Assessing Bioequivalence of Antiepileptic Drugs: Are the Current Requirements too Permissive?

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Abstract - Purpose: In order to evaluate the permissiveness of current bioequivalence requirements for antiepileptic drugs we investigated how accurate C_{max} and AUC_{0-t} of generic antiepileptic drugs approved in Brazil are in comparison to reference products. **Methods**: Data collected from assessment reports of approved bioequivalence studies archived in the Brazilian regulatory agency in 2007-2012 were: geometric mean ratios and 90% confidence intervals (CI) for C_{max} and AUC_{0-t}, intra-subject variability (CV) of C_{max} and AUC_{0-t} and number of subjects. **Results**: The average difference in C_{max} and AUC_{0-t} between generic and reference products was 5% and 3%, respectively. Maximum deviation from 1.00 of the CI of C_{max} can achieve 15-20% (demonstrated in 27% of studies); for AUC_{0-t}, 25% of studies showed the deviation can be >10%. All studies that used adequate number of subjects for a 90% CI of 0.90-1.11 complied with it for AUC_{0-t}, except one of carbamazepine, but only 33% complied with it for both AUC_{0-t} and C_{max}. The CV was strongly correlated to the maximum CI deviation for AUC_{0-t} (CV of approximately 15% corresponding to deviation of 10%). Studies that presented maximum CI deviation ≤ 10 % together with CV ≤ 15% for AUC_{0-t} represented 65% of the total. Weaker correlation was observed for C_{max} and no correlation was seen between maximum CI deviation and number of subjects. **Conclusions**: Modification in legislation for bioequivalence of antiepileptic drugs is suggested, not only with constraint of AUC_{0-t} 90% CI to 0.90-1.11, but also with limitation of the CV to 15%, as to assure similar variance in pharmacokinetics and diminish the risk of critical plasma-level fluctuation when switching between generic and reference formulations. Although most generics presented differences ≤ 10% in AUC_{0-t} compared to their references, some narrow therapeutic index drugs displayed differences that could be clinically significant after product substitution.

INTRODUCTION

Pharmacotherapy is the first option of treatment in most epilepsy cases. Almost 70% of the patients rely on the use of antiepileptic drugs (AEDs) (1); therefore the financial burden of a life-time medication is a matter of concern. Although the price of the innovator is usually much higher than that of the generic product (2, 3), the substitution of the brand name product has been subject of debate over the past 20 years (4). In addition, AED products may need to be substituted for other reasons, such as commercial accessibility or availability in the public health service. The critical issue about epilepsy is that a single breakthrough seizure for a seizure-free patient will destroy what he or she may have gained over many years: independent living capabilities, self-confidence, driving license, good employment, loss of stigmatization; and will put he or she in risk of injury, hospitalization and death (5).

To receive marketing authorization, generic medicines need to have comparable bioavailability to the reference product demonstrated through bioequivalence (BE) studies. Test and reference products are considered bioequivalent if the limits of the 90% confidence interval (CI) of the geometric mean ratios (GMRs) of the pharmacokinetic (PK) parameters peak plasma concentration (C_{max}) and area under the plasma concentration versus time curve (AUC) are ≥ 0.80 and ≤ 1.25 (6-8).

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Two one-sided tests are used to analyze the PK parameter data (9). One test certifies that the PK parameters of the generic product are not more than 20% less than that of the reference product. The second test verifies that the PK parameters of the reference product are not more than 20% less than that of generic product. The 20% criteria was based on the experience of the United States Food and Drug Administration (FDA) medical experts who supported that a ± 20% difference in blood concentrations would not be clinically relevant (10). Thus the ratios test/reference and reference/test have to be not less than 0.8. The upper limit of the CI reaches up to 1.25 because, by convention, all data are expressed as test/reference ratios and the reciprocal of 0.8 is 1.25.

For AEDs, however, many neurologists and researchers worry that the BE CI limits are not small enough to keep control of the seizures and adverse effects (2, 5, 11, 12). In addition, the traditional average BE approach does not guarantee that in all individuals the response of the generic product will be ≥ 0.80 and ≤ 1.25 times that of the innovator response. If a drug product produces variable responses within a subject, known as intra-subject variability, it is merely a matter of enrolling more subjects in the study to make the CI meet the adequate boundaries.

