Epilepsy Research 151 (2019) 75–77

Contents lists available at ScienceDirect

Epilepsy Research

journal homepage: www.elsevier.com/locate/epilepsyres

Brand-to-generic oxcarbazepine switch – A prospective observational study

Magdalena Bosak*, Agnieszka Słowik, Tomasz Dziedzic

Dept. of Neurology, Jagiellonian University Medical College, Krakow, Poland

ARTICLE INFO

Keywords:
Antiepileptic drugs
Oxcarbazepine
Generic
Substitution

ABSTRACT

Purpose: To determine the clinical outcomes of brand-to- generic oxcarbazepine (OXC) switch in patients with epilepsy.

Methods: This prospective observational study included 103 patients treated with OXC in the tertiary outpatient epilepsy clinic. In 2016 the price of the brand-name OXC in Poland increased by 10 times in comparison to the generic products. Assuming that the majority of the patients would be forced to switch to generic drugs due to financial issues we decided to follow them prospectively to evaluate the safety of switching from brand-name to generic OXC.

Results: A quarter of our cohort (26%) decided to continue on brand-name OXC, the majority (74%) switched to generic products. We did not find differences in terms of frequency of seizures and adverse events between patients continuing on brand-name OXC and those switching to generic AED.

Conclusion: The switching from brand-name to generic OXC seems to be safe, however, larger prospective studies are required in order to confirm our findings.

1. Introduction

Epilepsy is one of the most common neurological disorders with the point prevalence of active disease as high as 0.64% of the general population (Fiest et al., 2017). In the vast majority of patients, long-term or even lifelong treatment with antiepileptic drugs (AEDs) is required. The use of generic AEDs may substantially decrease the cost of treatment (Vossler et al., 2016). However, the generic substitution of brand-name AEDs and the switching among generic AED products remains controversial. Switching from innovator to generic drugs has raised particular concerns among physicians and patients regarding an increase in the frequency of seizures and occurrence of adverse events. Several retrospective studies based on health insurance data have suggested a loss of seizure control and high switchback rates after the generic substitution of brand-name AEDs (Andermann et al., 2007; Lelorier et al., 2008; Labiner et al., 2010; Lang et al., 2018). However, a growing body of evidence, including recent prospective observational or randomized studies, did not report changes in seizure frequency and tolerability after the switch from brand-to-generic drugs (Privitera et al., 2016; Trimboli et al., 2018). The majority of studies that analyzed switch from innovator to generic AEDs included patients taking various AEDs, lamotrigine, or levetiracetam (Zachry et al., 2009; Gagne et al., 2010; Hartung et al., 2012; Bosak et al., 2017; Gha-Hyun and Dae, 2018).

To our best knowledge, no study that assesses the safety of switching from brand-name to generic oxcarbazepine (OXC) has been published.

The pharmaceutical policy in Poland includes reimbursement of some medications, including AEDs. Every 2 months, the Ministry of Health issues a list of the medications that are refunded either by specific proportion (e.g., 50%) or to the specified price. From the 1st January 2016, the price of the brand-name OXC has been gradually increasing by about 10 times in comparison to the generic formulation. Assuming that the majority of the patients would be forced to switch to generic drug due to financial issues, in this study, we decided to follow them prospectively to evaluate the safety of switching from brand-name to generic OXC.

2. Material and methods

This study was the prospective analysis of patients who were treated with brand-name OXC in the tertiary epilepsy clinic at the Department of Neurology, Hospital University of Krakow, Poland. We have included all patients diagnosed with epilepsy who were treated with OXC from the 1st July 2015, to the 31st, December 2017. Patients had to be treated for at least 6 months before the inclusion to the study. All patients were informed about the increase in the price of brand-name OXC and counseled on the therapeutic equivalence of brand and generic

* Corresponding author at: Dept. of Neurology, Jagiellonian University Medical College, Botaniczna 3, 31-503 Krakow, Poland.
E-mail address: magdalena.bosak@uj.edu.pl (M. Bosak).

https://doi.org/10.1016/j.eplepsyres.2019.02.017
Received 5 January 2019; Received in revised form 11 February 2019; Accepted 26 February 2019
Available online 27 February 2019
0920-1211/

products. They were counseled on the changes in shape and color of the tablets and packages and the need for good medication adherence. The decision to switch or not to switch was made by patients alone and was based on financial reasons.

The following demographic and epilepsy data were collected using a structured questionnaire: age, age at onset of epilepsy, type of epilepsy (generalized, focal, or undetermined), treatment of epilepsy (mono- or polytherapy and AEDs used), and dose and formulation of OXC. The type of epilepsy was classified based on the interview, neurological examination, neuroimaging, and electroencephalogram according to the new International League Against Epilepsy (ILAE) position paper on the classification of epilepsies (Scheffer et al., 2017). We analyzed the data from the visit before the point "O" and from the visit after the point "O." Point "O" was the date when patients decided to switch or not to switch from the brand-name to the generic OXC. The interval between visits was typically 4 months. Dosage of OXC and concomitant AEDs remained unchanged during the study. Data on seizure frequency were collected prospectively from the personal seizure diaries. We have also registered potential adverse events. All data was collected by the senior author (MB).

