilância Sanitária - Anvisa) in Brazil – determines that it has a performance as good as the reference drug, based on a series of criteria, such as bioequivalence tests. To consider that a generic drug is bioequivalent to a reference drug is to assume that they will have equivalent therapeutic effects.[1]

Aiming at assuring the offer of quality and low-cost drugs to the market and at promoting the population access to those products, in 1999 the generic drugs were established. Their interchangeability with the reference drugs is assured through pharmaceutical equivalence and bioequivalence tests.[2]

According to Anvisa, the generic drug is similar to a reference or innovating product, with which it is meant to be interchangeable, and is usually produced after the expiration or revoking of the patent protection or other exclusivity rights, once proved its efficacy, safety, and quality.[3]

The current legislation on bioequivalence assures interchangeability of generic drugs and some similar drugs with their respective reference drugs, but interchangeability between two generic or similar drugs has not been established.

According to Chow and Liu,[1] interchangeability between drugs relates to the change of one drug for another alternative product with the same pharmacokinetic characteristics, being, thus, safe and effective. However, patients often replace not only a reference drug for the corresponding generic or similar drug, but also one generic drug for another generic drug, or one generic drug for a similar drug. The reason for that is, when acquiring a generic drug, usually there is no instruction not to change the pharmaceutical company that manufactures the drug used.[4]

Considering that the consumption and number of commercially available generic drugs increase on a daily basis, to assure their quality, safety, and efficacy is a matter of public health. Thus, a meta-analysis aims at bringing together the results of several bioequivalence studies of a same active principle and generates information capable of evidencing or not the interchangeability between several formulations of a single drug.

One class of drugs that deserves special attention is that of the antihypertensive agents, because, in addition to being used in approximately 20% of the Brazilian population, there is currently in the Brazilian market a great number of different formulations of generic and similar drugs used for the treatment of arterial hypertension. Only for the two active principles selected for this study, 59 different products were found, many of them available in the Farmácia Popular program.[5] Considering that those drugs are of continuous use, mainly by older individuals, among whom the prevalence of arterial hypertension is extremely high, almost reaching 60%,[6] determining the interchangeability between drugs is paramount from the clinical view point.

Thus, this study consisted in applying a systematic review of several bioequivalence studies to assess safety in interchangeability between different generic and similar drugs containing Hydrochlorothiazide and Enalapril Maleate in their formulations, because those medications are frequently used by innumerous patients and are part of the Farmácia Popular program of the Brazilian Ministry of Health (MH).

Material and Methods

To apply the meta-analysis methodology, we used data from bioequivalence studies of generic and similar drugs approved and registered by Anvisa, under the following conditions:

I. The number of volunteers was not very different.

II. Same experimental design applied to all studies: crossover 2x2 (delineation for two periods and two formulations: reference and test).

III. Drugs whose parameters of bioavailability were within the limits accepted by Anvisa.

Regarding the selection of studies to be included in the analysis, an instrument was defined assuring the reproducibility of the form of selection (protocol of meta-analysis). The search was conducted in the database of bioequivalence studies of Anvisa, according to the criteria defined in the selection protocol and the above described requirements. The identity of the supporters of the studies and drug manufacturers tested were protected.

The variables analyzed were the following pharmacokinetic measures: area under the curve of plasma concentration versus time (AUC_{0-t}) and maximum plasma concentration observed (C_{max}). Two drugs are considered bioequivalent if the upper and lower limits of the 90% confidence interval of the AUC and C_{max} variables are within the 80% and 125% limits.[7]

To determine the differences of the means of the AUC_{0-t} and C_{max} pharmacokinetic parameters, the method proposed by Chow and Liu[8] of meta-analysis in bioequivalence studies was applied. A 90% confidence interval for the difference of the means was constructed for each possible combination of the drugs studied to assess the interchangeability between them.

A *Chi*-square test was applied to test the hypothesis of statistical homogeneity between data from several studies as a prerequisite to combine them in the same analysis.