A number of studies have reported that the rates of generics to references switchbacks are about 3 to 4-fold higher for AEDs than for non-AEDs (13-15) and that seizure episodes and adverse effects increased after reference product substitution (2, 5, 11, 12, 16, 17). While it is possible that a number of other factors may have played a role in those outcomes, it nevertheless incites concern among patients, prescribing doctors and the public health service toward product substitution in epilepsy treatment. In a survey carried out in Brazil, nearly 57% of epilepsy patients who switched AED formulations complained of increased number of seizures after the change and nearly 48% reported increased side effects (18). Although the percentage of seizures in the patients who did not change the formulations was not reported, such high values raised interest on the performance of AED products approved by the Brazilian Health Surveillance Agency (ANVISA). In this study we assessed the accuracy of generic AED products in comparison to their respective reference products based on the results of BE studies approved by ANVISA. Subsequently, we proposed further constraints to the current requirements for bioequivalence of AED products, taking in consideration the pharmacological characteristics of those drugs.

ABBREVIATIONS

AED – Antiepileptic Drug
ANVISA – Brazilian Health Surveillance Agency
AUC – Area under the plasma concentration versus time curve
AUC_{0-t} – AUC until the last sampling time t
BE – Bioequivalence
CI – Confidence Interval
C_{max} – Maximum plasma concentration
CV – Intra-subject variability or Coefficient of variation
FDA – Food and Drug Administration
GMR – Geometric mean ratio
PK – Pharmacokinetics

METHODS

Bioequivalence study selection and assessed data

BE studies were selected from a database maintained by the Bioequivalence Department of ANVISA. Rejected BE studies were excluded. For convenience, only studies with statistical assessment reports archived in the electronic database were selected (i.e., from 2007 to 2012).

Data assessed were C_{max} and AUC_{0-t} (AUC until the last sampling time t) GMRs and 90% CIs, intra-subject variability or coefficient of variation (CV) for C_{max} and AUC_{0-t} and number of subjects who completed the studies. Demographic data available were gender and health conditions (healthy subjects or patients). The ethnicity data were not available, only the countries where the clinical phases were conducted.

Bioequivalence evaluation

GMRs were taken from ANVISA's assessment reports and tabulated. The range of GMRs values was indicated. The absolute differences between the test and reference were calculated by subtracting the GMRs from 1.00, with percentage values displayed. For GMRs higher than 1.00 we used the reciprocal value, so that the scale would be symmetrical for comparison.

The maximum deviation from 1.00 of AUC_{0-t} and C_{max} GMRs was indexed based on the limits of the 90% CI. For upper limits higher than 1.00 the reciprocal value was used for the reasons already mentioned. Thus, values above 20% have not appeared in the graphs, even if the upper limit of the CI was 1.25. The maximum differences were arranged by AED in ranges of 5%. We also determined the number of studies for which the 90%

CI included 1.00 (i.e. the point where the two products are identical to one another). CV values were extracted from the reports and graphically presented in ranges of 10% for each AED.

Bioequivalence estimation for 90% CI of 0.90-1.11

For some regulatory agencies, the 90% CI is tightened to 0.90-1.11 for narrow therapeutic index (NTI) drugs (7, 19) or in case of AEDs (20). We calculated the number of subjects that should be enrolled in each study in order to have enough power (80%) for a 90% CI of 0.90-1.11, based on the CV of AUC_{0-t} and C_{max}. The formula used was (21):

$$N = (2 * S_w^2 * (Z_{1-(\beta/2)} + Z_{1-\alpha})^2) / (\ln 1.11)^2 \quad (1)$$

Where, S_w^2 is ln $(1 + CV^2)$, $Z_{1-(\beta/2)}$ is the inverse of the two-tailed Student's t-distribution (0.1) for 80% 1-β, and $Z_{1-\alpha}$ is the inverse of the two-tailed Student's t-distribution (0.05) for 5% α.

The number of subjects considered was the next higher even number of the estimated value; i.e., if N = 25.3 we rounded off to 26, if N = 26.3, we considered 28. The studies for which the number of subjects included in the statistical analysis was equal or higher than the considered value, we judged to be adequate. Among them, we identified those with 90% CI interval between 0.9 and 1.11.

Relationship of CV and number of subjects versus accuracy of NTI and non-NTI drugs

Correlation was investigated between CV and number of subjects of the studies versus maximum deviations of the PK parameters to evaluate how those variables affected the CI for NTI and non-NTI AEDs and if any constraint could be applied to them. The relationship was graphically illustrated and determined by calculating the Pearson correlation coefficient (r). Based on a list provided by Anvisa, the following were considered NTI drugs: carbamazepine, divalproex, phenytoin and oxcarbazepine (22).