The protocol of this study followed the principles included in the Declaration of Helsinki and was approved by the Bioethical Committee of the Jagiellonian University of Krakow. All patients provided their informed consent to participate in the study.

3. Statistics

The χ^2 test was used to compare proportions, while the Mann–Whitney *U* test was used to compare continuous variables between groups. The *Wilcoxon* signed-rank *test* was used to compare the frequency of seizures before and after drug change. The calculations were performed using the program STATISTICA for Windows (version 12.5, Statsoft, Poland).

4. Results

103 patients (59; 57.3% female) who were treated with brand-name OXC (Trileptal, Novartis) were included to the study. The mean age at the inclusion was 37.1 years (SD ± 11.1) and the mean age at onset of epilepsy 17.8 years (SD ± 13.3). The majority of patients were diagnosed with focal epilepsy (97 (94.2%), and 5 patients were diagnosed with Genetic Generalized Epilepsy with Generalized Tonic-Clonic Seizures Alone. 40 (38.8%) patients were in remission and 32 (31%) were taking OXC as monotherapy. Of patients on polytherapy the majority (55, 77.5%) were prescribed two drugs, the reminder (16, 22.5%) three AEDs. Other AEDs most commonly used by patients treated with OXC included valproic acid, levetiracetam, lamotrigine or topiramate.

27 (26.2%) patients decided to continue on Trileptal, 76 (73.8%) switched to generic AEDs (73 (96%) to Oxepilax (Adamed) and 3 (4%) to Karbagen (Mylan). After point "O," patients used the same formulation of OXC (tablets), the same dose per tablet, and the same daily dose.

Table 1 provides a comparison between patients who continued Trileptal and those who switched to a generic drug. Patients continuing on brand-name OXC were more often in remission and on OXC monotherapy.

No substantial difference was found in terms of number of seizures before and after point "O" in patients on brand-name and generic OXC. The frequency of seizures after switching to generic drug was comparable to the frequency of seizure before switching (P = 0.60, Wilcoxon signed-rank test).

Adverse events were recorded in 5 patients (4.8%) (1 on Trileptal, 4 on Oxepilax) at the first follow-up visit after point "O," which included dizziness (3 patients) and abdominal discomfort (2 patients). All adverse events resolved at the second follow-up visit. No patient switched back to the brand-name drug.

Table 1
Comparison of demographic features, characteristics of epilepsy, and antiepileptic medications between patients who continued Trileptal and those who switched to a generic drug.

Variable	Patients continuing on Trileptal (n = 27)	Patients switched to generic AED (n = 76)	P value
Age [years]; mean (SD)	38.4 (± 11.0)	36.7 (± 11.1)	0.48
Age at onset of epilepsy [years]; mean (SD)	20.4 (± 13.5)	16.8 (± 13.2)	0.14
Sex (women) n (%)	16 (59.3%)	43 (56.6%)	0.81
Epilepsy type			0.65
Generalized	2 (7.4%)	3 (4.0%)	
Focal	25 (92.6%)	72 (94.7%)	
Undetermined	0 (0%)	1 (1.3%)	
Patients in remission	12 (44.4%)	28 (36.8%)	0.49
OXC monotherapy	10 (37%)	22 (28.9%)	0.43
Daily dose of OXC [mg]; (± SD)	1161.1(469.9)	1261.1(542.3)	0.42
Seizure frequency (mean per 3 months) (± SD)			
Before point "0"	3.8 (± 8.7)	4.6 (± 8.1)	0.27
After point "0"	3.7 (± 7.7)	4.9 (± 9.9)	0.89
Adverse events	1 (3.7%)	4 (5.3%)	0.75

5. Discussion

In this prospective, open-label, nonrandomized study, we have evaluated the risk of generic substitution of OXC in a real-life clinical setting. To the best of our knowledge, this study is the first report related to generic substitution of OXC. We did not find differences in terms of frequency of seizures and adverse events between patients continuing on brand-name OXC and those switching to generic AEDs. Our results are consistent with numerous recent clinical and bioequivalence studies suggesting a very little risk from switching to generic AEDs (Ting et al., 2015; Privitera et al., 2016; Trimboli et al., 2018). Counseling patients on the changes in shape and color of the tablets and containers before the switch may have lowered a risk of non-adherence. Changes in pill shape and color was found to be associated with non-persistence with cardiovascular medications and AEDs (Kesselheim et al., 2013, 2014). However this finding was not confirmed for AEDs in the study of Kesselheim et al. (2016).

This study provided reassuring findings for physicians and patients concerned about the loss of seizure control and/or adverse events with OXC's generic equivalent products.

