

Interchangeability among carbamazepine formulations: the impact over epilepsy patients

Virgínia Paula Frade^{1*}, Maria José Nunes de Paiva², Isarita Martins³,
Whocely Victor de Castro¹, Vinícius Silva Belo¹, André Oliveira Baldoni¹,
Priscila de Freitas Lima⁴, Cristina Sanches¹

¹Federal University of Sao Joao del-Rei (UFSJ), Brazil, ²Federal University of Minas Gerais (UFMG), Brazil, ³Federal University of Alfenas (UNIFAL), Brazil, ⁴Barão de Mauá University Center, Brazil

The treatment of epilepsy is complex and a matter of concern is the interchangeability among different formulations available for antiepileptic drugs. To evaluate the effects of interchangeability among carbamazepine formulations on patients with epilepsy. This is a prospective cohort study that included adult outpatients diagnosed with epilepsy and under pharmacological treatment with carbamazepine. Before switching the brand/manufacturer, the “Interchangeable Pharmaceutical Product in the Treatment of Epilepsies” questionnaire was applied. The questionnaires “Adverse Events Profile” and Quality of Life in Epilepsy-31, so as the plasma carbamazepine concentrations, were evaluated before and after the brand/manufacturer switch. Physical-chemical tests aiming to assess tablets quality were performed in accordance with the Brazilian Pharmacopoeia 5th edition. The study population was composed by 14 patients (mean age: 44.6 years), with 10 of females. From those interviewed, 10 had no knowledge about the three antiepileptic drugs formulations available. The frequency of adverse event “problems with skin” increased ($p=0.023$) and “upset stomach” decreased ($p=0.041$) after the changeover. The adverse events profile was associated with only two quality of life domains: “energy/fatigue” ($p=0.048$) and “total score” ($p=0.018$). Divergent results between generic and reference formulations were observed in purity-water test (reference: 1.96%, generic: 4.84%) and dissolution test, in which the generic formulation presented 66.27 to 85.77% of carbamazepine dissolved after the third level. **Conclusions:** Objective differences before and after the brand/manufacturer switch were not observed, in spite of patients’ perceptions. Despite that, more studies in the field are necessary, especially on the interchangeability among generic antiepileptics, in order to better elucidate switching consequences on patients’ life.

Keywords: Antiepileptic drugs. Carbamazepine. Epilepsy. Generic medications. Interchangeability.

INTRODUCTION

The treatment of epilepsy is considered complex and its main purpose is to achieve the seizure control with the minimal toxicity as possible (Jarvie, Mahmoud, 2018). Among the antiepileptic drugs available, carbamazepine shows high levels of evidence in terms of efficacy,

being widely used worldwide (Gierbolini, Giarratanob, Benbadisc, 2016).

In clinical practice, a matter of concern relates to the interchangeability among the different formulations of commercially available antiepileptic drugs. Studies suggest that switching among formulations may increase the risks of seizures occurrence and intoxication, what might affect the patients’ quality of life (Guilhoto *et al.*, 2009; Trinkka, Kramer, Graf, 2011). Perucca *et al.* (2006) do not recommend switching from a reference to a generic drug in case of those patients who achieved seizure remission, as well as

*Correspondence: V. P. Frade. Federal University of Sao Joao del-Rei (UFSJ). Campus Centro-Oeste Dona Lindu. Rua Sebastião Gonçalves Coelho, 400. CEP 35501-296, Divinópolis, MG, Brazil. Phone: + 55 37 32211164. E-mail: virginiafrade20@yahoo.com.br
ORCID: <https://orcid.org/0000-0002-8769-3297>

avoiding switching among generic drugs from different manufacturers and among extended release formulations.

In Brazil, the regulatory agencies afford three different types of formulations, i.e., generic, similar and reference. According to the Brazilian Health Regulatory Agency (ANVISA), a generic drug is the one that contains the same active principle, in the same dose and pharmaceutical form, is administered by the same route and with the same dosage and therapeutic indication of the reference drug, presenting efficacy and safety equivalent to the reference drug product and may be interchangeable with it.

Patients usually switch not only a reference for a generic or similar drug, but also a generic for a similar, or a generic for another generic from a different manufacturer (Lopes, Neves, 2010; Brasil, 1993; Brasil, 1998). It occurs due to the way medications are acquired by the Brazilian National Health System, performed by public administration through bidding process. In this case, the most advantageous offer is processed and judged, prevailing the choice for the lowest price (Brasil, 1993).

Few Brazilian studies evaluate the switching among such formulations and its consequences, and yet do not show significant clinical differences (Guilhoto *et al.*, 2009; Trinkka, Kramer, Graf, 2011; Lang *et al.*, 2018; Lancker *et al.*, 2019). Thus, it is pivotal to evaluate the effects of interchangeability in clinical practice, mainly in case of patients relying on the Brazilian National Health System. Therefore, the main purpose of the present study was to evaluate the effects of interchangeability among carbamazepine formulations in patients with epilepsy before and after switching the formulations.