RESULTS

Data of interest were accessible for 60 approved BE studies of AEDs, corresponding to 10 different substances and 58 formulations. Out of those, 55 were immediate drug release products, two prolonged drug release products (one carbamazepine and one divalproex), and one delayed drug release product (divalproex). The majority was solid oral formulations, only three were oral suspensions. Almost 60% of these products were manufactured in Brazil.

Only two studies were performed under fed conditions. All enrolled healthy volunteers. About 63% of confinements were conducted in Brazil and the others in India. Detailed demographic data were not provided in the assessment reports.

Bioequivalence evaluation

The GMR ranges and mean percent difference in geometric means for C_{max} and for AUC_{0-t} are shown in Table 1. The highest difference for AUC_{0-t} was 9.14% (lamotrigine); for 83% of studies the difference was below 5%. For C_{max}, 15% of studies had difference greater than 10% up to 13.14%.

90% CIs were also evaluated to see how much they deviated from 1.00. In 73.3% of BE studies C_{max} CI deviated ≤ 15% and in 40% of studies, ≤ 10%. For AUC_{0-t} the deviation from 1.00 was ≤ 10% in 75% of BE studies and ≤ 15% in 91.7% of studies (Figure 1). The CIs for C_{max} and AUC_{0-t} were 1.00 in 66.7% and in 85% of studies, respectively.The CV of the BE parameters of each study are plotted in Figure 2. Again the CV is in general higher for C_{max} than for AUC_{0-t}. For some substances such as carbamazepine, clonazepam, divalproex and oxcarbazepine the CV fluctuated from the 0-10%-range to the >30%-range, indicating inconsistent variability.

Bioequivalence estimation for 90% CI of 0.90-1.11

Considering the CV of AUC_{0-t} obtained in each BE study, 37 studies used adequate number of subjects for that interval. Among the 36 products that they represent, only one (carbamazepine) had AUC_{0-t} out of the interval, with an upper interval limit of 1.12. All products of clonazepam, phenobarbital, pregabalin and topiramate fit the tighter interval. Drugs for which the studies have not enrolled enough number of subjects and presented CIs beyond the 0.9-1.11 limits for AUC_{0-t} are carbamazepine, divalproex, gabapentine, lamotrigine, oxcarbazepine and phenytoin. Studies in which the number of subjects was adequate for both AUC_{0-t} e C_{max} summed 18. For six of them the CI of C_{max} was out of 0.90-1.11, referring to products of carbamazepine, phenytoin, lamotrigine and oxcarbazepine

Table 1. Geometric Mean Ratio Ranges and Percent Differences in Geometric Means of Bioequivalence Parameters obtained in Bioequivalence Studies of AED products.

Parameter	Geometric Mean Ratio Range	Mean Difference (%)[a]
C_{MAX}	0.87 - 1.14	4.84 ± 3.73
AUC_{0-t}	0.91 - 1.10	3.02 ± 2.10