The calculations required for the meta-analysis were performed in specific programs for statistic analyses, the Minitab®, version 14, and the Microsoft Excel 2003®.

Protocol for selecting the studies for the meta-analysis

The present protocol was developed prior to the selection of the studies comprising the meta-analysis, aiming at standardizing the methods for the inclusion/exclusion of studies.

The protocol was divided into three parts: the first, aiming at sorting the studies; the second, to assess the availability and adequacy of the studies; and the third, to check the epidemiological criteria, that is, if data were compatible with the analysis, from the view point of the study design, sample size, and population.

First part: The studies should:

I. Be the most recent and registered at Anvisa between 2003 and 2009.
II. Comprise the conclusion of bioequivalence.
III. Be analyzed and approved by Anvisa.
IV. Not be repeated (excluding the copies).

Second part:

I. The drugs should be part of the list of the Farmácia Popular program of the MH.
II. The drugs should be commercialized according to the list of the Chamber of Regulation of the Drug Market.
III. Data should be available at Anvisa for analysis.

Third part:

I. Data should be compatible for the analyses (epidemiological criteria), study design, sample size, and population studied.

The compatibility of the data of each study was assessed according to the criteria defined by Chow and Liu8 for meta-analysis. The studies meeting the previously described criteria were selected and included in the calculation of the meta-analysis.

Results

Meta-analysis of hydrochlorothiazide

For the meta-analysis of Hydrochlorothiazide, seven studies were selected. One of them could not be included in the combined final calculations, due to lack of homogeneity of the data of the reference drug, and three others were excluded because they were not part of the list of the Farmácia Popular program.[5] Thus, three studies were included in the final calculations of the meta-analysis. All of them used the same reference drug with different batches.

The 90% confidence intervals of the meta-analysis between the combinations of the test products 1, 2, and 3 for the C_{max} and AUC pharmacokinetic parameters are shown in Table 1 and 2, and Figures 1 and 2, respectively.

In Table 1 and Figure 1, the comparison between the three studies shows that the test drugs are very similar, except for a small difference in the rate of absorption (C_{max}) between products 1 and 3, in which the confidence interval was borderline (79.96% to 106.19%), classifying them as non bioequivalent. The other comparisons show no difference between the Hydrochlorothiazide formulations. On the other hand, in the analysis of the extent of absorption, assessed by AUC (Table 2 and Figure 2), no significant difference was observed between the several formulations, considering that the confidence intervals were between 85.88% and 117.26%.

Table 1 Confidence intervals of Cmax and conclusion of the combinations of studies in the meta-analysis of three pharmaceutical formulations containing Hydrochlorothiazide

	$LnC_{máx}$					
Comparison	D^*	Var (D^)*	Ratio**	Lower limit**	Upper limit *	Confirmation of bioequivalence
All studies	-0.0729	0.0005549	92.96825	89.39	96.69	Yes
Test 1 x 2	-0.0142	0.0063659	98.58760	86.31	112.61	Yes
Test 1 x 3	-0.0818	0.0072467	92.14990	79.96	106.19	No
Test 2 x 3	-0.0675	0.0066222	93.47007	81.62	107.04	Yes

*= logarithmic scale; **= original scale, $D\hat{}_{hh} = (\hat{Y}_{Th} - \hat{Y}_{Rh}) - (\hat{Y}_{Th} - \hat{Y}_{Rh})$.

Table 2 Confidence intervals of AUC and conclusion of the combinations of studies in the meta-analysis of three pharmaceutical formulations containing Hydrochlorothiazide

	LnASC					
Comparison	D^**	Var (D^)*	Ratio**	Lower limit**	Upper limit**	Confirmation of bioequivalence
All studies	-0.0150	0.000228	98.50439	96.05	101.02	Yes
Test 1 x 2	0.0263	0.006365	102.6627	89.88	117.26	Yes
Test 1 x 3	0.0096	0.007246	100.9668	87.61	116.35	Yes
Test 2 x 3	-0.0167	0.006622	98.34807	85.88	112.63	Yes

*= logarithmic scale; **= original scale, $D\hat{}_{hh} = (\hat{Y}_{Th} - \hat{Y}_{Rh}) - (\hat{Y}_{Th} - \hat{Y}_{Rh})$.