MATERIAL AND METHODS

Study design, ethical considerations and place of study

The present study was conducted at the Psychosocial Care Centre located in Divinópolis, southeast Brazil, which has approximately 18 thousand registered patients. The study project was approved by the Federal University

of Sao Joao Del-Rei's Ethics Committee. It is a before and after study in which patients followed at the Psychosocial Care Centre were approached in two different moments (study visits), both corresponding to the days of medical appointments. The time interval between the first and the second study visits varied from six to 12 months, which corresponds to the minimal amount of time necessary to a possible exchange of formulations to occur.

Patients' recruitment

Patients were considered eligible if they were in accordance with the following inclusion criteria: 1) \geq 18 years old; 2) in use of medications obtained through the Brazilian National Health System; 3) in use of carbamazepine for at least five weeks. The exclusion criteria were: 1) pregnant or breastfeeding women; 2) patients hospitalized at the time of the study.

Patients were instructed regarding blood sampling and questionnaires application, both performed by a trained researcher. Information about antiepileptic brand/manufacturer, batch number and expiration date were acquired. All patients included in the present protocol have signed the Written Informed Consent.

The protocol was repeated at the second study visit, approximately six to 12 months after the first visit, except for the application of the "Interchangeable Pharmaceutical Product in the Treatment of Epilepsies" questionnaire³, which was answered only at the first study visit. At this point, subjects whom: 1) were no longer taking the antiepileptic drug; or 2) did not switch among brands/manufacturers during the period, were excluded.

Variables and measurement sources

Study response variable consisted of brand/manufacturer switch and the explanatory variables were: adverse events, participant's quality of life, carbamazepine plasma concentration and quality of tablets distributed by the health system. The explanatory variables were measured through applied questionnaires, blood samples and carbamazepine tablets quality assays.

Questionnaires

The first questionnaire applied was the “Interchangeable Pharmaceutical Product in the Treatment of Epilepsies”, consisting of eleven questions (Guilhoto *et al.*, 2009). Seven out of the total refer to patients’ knowledge about the existing antiepileptic drugs formulations (reference, generic and similar). For these, a template was made, which was corrected and scored, ranging from 0 to 100% (the higher the score, the higher the patient understanding regarding the existing antiepileptic drugs formulations). The other four questions are related to evidences of clinical changes during the formulations exchanges in the last year, evaluated through questions about increased adverse events and/or crises. This questionnaire was answered only at the first study visit.

The second questionnaire was the “Adverse Events Profile” (AEP), which quantitatively evaluates the adverse events most frequently referred by the patients in use of antiepileptic drugs of the last four weeks, and has a total score of 19 to 76 points (high scores indicate high frequency of adverse events) (Martins *et al.*, 2011).

Finally, the third questionnaire was the “Quality of Life in Epilepsy-31” (QOLIE31), which assesses the quality of life of patients with epilepsy based on their perception also of the last four weeks. The participant classifies their quality of life and responds to questions about his disposition, nervousness, concern with crises, reduction of social activities, among others. The score varying from 0 to 100 points (with high values indicating better quality of life) (Da Silva *et al.*, 2007). The second and the third questionnaire were applied at the first study visit and repeated approximately after 6 months to 1 year.

Blood sampling

For both study visits, two serial blood samples were collected (3 mL each, at dosages intervals) in tubes with anticoagulant, with time interval of one hour between the first and the second sample. Plasma was separated in a centrifuge at 2000 rpm for 20 minutes and then kept at -20°C until analysis. The carbamazepine quantification was performed by High Performance

Liquid Chromatography (HPLC) with ultraviolet (UV). Acetonitrile was added to the plasma samples to precipitate the proteins. After centrifugation, 100 µL of the supernatant was transferred to a conical test tube and evaporated to dryness with nitrogen. The extract was reconstituted with 100µL of water and 10µL were used for chromatographic analysis. The mobile phase utilized was phosphate buffer pH 4.8 - acetonitrile-methanol (55:25:20 v/v/v) and the detection was performed with an ultraviolet detector at 210nm (Queiroz, Silva, Carvalho, 2000), with linear equation $y = 33336x + 12485$, $R^2 = 0.9962$. For values interpretation, the reference range of 4 to 12 µg/mL for carbamazepine plasma concentrations was adopted (Patsalos *et al.*, 2008).

Trough plasma concentrations calculation

The trough plasma concentration was predicted based on the following equation: $C_{\min} = e^{-[Kel(T_2 - T_1) - \ln C_1]}$, where Kel = elimination rate constant (calculated two hours after the drug administration); T_2 = hour according to the dosage frequency; T_1 = hour of the first blood sampling in relation to the administered dosage; $\ln C_1$ = natural logarithm of the plasma concentration from the first blood sampling (Winter, 2009).