[a]Mean ± SD

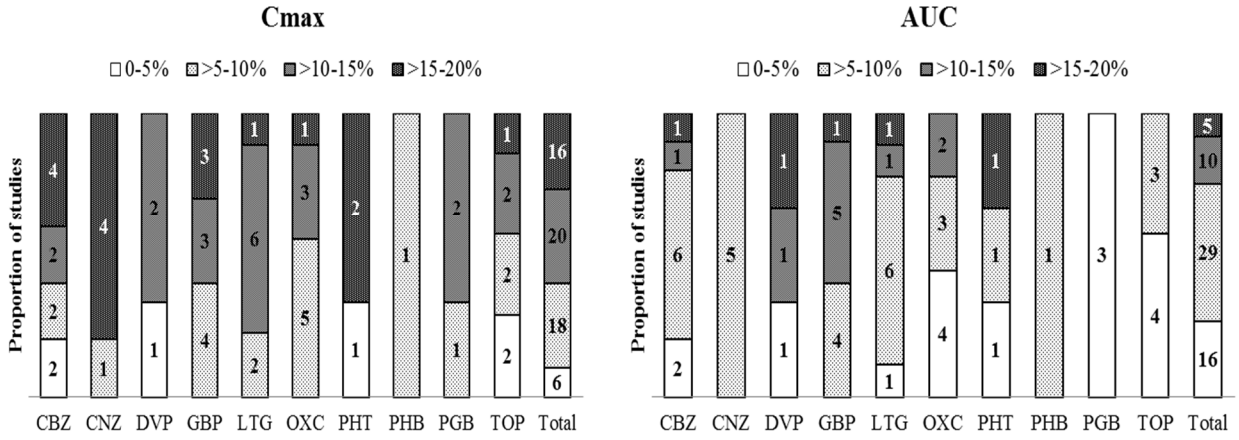

Figure 1. Maximum deviation of the 90% CI of C_{max} and AUC_{0-t} from BE studies approved by ANVISA. Results are arranged by drug in ranges of 5%. Number of studies within the range are indicated in the columns. Drug abbreviations: CBZ = Carbamazepine; CNZ = Clonazepam; DVP = Divalproex; GBP = Gabapentin = LTG: Lamotrigine; OXC = Oxcarbazepine; PHT = Phenytoin; PHB = Phenobarbital; PGB = Pregabalin; TOP = Topiramate.

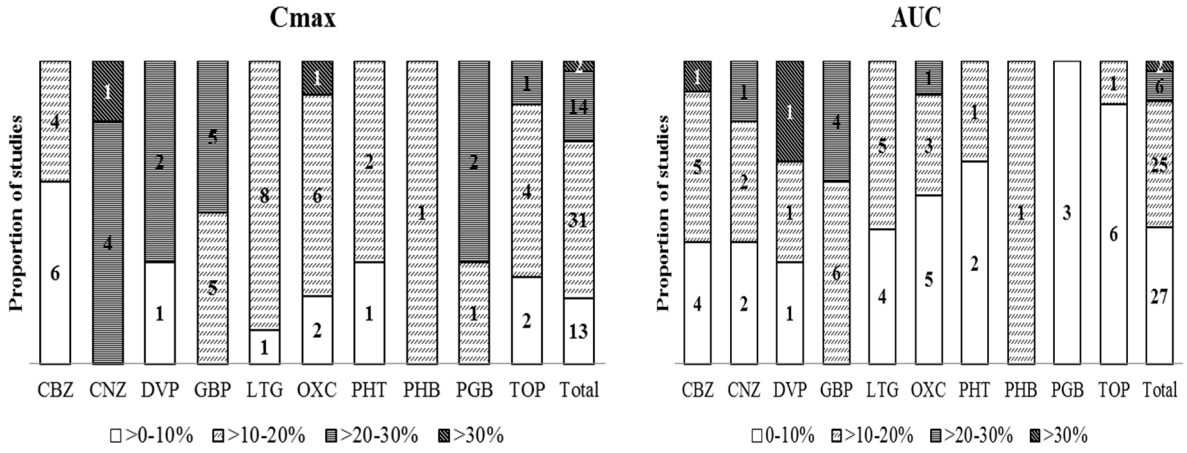

Figure 2. CV of C_{max} and AUC_{0-t} from BE studies approved by Anvisa. Results are arranged by drug in ranges of 10%. Number of studies within the range are indicated in the columns. Drug abbreviations: See Figure 1.

Relationship of CV and number of subjects versus accuracy of NTI and non-NTI drugs

Figures 3 and 4 show that for NTI as well as for non-NTI AED there was a strong correlation between the maximum deviation of CI versus the CV for AUC_{0-t}, but for C_{max} the correlation was weaker, especially for NTI drugs. For C_{max}, the CV values were mainly between 10 and 30% for non-NTI drug studies and between 5 and 20% for NTI drug studies, indicating more intra-subject variability in the absorption rate of non-NTI drug products. This would certainly reflect on the maximum deviation of CI, which was above 10% for almost 63% of non-NTI drugs and 56% of NTI drug studies. It was also observed that CV higher than 20% always led to deviations higher than 10%.

For AUC_{0-t}, almost 23 % of non-NTI and 28% of NTI drug studies presented CI with maximum deviation of AUC_{0-t} > 10%. The trend line equations (Figure 4) show that when the maximum deviation is 10%, the CV is nearly 15%. Approximately 71% of non-NTI drug studies and 72% of NTI drug studies presented CV of ≤15% for AUC_{0-t}, comprising all drug substances. Approximately 66% of non-NTI drug studies and 64% of NTI drug studies presented maximum deviation of the CI ≤ 10% together with CV ≤15% for AUC_{0-t}. Although very small, there was a tendency for negative correlation between maximum deviation and number of subjects enrolled in the BE studies.