Figure 1. Confidence intervals of C_{max} of the combinations of studies in the meta-analysis of three pharmaceutical formulations containing Hydrochlorothiazide.

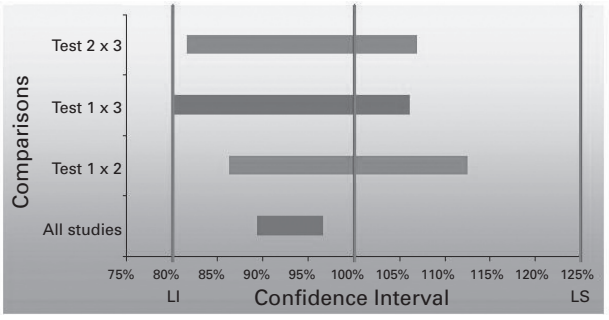
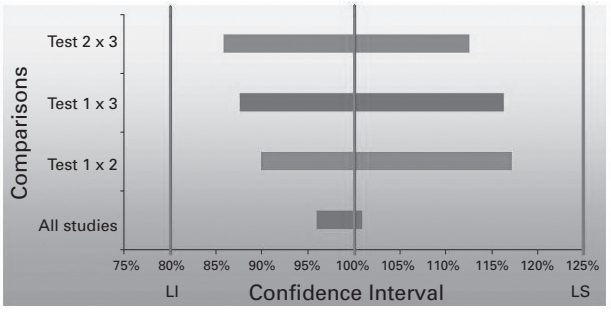


Figure 2. Confidence intervals of C_{max} of the combinations of studies in the meta-analysis of three pharmaceutical formulations containing Hydrochlorothiazide.



Meta-analysis of enalapril maleate

For the meta-analysis of the active principle Enalapril Maleate, 19 studies were selected, five of which were not part of the Farmácia Popular program,[5] four were repeated, one could not be included in the final calculations of the combination of studies, due to lack of homogeneity regarding the data of the reference drug, and another study because the reference drug was different. Thus, eight studies were included in the final calculations of the meta-analysis. All of them used the same reference drug of different batches.

The C_{max} and AUC parameters were analyzed in the logarithmic scale to test bioequivalence between the test and reference products. The C_{max} and AUC_{0-t} parameters were within the limits established by Anvisa in all studies.

The 90% confidence intervals of the meta-analysis between the combinations of test products 1 to 8 for the C_{max} and AUC pharmacokinetic parameters are shown in Tables 3 and 4, and Figures 3 and 4, respectively.

The analysis of C_{max} has shown a difference in the rate of absorption between the following products: T1xT3 (101.55% to 127.97%), T1xT5 (109.81% to 137.16%), T1xT6 (101.33% to 126.56%), T1xT7 (110.88 to 139.74%), T2xT3 (101.02% to 128.15%), T2xT5 (109.22% to 137.37%), T2xT6 (100.79% to 126.76%), T2xT7 (110.31% to 139.93%), T3xT8 (78.40% to 98.60%), T4xT5 (100.44% to 126.67%), T4xT7 (101.44% to 129.03%), T5xT8 (73.16% to 91.18%), T6xT8 (79.28% to 98.81%), and T7xT8 (71.80% to 90.30%). The confidence intervals exceeded the limits established for bioequivalence (Table 3 and Figure 3). In addition, the analysis of AUC has also shown that the 90% confidence intervals for the comparison between the following products were not within the limits of 80% to 125% (Table 4 and Figure 4): T1xT5 (107.39% to 127.36%), T1xT7 (109.03% to 130.19%), T2xT5 (104.61% to 124.72%), T2xT7 (106.22% to 127.47%), T6xT7 (106.36% to 126.80%), and T7xT8 (79.69% to 95.01%).