Carbamazepine tablets quality assays

The quality of the tablets was assessed for a batch from one generic carbamazepine manufacturer distributed by the Brazilian National Health System in comparison to one national commercially available reference homologue. The reference chemical substance was obtained from Zhejiang Jiuzhou Pharmaceutical Co., Ltd, batch 10101632, 99.20% declared content percentage. All the assays carried out followed the Brazilian Pharmacopoeia 5th edition parameters, namely: weight, friability, hardness, uniformity of unit dosage (based on the weight variation method), dissolution, purity–water and assay. Method A was adopted for the assay, wherein drug quantification technique is ultraviolet spectrophotometry (Brasil, 2010a; Brasil 2010b).

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) software, version 19, was employed for data record and analysis. The data distribution pattern was analyzed based on normal quantile plots and Shappiro Test. In order to compare the profiles from concluding versus non-concluding patients, Chi-square or Exact Fisher Test was used for qualitative variables, and Mann-Whitney Test for quantitative variables. Regarding the adverse events profile between the two study visits, patients were classified as showing “improvement” or “worsening”. Therefore, the association between this outcome in relation to the variables “sex” and “schooling” was analyzed by means of the Chi-square Test or Fisher Exact Test. The association between the occurrence of improvement or worsening on adverse events profile and the trough concentrations and variables referred to quality of life was analyzed through the Mann-Whitney Test. Finally, the differences in values of all variables quantified before and after the brand/matrix switch were analyzed based on the Wilcoxon Test. For all the procedures, the level of significance adopted was of 5%.

RESULTS

Among the 18 thousand patients registered at the local Psychosocial Care Centre, 255 were in use of carbamazepine and, from those approached for the study, 23 were in accordance with the inclusion criteria and accepted to be enrolled in the present protocol. Six patients were no longer followed by the service during the study, and three had to be excluded for not switching the antiepileptic brand/matrix. Carbamazepine plasma concentrations were quantified from 11 patients who agreed to undergo the blood sampling procedure. Statistically significant differences were not found among the concluding and non-concluding patients

regarding age, sex, schooling degree, other medications in use, adverse events, AEP score, quality of life and carbamazepine trough concentrations. Among the concluding participants of both protocol steps, 10 were women, with mean age of 44.6 years (18-58 years) and seven did not finish the elementary school (Table I). Not every patient answered to all the applied questionnaires.

TABLE I - Patients sociodemographic data (n=14)

Variables	Frequency (n)
Sex	
Female	10
Male	4
Age (years)	
18-40	5
41-58	9
Schooling degree	
Illiterate	2
Elementary education (incomplete)	5
Elementary education	2
High school education (incomplete)	2
High school education	1

Regarding the “Interchangeable Pharmaceutical Product in the Treatment of Epilepsies” questionnaire answered by the 14 concluding patients, the mean number of right answers for the questions about their knowledge on antiepileptic available formulations was of 47.8%. Only six of the patients interviewed correctly answered 50% of the questions or more and the majority (n=10) did not know about the three types of formulations available for antiepileptic drugs (reference, generic and similar). Amongst the participants, four answered that

the first formulation produced is the reference drug, and only one person knew that the similar drug is its copy. The patients interviewed were well informed about what a generic drug is (n=12) and only one was not aware of its lower price. The quality of the generic antiepileptic drugs was considered equivalent to the reference medications by eight of the patients, yet only four knew details about the generic drugs packaging that characterize them. From the patients interviewed, nine reported receiving an antiepileptic formulation different from the one prescribed by the physician, and one of the patients did not answer to this question. During the last year, six of the patients assumed having switched the medication brand/manufacture, and from those, one patient reported an increase in seizure frequency and four reported increases in adverse events after such changes.

About adverse events, quality of life and carbamazepine plasma concentrations before and after the brand/manufacture switch, significant differences were observed only for adverse events, in which “problems with the skin” (p=0.023) presented an increase in frequency in the second study visit and “upset stomach” event (p=0.041) presented a decrease in frequency (Table II). Notwithstanding, a meaningful variability on carbamazepine plasma concentration values was observed, which fluctuated in and out the reference range after the brand/manufacture exchange (one moved from below the lower limit to within the reference range, one moved from within the reference range to below its lower limit, one moved from below the reference range lower limit to above its upper limit, and, at last, one moved from above the upper limit to below the reference range lower limit).

