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SHORT COMMUNICATION

Safety of Overnight Switch from Brand-Name to Generic Levetiracetam

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Abstract

Background and Objective Concerns that antiepileptic brand-to-generic interchange results in disruption of seizure control are widespread. The objective of this study was to evaluate the safety and tolerability of the brand-to-generic levetiracetam switch in patients with focal or generalized epilepsy.

Methods A prospective study in patients with primary, cryptogenic or symptomatic epilepsy, who were taking branded levetiracetam and were switched to generic levetiracetam. Patients were consecutively recruited from January 2013 to January 2015. We evaluated efficacy, tolerability and compliance before switching (T0) and after 6 months of therapy (T1). Evaluations were scheduled as follows: baseline, 7 and 15 days, 1, 3 and 6 months. At each visit clinical diary seizures, physical and neurological examination, laboratory parameters and electroencephalogram were evaluated.

Results Fifty-nine patients, equally mixed by sex, were included in the study. Mean age was 26.1 years. Forty-seven per cent of the patients enrolled received levetiracetam as monotherapy. One patient was lost during the follow-up: so at T1 we had 58 patients (28 monotherapy and 30 polytherapy). At T0 and at T1, there was no statistically significant difference in terms of seizure frequency and intensity, occurrence of adverse events, laboratory parameters and electroencephalographic features. Two patients stopped treatment with the generic (both at 3 months after the switch) and restarted therapy with brand levetiracetam because of seizure increase. At the end of the study, the switchback rate was 3.4 %.

Conclusions No increase of seizures and adverse effects were observed when branded levetiracetam was interchanged to a generic equivalent. More studies should be conducted with a larger series of patients to confirm these results.

Key Points

No significant increase of seizures was observed after the switch from branded-name to generic levetiracetam.

No severe adverse effects were reported during the study.

The efficacy and safety of generic antiepileptic drugs for patient with epilepsy should be explored in further larger studies.

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1 Introduction

Concerns about medication costs and drug safety have increased attention to the role and clinical equivalence of generic drugs. These products have the same active ingredients as their brand-name counterparts, but may differ in some excipients and inactive ingredients, and the specific manufacturing process.

In patients with epilepsy, loss of response after switching from brand name to bioequivalent generic formulation is a well-known phenomenon [1]. It is known to be of wide-spread concern that the generic drugs are not as effective as branded drugs because the bioavailability may be different from branded counterparts and because of the use of other excipients that are used to make generic medications [2].

The American Academy of Neurology has issued guidelines opposing generic substitution of antiepileptic drugs (AEDs) without the attending physician's approval [3].

The safety and efficacy of generics have been questioned, particularly when there is generic substitution of antiepileptic, immunosuppressant, and psychotropic drugs [4].

Increased seizures and side effects have been reported after AED generic substitution, attributed to differences in bioavailability allowed between brand and generic products [5]. At the same time, other organizations such as the US Food and Drug Administration (FDA) and the American Society of Health-System Pharmacists maintain that generic and branded products are therapeutically interchangeable. On the other hand, on September 17, 2012 the Italian Medicines Agency of the Drug suggested avoiding the switch from brand to generic formulation of levetiracetam. These conflicting viewpoints regarding generic substitution underscore the importance of evidence-based research [6]. Although AEDs are not particularly expensive compared to others, due to the high prevalence of the disease and the long duration of treatment, the pharmaceutical expenditure related to epilepsy is not negligible. Among the AEDs, levetiracetam is one of the most common used for the treatment of epilepsy.

Levetiracetam is an AED widely used for the treatment of partial or generalized epilepsy in children and adults. Levetiracetam is effective and well tolerated [7, 8].

The purpose of this study is to compare the efficacy and safety of branded and generic levetiracetam in terms of effectiveness and incidence of side effects.

2 Patients and Methods

This was prospective, multicenter study involving six Italian epilepsy centres from January 2013 to January 2015. We enrolled consecutively 59 patients (29 males and 30 females).

Patients involved in the study were suffering from idiopathic epilepsy (33 patients), cryptogenic epilepsy (2 patients) or symptomatic epilepsy (24 patients). Thirty-one patients were suffering from focal epilepsy, 12 patients were affected by focal epilepsy with secondary generalization, and 16 patients by generalized epilepsy.

In these series, some patients were on branded levetiracetam (Keppra 500 mg, manufactured by UCB—Anderlecht, Belgio) as monotherapy (47 %), and other patients (53 %) branded levetiracetam as polytherapy in association with one or more other AEDs (with valproate, topiramate, lamotrigine, carbamazepine, phenobarbital, phenytoin, pregabalin, zonisamide, valproate + lamotrigine or valproate + topiramate + clonazepam).

Monotherapy was defined as the patient taking only levetiracetam for seizure control 90 days prior to the compulsory switch, and polytherapy was defined as those patients using at least one other AED at the same time as levetiracetam.

All the patients enrolled did not have any comorbidity.

At the start of the study, subjects were abruptly switched from branded levetiracetam to generic levetiracetam at identical dosages and concomitant medications remained unchanged. All our patients used only one type of generic drug (Levetiracetam, Matever 500 mg, manufactured by Ecupharma—Milano, Italy).

There was not the possibility to change or adapt the dosage of the drug during the observational period.

Generic medication had the same dose and form as the brand name and had been studied and determined to have equivalent bioavailability on the brand name. For the study, 500 mg levetiracetam oral tablet formulation was used.