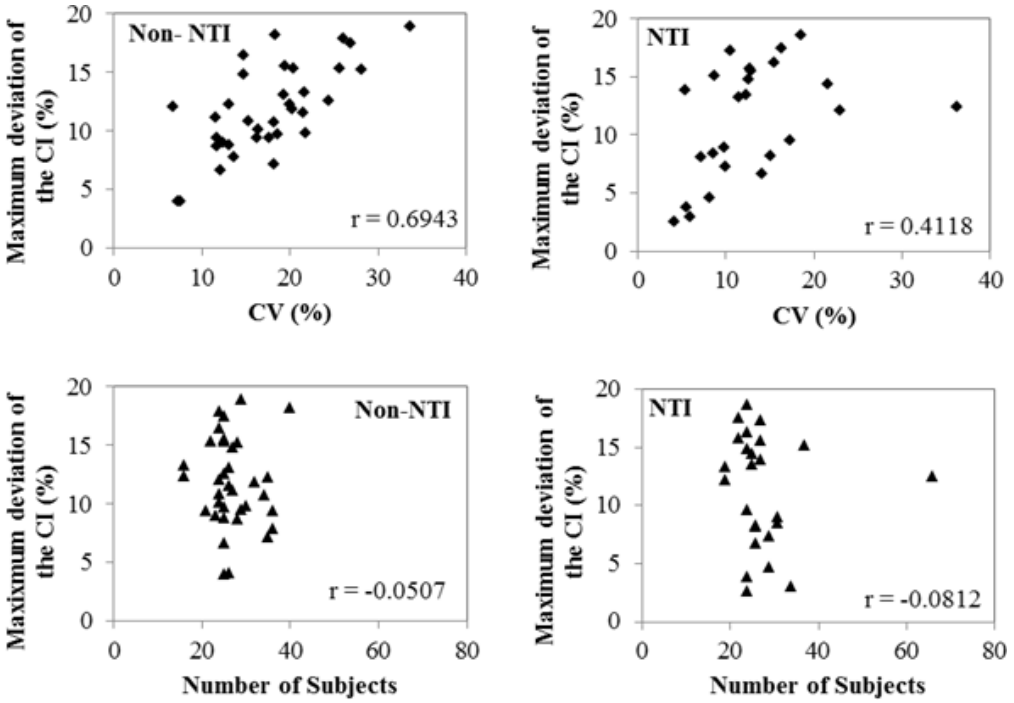

Figure 3. Maximum Deviation of the 90% CI of C_{max} and Their Correlation with CV and Number of Subjects for Non-NTI and NTI AEDs .