TABLE II - Adverse events profile, quality of life and carbamazepine plasma concentrations before and after the brand/manufacture exchange

Variable	First study visit Median (IQR)	Second study visit Median (IQR)	P value*
Adverse event (n=12)			
Unsteadiness	3.0 (3.0)	3.0 (3.0)	0.414
Tiredness	3.5 (1.8)	4.0 (1.0)	0.518
Restlessness	4.0 (1.0)	3.5 (1.0)	0.317
Nervousness +/- aggression	4.0 (1.0)	4.0 (0.0)	0.480
Feeling of aggression	3.0 (2.0)	2.5 (3.0)	0.589
Headache	3.0 (2.8)	2.5 (3.0)	0.705
Hair loss	1.0 (3.0)	1.5 (3.0)	0.581
Problems with skin	1.0 (0.0)	3.0 (3.0)	0.023
Double or blurred vision	3.0 (3.0)	4.0 (3.0)	0.618
Upset stomach	2.5 (3.0)	1.0 (1.8)	0.041
Difficulty in concentrating	4.0 (1.8)	4.0 (0.0)	0.524

(continues on the next page...)

TABLE II - Adverse events profile, quality of life and carbamazepine plasma concentrations before and after the brand/manufacturer exchange

Variable	First study visit Median (IQR)	Second study visit Median (IQR)	P value*
Trouble with mouth or gums	1.0 (3.0)	1.0 (0.0)	0.074
Shaky hands	3.0 (2.8)	3.0 (2.0)	0.260
Weight gain	2.0 (3.0)	1.0 (3.0)	0.129
Dizziness	3.5 (2.5)	3.0 (3.0)	0.258
Sleepiness	2.5 (2.8)	3.5 (3.0)	0.666
Depression	4.0 (1.0)	3.5 (3.0)	0.088
Memory problems	4.0 (1.0)	4.0 (1.0)	0.751
Disturbed sleep	4.0 (1.8)	4.0 (3.0)	0.180
Total Adverse Events	50.5 (16.0)	50.0 (8.5)	0.694
Quality of life (n=14)			
Seizure worry	16.0 (59.0)	40.0 (51.3)	0.307
Medication effects	16.67 (64.58)	16.66 (100.00)	0.398
Social function	27.50 (56.5)	30.00 (51.30)	0.838
Cognitive function	26.66 (69.45)	16.67 (33.34)	0.203
Energy/fatigue	30.00 (35.00)	2.50 (52.50)	0.229
Emotional well-being	42.00 (39.00)	26.00 (53.00)	0.241
Overall quality of life	51.25 (28.75)	38.75 (24.40)	0.637
Total score	34.35 (35.82)	22.85 (28.02)	0.347
C _{min} ^{ss} (n=11)	3.61 (6.14)	3.76 (5.95)	0.754

*Sign test; IQR = interquartile range; Reference range for carbamazepine plasma concentrations: 4-12 µg.mL⁻¹

It was observed that, among those responding to the AEP questionnaire before and after the brand/manufacturer switch (n=12), seven presented worsening and five presented improvement on adverse events total score. When evaluating which factors were associated

with such improvement or worsening, significant results were obtained for “quality of life”. Improvement on “Energy/fatigue” domain and on quality of life total score were associated with improvement on adverse events total score between the study visits (Table III).

TABLE III - Analysis on the association of the following factors: age, sex, schooling degree, quality of life, trough concentration and variation on reference plasma carbamazepine concentration with improvement/worsening of adverse events (n=12)

Variable	Adverse events total score			P value
	Unity	Improvement (n= 7)	Worsening (n =5)	
Age	Median (IQR)	50.0 (15.0)	51.0 (25.0)	1.000 ^a
Sex	n (%)			
Female		6 (85.7)	3 (60.0)	0.523 ^b
Male		1 (14.3)	2 (40.0)	
Schooling degree	n (%)			
Illiterate		1 (14.3)	1 (20.0)	0.308 ^c
Elementary education (incomplete)		3 (42.9)	1 (20.0)	
Elementary education		2 (28.6)	0 (0.0)	
High school education (incomplete)		0 (0.0)	2 (40.0)	
Quality of life	Median (IQR)			
Seizure worry		25.0 (61.0)	-20.0 (72.5)	0.149 ^a
Medication effects		0.0 (33.3)	0.0 (56.7)	0.755 ^a
Social function		0.0 (32.0)	-4.0 (62.5)	0.343 ^a
Cognitive function		0.0 (45.8)	-22.8 (54.6)	0.149 ^a
Energy/fatigue		0.0 (30.0)	-45.0 (70.0)	0.048^a
Emotional well-being		-12.0 (52.0)	-16.0 (44.0)	0.343 ^a
Overall quality of life		15.0 (40.0)	-17.5 (48.5)	0.073 ^a
Total score		5.5 (26.9)	-24.5 (35.0)	0.018^a
Trough concentration	Median (IQR)	-0.2 (14.3)	1.2 (4.2)	0.556 ^a
Variation on reference concentration	n (%)			
Yes		3 (42.9)	0 (0.0)	0.167 ^b
No		2 (28.6)	4 (80.0)	

IQR = interquartile range; ^aMann–Whitney Test; ^bFisher Exact Test; ^cChi-square Test.