Discussion

Anvisa, in one of its resolutions regarding medicine dispensing, allows the pharmacist to replace the reference drug prescribed by the physician with the corresponding generic drug, except in case of explicit restriction by the prescriber. When the drugs are prescribed by their generic names, that is, according to the Brazilian Common Denomination (Denominação Comum Brasileira - DCB) or to the International Common Denomination (ICD), the pharmacist can dispense either the reference drug or the corresponding generic or similar drugs.[9]

However, it has not been established if a generic drug can be replaced by another generic drug. This is an important issue not only because the number of approved generics of the same reference drug can be very high – 67 in Brazil and greater than 160 in the United States – but also because those medicines are not identical regarding their inactive ingredients,

Table 3 Confidence intervals of Cmax and conclusion of the combinations of studies in the meta-analysis of eight pharmaceutical formulations containing Enalapril Maleate

	LnCmax					
Comparison	D^*	Var (D^)*	Ratio**	Lower limit**	Upper limit**	Confirmation of bioequivalence
All studies	0.0158	0.00015	101.59967	99.56	103.68	Yes
CI Test 1 x 2	0.0019	0.00489	100.19169	89.25	112.47	Yes
CI Test 1 x 3	0.1310	0.00489	113.99703	101.55	127.97	No
CI Test 1 x 4	0.0844	0.00501	108.80593	96.79	122.31	Yes
CI Test 1 x 5	0.2048	0.00452	122.72343	109.81	137.16	No
CI Test 1 x 6	0.1244	0.00452	113.24590	101.33	126.56	No
CI Test 1 x 7	0.2190	0.00489	124.47695	110.88	139.74	No
CI Test 1 x 8	0.0023	0.00452	100.23071	89.68	112.02	Yes
CI Test 2 x 3	0.1291	0.00518	113.77893	101.02	128.15	No
CI Test 2 x 4	0.0825	0.00530	108.59777	96.29	122.48	Yes
CI Test 2 x 5	0.2028	0.00481	122.48863	109.22	137.37	No
CI Test 2 x 6	0.1225	0.00481	113.02924	100.79	126.76	No
CI Test 2 x 7	0.2170	0.00518	124.23880	110.31	139.93	No
CI Test 2 x 8	0.0004	0.00481	100.03895	89.20	112.19	Yes
CI Test 3 x 4	-0.0466	0.00530	95.44629	84.63	107.65	Yes
CI Test 3 x 5	0.0738	0.00481	107.65493	96.00	120.73	Yes
CI Test 3 x 6	-0.0066	0.00481	99.34110	88.58	111.41	Yes
CI Test 3 x 7	0.0879	0.00518	109.19315	96.95	122.99	Yes
CI Test 3 x 8	-0.1287	0.00481	87.92396	78.40	98.60	No
CI Test 4 x 5	0.1204	0.00493	112.79112	100.44	126.67	No
CI Test 4 x 6	0.0400	0.00493	104.08063	92.68	116.88	Yes
CI Test 4 x 7	0.1346	0.00530	114.40273	101.44	129.03	No
CI Test 4 x 8	-0.0821	0.00493	92.11879	82.03	103.45	Yes
CI Test 5 x 6	-0.0804	0.00444	92.27733	82.65	103.02	Yes
CI Test 5 x 7	0.0142	0.00481	101.42884	90.44	113.75	Yes
CI Test 5 x 8	-0.2025	0.00444	81.67202	73.16	91.18	No
CI Test 6 x 7	0.0946	0.00481	109.91740	98.01	123.27	Yes
CI Test 6 x 8	-0.1221	0.00444	88.50714	79.28	98.81	No
CI Test 7 x 8	-0.2166	0.00481	80.52150	71.80	90.30	No

* = logarithmic scale; **= original scale; $D\hat{}_{hh} = (\hat{Y}_{Th} - \hat{Y}_{Rh}) - (\hat{Y}_{Th} - \hat{Y}_{Rh})$.