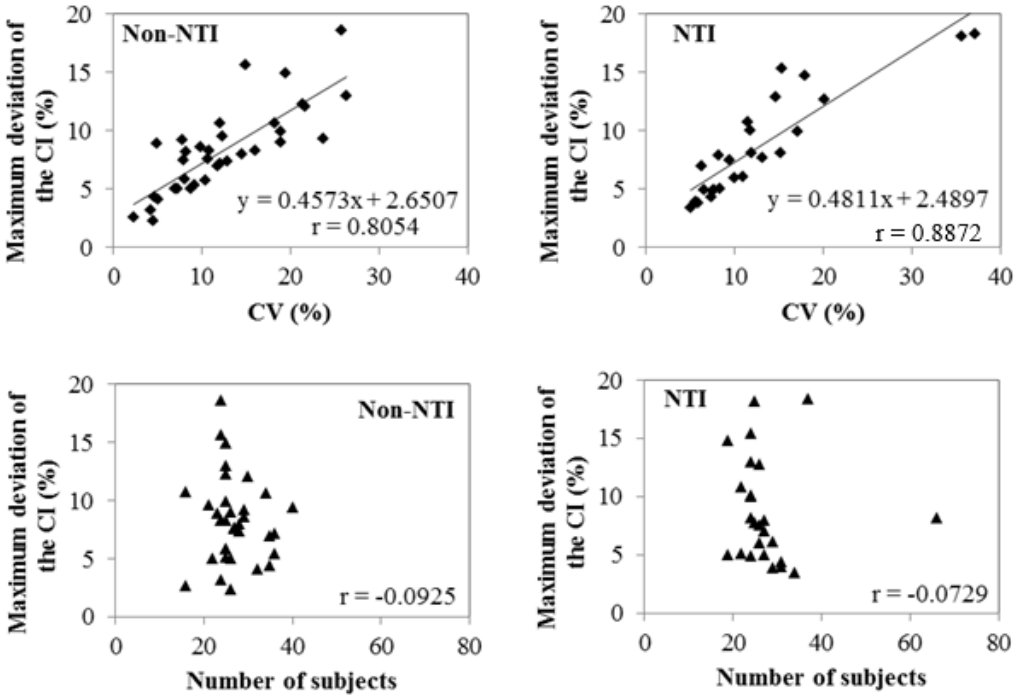

Figure 4. Maximum Deviation of the 90% CI of AUC_{0-t} and Their Correlation with CV and Number of Subjects for Non-NTI and NTI AEDs.

DISCUSSION

Although the number of BE studies of AED products with available assessment reports was small compared to other similar published surveys, when we look at the GMRs of C_{max} and AUC_{0-t} we see that our results are comparable to the others, in which generic and reference drug products were considered very similar (23-25). GMR, however, indicates the formulation performance in a sample of subjects. In BE studies, the target is the real mean ratio, since that BE result will be extrapolated to the whole population. For that, a CI is calculated, which is likely to contain the true population parameter (26, 27). When we compare our CI data to those of Krauss and co-workers, we observe that they found better results when they evaluated 258 AED BE studies approved by FDA (28). In their data set, mean AUC_{0-t} values differed by <10% in 83% and <15% in 98.8% of BE studies and C_{max} by 15 to 25% in 11% of studies. It is important to mention that in that study, the reciprocal values of GMRs higher than 1.00 were not used for deviation measurement. Hence values as high as 25% appear in the survey. For comparison, when we used the same calculation method as in Krauss et al., our results were 71.7% of BE studies with maximum difference of ≤10% and 91.7% of BE studies with AUC_{0-t} of ≤15%. For C_{max} the result would have been 28.3% of BE studies with maximum difference of 15-25%. It is well-known that C_{max} is a much variable parameter, since it is a single point estimation that depends, among other things on the time of sampling.

Drug characteristics, such as low oral bioavailability and extensive first pass metabolism, certainly play a role in the variability of product performance in vivo (29). However it was noted that among studies of the same drug substance, differences >10% in AUC_{0-t} were minority (except for divalproex and gabapentin), indicating more of a product performance issue than of a drug matter per se. Indeed, when we look at the CVs of the studies we see inconsistent variability for some drug substances, which means that they were highly variable in some BE studies (CV >30%) but not in others (29).

As already mentioned, the limits of the regular BE CI (0.80-1.25) in the bioavailability of generic and reference AEDs is controversial. In Denmark, generic formulations of AEDs (except for levetiracetam and benzodiazepines) must meet the 90% CI of 90-111% for C_{max} and AUC (20). The European Medicines Agency and the Health Canada advocates that the CI of AUC should be tightened to 0.90-1.11 and to 0.90-1.12, respectively, only for NTI drugs (7, 19), assuming that 10% or lower variation in PK would not lead to a clinically relevant difference. The FDA has been discussing the application of scaled average BE approach for NTI drugs, in which the 90% CI is tightened based on the CV of the reference product, with BE limits of 0.80-1.25 for CV higher than 21.42% (11, 30). If we take a look at our results, 75% of studies would fit the interval 0.90-1.11 for AUC_{0-t} and only 35% would fit it for both AUC_{0-t} and C_{max}. One could argue, though, that the number of subjects enrolled would have not given enough power to a tighter interval. Considering just the studies that used sufficient number of subjects to conclude BE in the 90% CI of 0.90-1.11 for AUC_{0-t}, only one was out of the interval, with an upper interval limit of 1.12 for carbamazepine. Therefore, all of them would have met the Canadian criteria. If a more restrictive criterion is applied, such as that of the Danish authority, according to which both AUC_{0-t} and C_{max} have to meet that interval, one third of studies that enrolled sufficient number of individuals would not demonstrate BE.

Even though we showed that in general the differences between generic medicines and their reference products approved by the Brazilian regulatory agency are small, it raises attention that six products of carbamazepine, divalproex (prolonged release), oxcarbazepine and phenytoin (corresponding to 24% of studies of NTI AEDs) were approved with differences that could be higher than 10% in the population (CI exceeded the limits of 0.90-1.11 for AUC_{0-t}). If adequate number of subjects to a tighter interval had been used in those studies, we would have a more precise scenario regarding the similarity of those AEDs.