At last, regarding the physical-chemical assays, all the evaluated carbamazepine tablets, reference and generics, coming from a batch distributed to Brazilian National Health System patients, they were all in agreement with the specifications from

the Brazilian Pharmacopoeia 5th edition in terms of weight, disintegration and friability. For hardness determination, the generic medication showed twice the mean hardness in comparison to the reference medication (Table IV).

TABLE IV - Weight, hardness, disintegration and friability for carbamazepine reference and generic tablets

Assays	Weight (%) (n=20)	Hardness (N) (n=10)	Disintegration (n=6)	Friability (%) (n=20)
Specifications	Limit of variation of $\pm 5.0\%$	*	Max disintegration time of up to 5 min for every unit	Weight loss $\leq 1.5\%$
Reference carbamazepine	Appropriate (-1.0 to 0.7)	54.30 \pm 9.04	Appropriate	Appropriate (0.6)
Generic carbamazepine	Appropriate (-1.2 to 1.1)	111.05 \pm 12.02	Appropriate	Appropriate (0.1)

* Informative Test.

Concerning weight variation and assay, every tablet presented results within the specifications. In dissolution analysis, the reference medication accomplished the established requirements at the second level, conducted with 12 units. Generic medication did

not present results within the specified limits at 15 min after fulfilling the third level, conducted with 24 units. As a result, generic carbamazepine tablets were considered in disagreement with the dissolution test (Table V).

TABLE V - Weight variation, assay and dissolution for generic and reference carbamazepine tablets

Test	Weight variation (AV) (mg)	Assay (%) (n=10)	Dissolution (%)	
			15 min	60 min
Specifications	10 units: AV not greater than L1 30 units: AV not greater than L1 and active compound amount from any single unit lower than $(1 - L2 \times 0.01) M$ -or greater than $(1 + L2 \times 0.01) M$.	92.0 to 108.0	L1: individual result within 45% and 75%; L2: average from 12 tested units within 45 and 75% and any single unit greater than 85%.	L1: resultado individual acima de 75%. L2: média de 12 unidades testadas acima de 75% e nenhum resultado individual inferior a 65%.
Reference carbamazepine	Appropriate AV=6.4* (294.3 to 301.1)	94.0	Appropriate 59.60 – 77.76*	Appropriate 84.12 – 104.76*
Generic carbamazepine	Appropriate VA=1.73* (286.4 to 293.4)	99.4	Inappropriate 66.27 – 85.77**	Inappropriate 77.16 – 111.33**

AV = acceptance value; L1=15; L2=25; *AV for 10 tested units; Dissolution: L1 = Level 1; L2 = Level 2; *After level 2 (12 tested units); **After level 3 (24 tested units).

For purity testing, the water content found for the reference medication was of 1.9% and 4.8% for the generic, with this value above the established (up to 3.0%).

DISCUSSION

The present study analyzed the effects of carbamazepine formulations interchangeability on patients with epilepsy followed by the public Brazilian

National Health System in a town from southeast Brazil. Although the patients' perceptions of differences before and after the antiepileptic brand/manufacturer switch, no significant results were found regarding quality of life, adverse events profile and plasma concentrations after the exchange.

Some studies describe the occurrence of adverse events, clinical deterioration and pharmacokinetic alterations after the substitution from a reference antiepileptic drug for a generic one (Desmarias, Beauclair, Margolese, 2011; Hensler *et al.*, 2013; Lancker *et al.*, 2019; Prasaja *et al.* 2019; Euen, Fadda, 2019). Conversely, literature regarding exchanges between different generic options is scarce (Krauss *et al.*, 2011). The formulations switch is a common practice in public health services, including by the patients themselves, who prefer the lowest price when choosing among commercially available options.

In the present study, this switching practice occurred with the majority of the participants. Although an increase in adverse events following the formulations exchange was reported in the first study visit, most of the patients had no knowledge about the three formulations (reference, generic and similar) available for the epilepsy treatment, having more information only on generics. Additionally, no significant differences were observed before and after the brand/manufacturer switch in terms of quality of life and plasma carbamazepine concentrations. Regarding the frequency of adverse events, differences were seen only for "problems with skin" (which increased) and "upset stomach" (which decreased) and this parameter improvement or worsening was not related with plasma concentrations, but with quality of life aspects.

Thus, although some physicians and pharmacists are still concerned about the generic substitution of antiepileptic, (Desmarias, Beauclair, Margolese, 2011; Euen, Fadda, 2019) in the present study we did not observe factors corroborating such hypothesis. However, dissonant results were found between generic and reference medications in terms of physical-chemical analysis. These results highlight the need to consolidate regulatory actions as a way to guarantee quality for the finished product, as established by the National Medicines Policy since 1998 (Brasil, 1998).