Table 4 Confidence intervals of AUC and conclusion of the combinations of studies in the meta-analysis of eight pharmaceutical formulations containing Enalapril Maleate

	LnASC					
Comparison	D^**	Var (D^)*	Ratio**	Lower limit**	Upper limit**	Confirmation of bioequivalence
All studies	0.0149	0.00009	101.50165	99.93	103.09	Yes
CI Test 1 x 2	0.0236	0.00288	102.38930	93.70	111.88	Yes
CI Test 1 x 3	0.0551	0.00288	105.66389	96.70	115.46	Yes
CI Test 1 x 4	0.0808	0.00295	108.41705	99.11	118.60	Yes
CI Test 1 x 5	0.1566	0.00266	116.94935	107.39	127.36	No
CI Test 1 x 6	0.0256	0.00266	102.58923	94.20	111.72	Yes
CI Test 1 x 7	0.1751	0.00288	119.14091	109.03	130.19	No
CI Test 1 x 8	0.0361	0.00266	103.67348	95.20	112.90	Yes
CI Test 2 x 3	0.0315	0.00305	103.19818	94.20	113.06	Yes
CI Test 2 x 4	0.0572	0.00312	105.88709	96.56	116.12	Yes
CI Test 2 x 5	0.1330	0.00283	114.22029	104.61	124.72	Yes
CI Test 2 x 6	0.0020	0.00283	100.19527	91.76	109.40	Yes
CI Test 2 x 7	0.1515	0.00305	116.36070	106.22	127.47	No
CI Test 2 x 8	0.0125	0.00283	101.25422	92.73	110.56	Yes
CI Test 3 x 4	0.0257	0.00312	102.60558	93.56	112.52	Yes
CI Test 3 x 5	0.1015	0.00283	110.68053	101.37	120.85	Yes
CI Test 3 x 6	-0.0295	0.00283	97.09015	88.92	106.01	Yes
CI Test 3 x 7	0.1200	0.00305	112.75461	102.92	123.52	Yes
CI Test 3 x 8	-0.0190	0.00283	98.11629	89.86	107.13	Yes
CI Test 4 x 5	0.0758	0.00290	107.86989	98.69	117.91	Yes
CI Test 4 x 6	-0.0553	0.00290	94.62463	86.57	103.43	Yes
CI Test 4 x 7	0.0943	0.00312	109.89130	100.21	120.51	Yes
CI Test 4 x 8	-0.0447	0.00290	95.62470	87.48	104.52	Yes
CI Test 5 x 6	-0.1310	0.00261	87.72108	80.62	95.45	Yes
CI Test 5 x 7	0.0186	0.00283	101.87394	93.30	111.23	Yes
CI Test 5 x 8	-0.1205	0.00261	88.64819	81.47	96.46	Yes
CI Test 6 x 7	0.1496	0.00283	116.13393	106.36	126.80	No
CI Test 6 x 8	0.0105	0.00261	101.05689	92.87	109.96	Yes
CI Test 7 x 8	-0.1391	0.00283	87.01754	79.69	95.01	No

* = logarithmic scale; **= original scale; $D^{\wedge}_{hh} = (\hat{Y}_{Th} - \hat{Y}_{Rh}) - (\hat{Y}_{Th} - \hat{Y}_{Rh})$.

which can vary from one version to the other. This area of bioequivalence is usually ignored, but it actually requires immediate attention.[1,10]

Regulatory agencies are based only on the criterion of mean bioequivalence and do not require the calculations of individual and population bioequivalence, which assure interchangeability in different approaches (prescribability and switchability). Thus, Chow and Liu8 have suggested a meta-analysis combining data of different studies of bioequivalence, aiming at providing a systematic review of bioequivalence between generic and reference products.