It is reasonable to assume that fluctuations in plasma levels of AEDs could cause seizure/adverse effect in an otherwise controlled patient. Although such fluctuation can have a number of sources, one that particularly interests regulatory agencies is the quality of AED products available in the market/public health system. Therefore the question is, how much fluctuation is tolerable and how can this be controlled in terms of drug-product quality? So far, there are no studies in the literature to indicate precisely the level of fluctuation that will produce seizure/adverse effect. Thus the only alternative is to keep the fluctuation to a minimum. To this end, we believe that the safety of a switch between drug products should be also evaluated in terms of drug product performance variance within a given subject, by controlling the CV.

We showed that the CV values contributed strongly to the maximum deviation of CI of AUC_{0-t}, either for non-NTI or for NTI drugs. Because C_{max} is a very variable parameter, the correlation between CV and maximum deviation was weaker, but still significant. Surprisingly, no correlation was seen between the number of subjects enrolled in the studies and the maximum difference of a PK parameter in population. We think that the number of subjects used in each study was not considerably different to show any effect on the CI amplitude, but there was a tendency for a negative correlation, as expected.

Based strictly on the PK data presented in this survey, it seems that the regular BE CI criterion of 0.80-1.25 is too wide for the investigated AEDs. It would be conceivable to set the 90% CI of AUC_{0-t} within 0.90-1.11, for both NTI and non-NTI AEDs, because the majority of studies complied with that interval and all substances investigated had products with maximum difference ≤ 10%. Being more restrictive, the CV value for those drug products could be limited to 15%, which is approximately the CV obtained when the estimated maximum deviation is 10%, to avoid discrepancies in the variability of reference and generic formulations. Exceptions could be made for drug products whose references present intra-subject variability higher than 15%, and in those cases the CV value could be limited to not more than the CV of reference *versus* reference comparison. Considering the 60 studies evaluated here, 65% (comprising all drug substances) would comply with these requirements. The advantage of this proposal is that, by limiting the CV, we may be able to eliminate concerns about overpowered BE studies, where an exceeding number of subjects are enrolled in order to reach the required CI, because the CI would not be the only target to be achieved. In addition, replicate design studies would be needed only when there was a suspicion that the CV of the reference formulation was higher than 15% and not for every BE study as it is the case when scaled average BE approach is applied.

Those constraints, however, would not apply to C_{max}, since the majority of studies presented maximum deviations higher than 10% and a weaker correlation was seen between CV and the maximum deviation. Even though trend lines were to be traced in Figure 3, they would show that for NTI drugs the CV had to be nearly 9% in order to obtain a maximum deviation of 10%, which is a very low value if we consider that the precision of bioanalytical methods is allowed to be up to 15%. Thus, any further limitation imposed to C_{max}, without a known reason, could be too restrictive.

Finally, it is premature to suggest that the treatment failure reported by Guilhoto and co-workers (2009) is a result of differences larger than 10% in PK parameters and/or due to high variability of formulations, since other factors such as lack of treatment adherence and "nocebo" effect could have contributed as well. Further, it was not clear in their report if the switch was between reference and generic formulations or between generics; in the last case the difference in PK parameters after substitution can be much larger especially if the CI observed in the BE studies of the two generic formulations were shifted toward opposite BE limits.

CONCLUSIONS

In conclusion, our data indicate that generic and reference AED products registered in Brazil can be equally effective. Some products containing NTI drugs presented differences in AUC considered to be too high in other countries (i.e., >10%); for this reason we advise careful monitoring of patients when switching between formulations of carbamazepine, divalproex, oxcarbazepine and phenytoin. We also showed that constraining the AUC_{0-t} 90% CI to 0.90-1.11 and also limiting the CV to 15% in BE studies of AEDs is technically and commercially feasible since most AED products already adhere to the proposed requirements. Although we cannot state that such restrictions are necessary to guarantee treatment success, we believe that more restrictive regulations would enhance public confidence in product substitution once they would potentially improve the assurance that drug products deemed "bioequivalent" are indeed therapeutically equivalent and therefore interchangeable.

Disclosure of Conflicts of Interest

None of the authors has any conflict of interest to disclose. This article reflects the scientific opinion of the authors and not necessarily the policies of the regulatory agency.

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