We acknowledge some limitations of our study. Firstly, the study was open-label and nonrandomized. Secondly, we did not assess serum concentrations of monohydroxycarbazepine (MHD) before and after the switch. Measurement facility for MHD is not available at our laboratory. Thirdly, the number of patients included this study may have been insufficient to show a significant effect. The sample size was not sufficiently powered to a statistically significant difference in seizure and adverse event frequency. Post-hoc calculated power of our study was 9.4% (alpha level: 0.05). Fourthly, the purely observational design and self-selection of switching to a generic product may have introduced a bias into the study.

In conclusion, the switching from brand-name to generic OXC seems to be safe, however, larger prospective studies are required to confirm our findings.

Conflict of interest

MB received honoraria for publications and for the participation in advisory meetings from Sanofi; honoraria for lectures, travel expenses and conference fees from Sanofi, Adamed, Teva Pharmaceutical, Neuraxpharm, Glenmark, UCB Pharma.

AS received honoraria for lectures from Bayer, Boehringer

Ingelheim, Novartis, Polpharma, Bristol-Myers Squipp, Novartis, Biogen, Teva Pharmaceutical, Medtronic; for the participation in advisory meetings from Bayer, Boehringer Ingelheim, Novartis.

TD has nothing to declare.

Acknowledgements

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

Andermann, F., Duh, M.S., Gosselin, A., et al., 2007. Compulsory generic switching of antiepileptic drugs: high switchback rates to branded compounds compared with other drug classes. Epilepsia 48, 464–469.

Bosak, M., Słowik, A., Turaj, W., 2017. Safety of switching from brand-name to generic levetiracetam in patients with epilepsy. Drug Des. Dev. Ther. 11, 2287–2291.

Fiest, K.M., Sauro, K.M., Wiebe, S., et al., 2017. Prevalence and incidence of epilepsy: a systematic review and meta-analysis of international studies. Neurology 88, 296–303.

Gagne, J.J., Avorn, J., Shrank, W.H., et al., 2010. Refilling and switching of antiepileptic drugs and seizure-related events. Clin. Pharmacol. Ther. 88, 347–353.

Gha-Hyun, L., Dae, S.J., 2018. Brand name to generic substitution of levetiracetam in patients with epilepsy. Seizure 60, 127–131.

Hartung, D.M., Middleton, L., Svoboda, L., McGregor, J.C., 2012. Generic substitution of lamotrigine among medicaid patients with diverse indications: a cohort-crossover study. CNS Drugs 26, 707–716.

Kesselheim, A.S., Misono, A.S., Shrank, W.H., et al., 2013. Variations in pill appearance of antiepileptic drugs and the risk of nonadherence. JAMA Intern. Med. 173, 202–220.

Kesselheim, A.S., Bykov, K., Tong, A., et al., 2014. Burden of pill appearance changes for patients taking generic cardiovascular medications after myocardial infarction: cohort and nested case-control studies. Ann. Intern. Med. 161, 96–103.

Kesselheim, A.S., Bykov, K., Gagne, J.J., et al., 2016. Switching generic antiepileptic drug manufacturer not linked to seizures: a case-crossover study. Neurology 87, 1796–1801.

Labiner, D.M., Paradis, P.E., Manjunath, R., et al., 2010. Generic antiepileptic drugs and associated medical resource utilization in the United States. Neurology 74, 1566–1574.

Lang, J.D., Kostev, K., Onugoren, M.D., et al., 2018. Switching the manufacturer of antiepileptic drugs is associated with higher risk of seizures: a nationwide study of prescription data in Germany. Ann. Neurol. 84, 918–925.

LeLorier, J., Duh, M.S., Paradis, P.E., et al., 2008. Clinical consequences of generic substitution of lamotrigine for patients with epilepsy. Neurology 70, 2179–2186.

Privitera, M.D., Welty, T.E., Gidal, B.E., et al., 2016. Generic-to-generic lamotrigine switches in people with epilepsy: the randomized controlled EQUIGEN trial. Lancet Neurol. 15, 365–372.

Scheffer, I.E., Berkovic, S., Capovilla, G., et al., 2017. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia 58, 512–521.

Ting, T.Y., Jiang, W., Lionberger, R., et al., 2015. Generic lamotrigine versus brand-name Lamictal bioequivalence in patients with epilepsy: a field test of the FDA bioequivalence standard. Epilepsia 56, 1415–1424.

Trimboli, M., Russo, E., Mumoli, L., et al., 2018. Brand-to-generic levetiracetam switching: a 4-year prospective observational real-life study. Eur. J. Neurol. 25, 666–671.

Vossler, D.G., Anderson, G.D., Bainbridge, J., 2016. AES position statement on generic substitution of antiepileptic drugs. Epilepsy Curr. 16, 209–211.

Zachry 3rd, W.M., Doan, Q.D., Clewell, J.D., et al., 2009. Case-control analysis of ambulance, emergency room, or inpatient hospital events for epilepsy and antiepileptic drug formulation changes. Epilepsia 50, 493–500.