Figura 3. Confidence intervals of C_{max} of the combinations of studies in the meta-analysis of eight pharmaceutical formulations containing Enalapril Maleate.

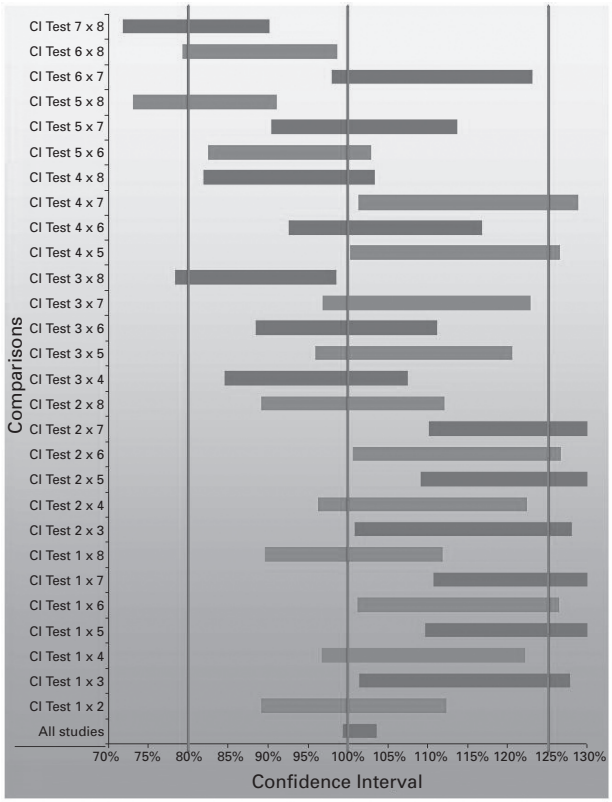
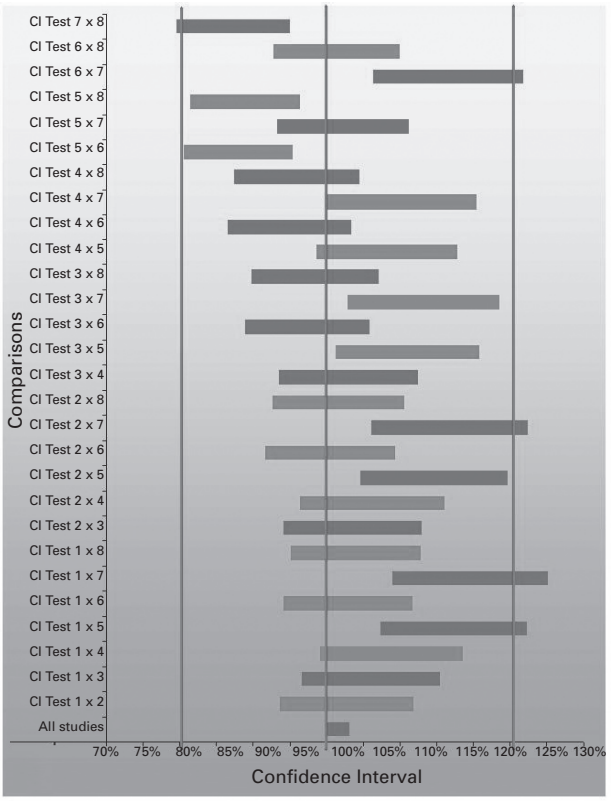


Figura 4. Confidence intervals of AUC of the combinations of studies in the meta-analysis of eight pharmaceutical formulations containing Enalapril Maleate.



Anvisa has all data relating to studies of bioequivalence and relative bioavailability already conducted for the registration of drugs in Brazil, which allow the use of meta-analysis to assess interchangeability between generics different from the reference drug.[4] Because generics have existed in Brazil for only ten years and because the requirement that similar drugs undergo bioequivalence studies has been even more recent (2003), that type of analysis is very useful for refining the criteria for granting registration or even as a tool for monitoring generic and similar drugs after registration. This can be especially applied to drugs that treat chronic diseases and are of continuous use, whose replacement for a new copy may not provide absorption levels required by the body to reach the aimed therapeutic results.