Among the physical-chemical properties analyzed, the reference medication quality was proved for every test, while the generic medication was in disagreement with some determinations, since it presented high water content and dissolution greater than the specified limit. Similar results were found by Tavares *et al.* (2016), in which the medication also presented rapid dissolution. Carbamazepine is known to have high dissolution variability for its tablets worldwide, and even for tablets from a given brand (Flicker, Eberle, Betz, 2011). This could be due to different polymorphs commercially available that present different properties and hence cause different results on dissolution profile and drug bioavailability and not due to errors during manufacturing workflow (Terra, Poppi, 2014). Four anhydrous polymorphs of carbamazepine were elucidated, in addition to various solvates, but only the P- monocyclic (III) form should be used as pharmaceutical ingredient. Nevertheless, excessive dissolution may cause toxic concentrations and harmful effects to the patient, once it may influence the drug pharmacokinetics (Tavares *et al.*, 2016). According to Medina *et al.* (2014), formulations performing differently in dissolution tests may also show differences in bioavailability.

Besides, differences in dissolution rates may be related to the composition from distinct excipients found in formulations (Al Ameri *et al.*, 2012). Polymorphic form can be the same for various commercially available presentations; however, different solvents and additives can be used for the crystallization of medication raw materials, what might result in altered solubility and dissolution profiles (Flicker, Eberle, Betz, 2011; Al Ameri *et al.*, 2012). Flicker, Eberle and Betz (2011) analyzed carbamazepine tablets with two types of commonly used fillers: mannitol (water-soluble) and microcrystalline cellulose (water-insoluble). They observed that mannitol, which dissolves very rapidly in comparison to carbamazepine, increased carbamazepine solubility and, subsequently, its release. Microcrystalline cellulose, in its turn, reduced the variability in drug release.

With regard to carbamazepine therapeutic monitoring, there were no statistically significant differences for concentration values before and after the brand/manufacturer switch. However, Desmarias

et al. (2011) discussed that most of the authors report increases in seizures and low drug concentrations with no changes in administered dosages for patients who switched from a reference to a generic formulations, despite not statistically proven. In terms of exchanges among generics, Krauss *et al.* (2011) suggest, based on bioavailability (AUC) and maximal concentrations (Cmax) differences modeled for 595 generic pairs, that switches among such formulations might cause greater differences in pharmacokinetics than a switch between generic and brand drug. Whatever, studies evaluating differences before and after exchanges among generics in patients with epilepsy are scarce. Atif, Azeem and Sarwar (2016) argue that the drug should be monitored both before and after the substitution. Bioequivalence investigations performed with reference and generics, though, are not clinical studies on efficacy and safety and may not be robust enough to evaluate the reasons behind changes in antiepileptics' plasma concentrations (Krauss *et al.*, 2011). In addition, contradictory inconclusive results are found in the studies published so far based on formulations switching (Rahman *et al.*, 2017). Therefore, more controlled studies based on brands exchanges are needed, including exchanges among generics themselves.

Adverse events profile is considered in clinical practice as a tool to monitor the epilepsy treatment, since health care professionals rely on patients' descriptions and clinical presentation. This is because most of the events are dose dependent and they are able to avoid, in this way, the therapeutic monitoring (Stepanova, Beran, 2015). However, it is presumed that clinical effects are better correlated to antiepileptics' plasma concentrations than to administered dosages (Patsalos *et al.*, 2008). In the present study, no association was found between adverse events total score and plasma concentration, but indeed was identified for quality of life. According to Perucca & Gilliam (2012), adverse events emerge as one of the most conspicuous predictors in health related to impaired quality of life. Yet, this parameter should not be isolated adopted when pursuing dose adjustment, i.e., plasma concentration values are also needed.

In spite of not finding consistent differences in terms of adverse events between study visits, it is noticed by both physicians and patients. In a study conducted by

Hensler *et al.* (2013) based on a structured questionnaire answered by antiepileptic drugs users, 23% of the respondents reported experiencing breakthrough seizures and 32% reported experiencing problems in general after switching for a generic medication. Also, it was observed that those patients who had never switched a brand for a generic antiepileptic drug were more concerned with this substitution than those who had already done such exchange.

It is believed, however, that the alarming matter regarding interchangeability among antiepileptic drugs is present in the context of patients with controlled seizures regardless of the formulation to be administered after the substitution, given that changes in plasma concentrations may occur even with bioequivalent medications. According to Jankovic & Ristic (2017), suggesting a generic, similar or reference drug should ideally occur only at the beginning of the pharmacological treatment, when the physician is responsible for indicating the most suitable option to the patient by choosing formulations consistently present in the market. Interchangeability is not recommended to seizure-free and adverse events-free patients, unless plausible reasons are present. If the switching is inevitable, it should be conducted with caution so as should be clinically monitored by using therapeutic drug monitoring as a follow-up tool.

To the best of our knowledge, this is the first study of therapeutic drug monitoring also evaluating tablets quality parameters. Moreover, in Brazil, there are no similar studies performed with first generation antiepileptic drugs, which are widely used by the population. The results obtained in the present study may contribute to clinical practice, in addition to promote the consolidation of regulatory actions. Likewise, there is a real need of pharmacovigilance by regulatory agencies nationwide and periodic evaluation on the effects of antiepileptic drugs interchangeability.