Meta-analysis has already been used in bioequivalence studies of immunosuppressive medications (mycophenolate mofetil) and antibiotics (amoxicillin) to support health professionals and patients in choosing between formulations of the same medicine.[4,11] Those studies have concluded that interchangeability was possible between the different formulations tested.

Aiming at analyzing interchangeability between the formulations of generic and similar drugs containing Hydrochlorothiazide and Enalapril Maleate, a systematic review was conducted with several studies of bioequivalence with those drugs submitted to Anvisa.

Meta-analysis of hydrochlorothiazide

The 90% confidence intervals for comparing test products 1, 2, and 3 obtained in the meta-analysis have shown that the test drugs had similar extent of absorption (AUC) values, because the confidence intervals were within the 80% to 125% limits.[7]

However, for the C_{max} parameter, a small difference was observed in the rate of absorption between products T1 and T3, in which the confidence interval was borderline (79.96% to 106.19%). According to the limits established by Anvisa, this hinders the conclusion of bioequivalence between formulations, and, consequently, their interchangeability. For the remaining combinations of the test products, the confidence intervals were within the limits, confirming the possibility of change between formulations.

In the case of Hydrochlorothiazide, the difference observed in the rate of absorption between products T1 and T3 should not have significant clinical repercussions in a patient's treatment, because of the following reasons: the difference was very small (0.04%); AUC was very similar; the drug has a wide therapeutic range; and its therapeutic effect does not depend on acute action, but on cumulative effect.

Meta-analysis of enalapril maleate

The comparison of the extent of absorption (AUC) values of some products containing Enalapril Maleate has shown significant differences between several products, considering that the confidence intervals were not within the 80% to 125% limits. 7 This has also been observed in the analysis of the rate of absorption (C_{max}) between products, in which several combinations had confidence intervals not within the established limits.

Regarding C_{max}, 14 of the 28 combinations of studies (50%) have concluded for non-bioequivalence between the tested formulations, and the most frequent were Tests 1, 2, 5, 7, and 8, which, according to data, were not interchangeable with four other drugs. None of the test products could be considered interchangeable with all the others. Regarding AUC, six of the 28 combinations (21%) have been concluded non-bioequivalent. Test product 7 was the most frequent, and non-interchangeability between other four copies was concluded. Although Enalapril Maleate is a very safe medicine, with a wide therapeutic window, the results have suggested that the replacement of a generic drug with another can determine differentiated therapeutic responses.

According to the instructions of Anvisa, the sum of those results hinders the conclusion of bioequivalence between the several formulations of Enalapril Maleate, indicating, thus, that those pharmaceutical products are not interchangeable. The clinical importance of those findings, in regard to safety and efficacy, still requires further investigation through clinical trials comparing the different pharmaceutical formulations of Enalapril Maleate. However, it is clear that a generic or similar drug cannot be always replaced by another. This is particularly important for a medicine of narrow therapeutic index, whose lack of therapeutic effect or presence of toxic effects can significantly impair efficacy and safety.

Conclusion

The results obtained indicate that, of the generic and similar antihypertensive drugs distributed by the Farmácia Popular program studied, the three Hydrochlorothiazide products can be safely interchanged. However, when assessing the interchangeability of the drugs with the Enalapril Maleate active principle, the products studied do not contemplate the intervals recommended by the national regulation. Thus, the pharmacokinetic response, and, consequently, the efficacy of the drug can be affected in some patients using different brands of generic or similar drugs for treating arterial hypertension and other cardiovascular diseases. Clinical trials comparing the therapeutic effects of different formulations are required for better assessing that question. New measures related to pharmacovigilance of drugs are necessary to assure a police of interchangeability between generic and similar drugs.

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