Some limitations should be pondered, namely, the small number of participants enrolled, what occurred due to the absence of medications at the local public health service during the study protocol. Furthermore, not all people taking carbamazepine at the time were included in the study and there were losses of follow-up. Additionally, the period between the two visits was

different for each participant, which may have interfered with the results found. However, this occurred because returns were scheduled by the health system itself, which varied for each patient.

Regarding the applied questionnaires, not every patient answered to all the questions and the presence of information bias (recall) should be considered. Besides that, several batches of carbamazepine in use over the same period were observed, a limitation that could not be avoided as it is a feature of public health system purchases. Finally, the tests performed to verify the carbamazepine tablets quality were conducted with only one batch of generics distributed by the Brazilian National Health System and such results may not be extrapolated to the other commercially available options.

Despite the limitations mentioned, it is worth mentioning the complexity and veracity of the present work, since it portrays the reality of people who use the Brazilian National Health System. Given this, the authors believe that the study was able to evaluate the treatment of epilepsy under the conditions to which participants were exposed at that time.

CONCLUSION

Differences in quality of life profiles and carbamazepine plasma concentrations before and after brand/manufacturer switch were not observed in the present study, in spite of the patients' perception. However, patients were not informed about the three existing antiepileptic formulations, especially about similar. In addition, discrepancies were found for physical-chemical analysis performed between the reference and a certain generic carbamazepine distributed by the Brazilian National Health System. Therefore, the present results suggest the need to expand studies in the field, especially on the interchangeability among generic antiepileptics, in order to better elucidate switching consequences on patients' life.

ACKNOWLEDGMENTS

The authors would like to thank the Psychosocial Care Centre staff from Divinópolis/MG, Dr. Patricia

Penido Maia (Federal University of Alfenas, Laboratory of Toxicant and Drug Analyses), "Fundação Ezequiel Dias" and FAPEMIG for the valuable contributions during the present research.

REFERENCES

- Al Ameri MN, Nayuni N, Kumar KGA, Perrett D, Tucker A, Johnston A. The differences between the branded and generic medicines using solid dosage forms: In-vitro dissolution testing. *Results Pharma Sci.* 2012;2:1-8.
- Atif M, Azeem M, Sarwar MR. Potential problems and recommendations regarding substitution of generic antiepileptic drugs: a systematic review of literature. *Springer Plus.* 2016;5(82):1-8.
- Brasil. Farmacopeia Brasileira. 5ª edição. Brasília: AGÊNCIA NACIONAL DE VIGILÂNCIA SANITÁRIA, 2010a. 548p. v.1.
- Brasil. Farmacopeia Brasileira. 5ª edição. Brasília: AGÊNCIA NACIONAL DE VIGILÂNCIA SANITÁRIA, 2010b. 546p. v.2.
- Brasil. Lei nº. 8.666, de 21 de junho de 1993. Regulamenta o art. 37, inciso XXI, da Constituição Federal, institui normas para licitações e contratos da Administração Pública e dá outras providências. *Diário Oficial da União, Brasília, seção 1, p.8269, 22 de junho de 1993.*
- Brasil. Portaria nº 3.916, de 30 de outubro de 1998. Dispõe sobre a aprovação da Política Nacional de Medicamentos. *Diário Oficial da República Federativa, Brasília, 30 outubro de 1998.*
- Da Silva TI, Ciconelli RM, Alonso NB, Azevedo AM, Westphal-Guitti AC, Pascalicchio TF, et al. Validity and reliability of the Portuguese version of the quality of life in epilepsy inventory (QOLIE-31) for Brazil. *Epilepsy Behav.* 2007;10(2):234-241.
- Desmarias JE, Beauclair L, Margolese HC. Switching from Brand-Name to Generic Psychotropic Medications: A Literature review. *CNS Neurosci Ther.* 2011;17(6):750-760.
- Euen BJ, Fadda HM. Community pharmacists' understanding and perceptions of FDA therapeutic equivalence standards. *Res Social Adm Pharm.* 2019;15(1):77-83.
- Flicker F, Eberle VA, Betz G. Variability in commercial carbamazepine samples – Impact on drug release. *Int J Pharm.* 2011;410(1-2):99-106.
- Gierbolini J, Giarratanob M, Benbadisc SR. Carbamazepine-related antiepileptic drugs for the treatment of epilepsy

- a comparative review. *Expert Opin Pharmacother.* 2016;17(7):885-8.
- Guilhoto LMFF, Alexandre V, Martins HH, Santos CM, Lin K, Silva ARCO, et al. Há riscos na utilização de diferentes formulações de drogas antiepilépticas? Relato da ABE através de entrevista de pessoas com epilepsia. *J Epilepsy Clin Neurophysiol.* 2009;15(1):41-49.
- Hensler K, Uhlmann C, Porschen T, Benecke R, Rosche J. Generic substitution of antiepileptic drugs – A survey of patients' perspectives in Germany and other German-speaking countries. *Epilepsy Behav.* 2013;27(1):135-139.
- Jankovic SM, Ristic DI. Is bioavailability altered in generic versus brand anticonvulsants? *Expert Opin Drug Metab Toxicol.* 2017;11(3):329-332.
- Jarvie D, Mahmoud SH. Therapeutic Drug Monitoring of Levetiracetam in Select Populations. *J Pharm Pharm Sci.* 2018;21(1s):149s-176s.
- Krauss GL, Caffo B, Chang YT, Hendrix CW, Chuang K. Assessing bioequivalence of generic antiepilepsy drugs. *Ann Neurol.* 2011;70(2):221-228.
- Lancker GV, Bortel LV, Delafontaine B, Boussery K, Swart E, Chahbouni A, et al. Switchability of gabapentin formulations: a randomized trial to assess bioequivalence between Neurontin and gabasandoz on the individual subject level. *Clin Pharmacol Ther.* 2019;106(1):195-202.
- Lang JD, Kostev K, Onugoren MD, Gollwitzer S, Graf W, Muller T, et al. Switching the manufacturer of antiepileptic drugs is associated with higher risk of seizures: a nationwide study of prescription data in Germany. *Ann Neurol.* 2018;84(6):918-925.
- Lopes RA, Neves FAR. Metanálise de estudos de bioequivalência: a intercambiabilidade de genéricos e similares que contêm Hidroclorotiazida é possível, mas não àqueles com Maleato de Enalapril. *J Bras Nefrol.* 2010;32(2):173-181.
- Martins HH, Alonso NB, Vidal-Dourado M, Carbonel TD, de Araújo Filho GM, Cabloco LO, et al. Are adverse effects of antiepileptic drugs different in symptomatic partial and idiopathic generalized epilepsies? The Portuguese-Brazilian validation of the Liverpool Adverse Events Profile. *Epilepsy Behav.* 2011;22(3):511-517.
- Medina JR, Salazar DK, Hurtado M, Cortés AR, Domínguez-Ramírez AM. Comparative in vitro dissolution study of carbamazepine immediate-release products using the USP paddles method and the flow-through cell system. *Saudi Pharm J.* 2014;22(2):141-147.
- Patsalos PN, Berry DJ, Bourgeois BF, Cloyd JC, Glauser TA, Johannessen SI, et al. Antiepileptic drugs – best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. *Epilepsia.* 2008;49(7):1239-1276.
- Perucca E, Albani F, Capovilla G, Bernardina BD, Michelucci R, Zaccara G. Recommendations of the Italian league against epilepsy working group on generic products of antiepileptic drugs. *Epilepsia.* 2006;47(S.5):16-20.
- Perucca P, Gilliam FG. Adverse effects of antiepileptic drugs. *The lancet neurology.* 2012;11(9):792-802.
- Prasaja B, Harahap Y, Lusthom W, Hardiyanti, Sinandang T, Yusvita LY, et al. Comparative bioavailability of two valproic acid delayed-release tablets in healthy volunteers with tighter acceptance criteria to anticipate breakthrough seizures. *Pharm Sci Asia.* 2019;46(1):12-18.
- Queiroz MEC, Silva SM, Carvalho D. Simultaneous determination of six antiepileptic drugs by high-performance liquid chromatograph. *Rev Bras Toxicol.* 2000;13(2):35-40.
- Rahman MM, Alatawi Y, Cheng N, Qian J, Plotkina AV, Peissiq PL, et al. Comparison of brand versus generic antiepileptic drug adverse event reporting rates in the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS). *Epilepsy Res.* 2017;135:71-78.
- Stepanova D, Beran RG. The benefits of antiepileptic drug (AED) blood level monitoring to complement clinical management of people with epilepsy. *Epilepsy Behav.* 2015;42:7-9.
- Tavares G, Pires CC, Souza JD, Tasso L. Avaliação do polimorfismo e Perfil de Dissolução de Formulações de Carbamazepina. *Sci Cum Ind.* 2016;4(3):161-166.
- Terra LA, Poppi RJ. Monitoring the polymorphic transformation on the surface of carbamazepine tablets generated by heating using near-infrared chemical imaging and chemometric methodologies. *Chemom Intell Lab Syst.* 2014;130:91-97.
- Trinka E, Kramer G, Graf M. Requirements for generic antiepileptic medicines: a clinical perspective. *J Neurol.* 2011;258(12):2128-2132.
- Winter ME. Part I Basic Principles-Maximum and Minimum Plasma Concentrations. In: WINTER, M. E. *Basic Clinical Pharmacokinetics.* India: Wolters Kluwer Health, 2009, p.54-57.

Received for publication on 10th August 2019

Accepted for publication on 16th March 2020