We evaluated treatment efficacy, tolerability and compliance before switching (T0) and after 6 months of therapy (T1). Demographic and clinical data of each patient were also collected. We studied all of the subjects overall; moreover, the patients were subdivided into two groups: monotherapy and polytherapy.

Evaluations after the switch performed at the following times: baseline, 7 days, 15 days, 1 month, 3 months and 6 months. On each occasion, evaluations were made of clinical diary seizures, physical and neurological exami-

nation, evaluation of laboratory parameters and electroencephalogram (EEG).

Efficacy of treatment was assessed by seizure frequency (number of seizures per month), seizure control rate (percentage of seizure-free patients), and EEG characteristics (normal; focal/generalized abnormalities). Daily seizure frequency was recorded in a seizure diary by the patients/caregivers. Tolerability of treatment was evaluated by monitoring clinical adverse reactions and abnormalities in selected laboratory values. Adverse events (AEs) were recorded by patients and communicated to the staff. Compliance was assessed by administering a diary of therapy and seizures, and through periodic interviews to the patient by the medical staff.

After 6 months, the persistence to treatment was evaluated through an interview with the patient and review of the diary of seizures and therapy.

Statistical analysis was performed with SPSS statistical package (version 17.0, SPSS Inc., Chicago, IL, USA). The results were expressed as means (±SD) for continuous variables and absolute number/percentage for categorical variables. Comparisons between categorical data were evaluated by chi-square test and Fisher's test, whereas continuous variables were compared using Student's *t*-test. Statistical significance was defined as a p value 0.05.

This was a prospective, multicenter study with the following properties: Alpha = 0.10, Beta = 0.10 (power = 0.80), *Ho*: $p = 0.20$ (null hypothesis), *H*1: $p = 0.40$ (response rate).

Prior to data collection, the study was approved by Ethics Committee of the participating centers.

Table 1 Patients' characteristics

Characteristic	Value
No. of patients	59
Mean age ± SD (year)	26.1 ± 41.9
Female, *n* (%)	30 (51.7)
Idiopathic epilepsy, *n* (%)	33 (56.9)
Cryptogenic epilepsy, *n* (%)	2 (3.4)
Symptomatic epilepsy, *n* (%)	24 (41.4)
Polytherapy, *n* (%)	31 (53.4)
Discontinued treatment, *n* (%)	2 (3.4)
Drop out, *n* (%)	1 (1.7)
Did not switchback, *n* (%)	56 (96.5)

Table 2 Switchback rates

Patient characteristic, *n* (%)	Switchback rate
Total	2 (3.4)
Gender	
Male	2 (3.4)
Female	0 (0)
Monotherapy vs polytherapy	
Monotherapy	0 (0)
Polytherapy	2 (3.4)
Epilepsy type	
Idiopathic	1 (1.7)
Symptomatic	0 (0)
Cryptogenic	1 (1.7)
Increased adverse effects on generic levetiracetam	2 (3.4)
Increased seizure on generic levetiracetam	2 (3.4)

3 Results

We enrolled 59 patients, mean age 26.1 years (range 6.9–78.0 years) (Table 1). Among these, 28 patients (47 %) were on branded levetiracetam as monotherapy, and 31 patients (53 %) were taking branded levetiracetam as polytherapy in association with other AEDs; eight patients were taking levetiracetam in association with valproate, six patients in association with topiramate, four patients in association with lamotrigine, seven in association with carbamazepine, one with phenobarbital, one with phenytoin, one with pregabalin, one with zonisamide, one with valproate and lamotrigine, and one with valproate, topiramate and clonazepam (see Electronic Supplementary material Table S1).

The 59 patients were subjected to switching "overnight" from branded levetiracetam to generic levetiracetam (mean dose ± SD: 1092.6 ± 525 mg/day).

One patient was lost during the follow-up, so at T1 (after 6 months) we had 58 patients (28 in monotherapy and 30 in polytherapy). Comparing the patients at T0 at T1, we found no statistically significant differences in terms of seizure frequency, occurrence of AEs, laboratory parameters and EEG features.

The same results were also observed in intermediate stages of the study: +7 days + 15 days + 3 months. Compliance was similar between patients at T0 and T1.

At the end of the 6-month follow-up, 56 of the 58 patients had continued to use generic levetiracetam. At the end of the study, the switchback rate for the total population included was 3.4 % (Table 2). Only two patients stopped treatment with the generic (both after 3 months' trial) and restarted therapy with branded levetiracetam. A 22-year-old patient was suffering from severe myoclonic epilepsy of infancy (Dravet Syndrome) and he had weekly seizures before the switch of therapy; after 1 week of treatment with generic levetiracetam he had presented irritability and after 3 months increased (daily) seizures; therefore, he suspended the treatment on the third month of follow-up.

The other patient was a 77-year-old male with cryptogenic epilepsy. Before the switch he presented daily partial seizures and monthly generalized seizures; on the seventh day of treatment with generic levetiracetam he presented irritability and after 3 months seizure frequency increased with secondary generalization. Both patients were taking levetiracetam in polytherapy (one levetiracetam and lamotrigine, and the other levetiracetam and topiramate).

We observed that polytherapy was significantly associated with an increase in seizure frequency, when using generic levetiracetam compared to those on monotherapy.

4 Discussion

Epilepsy is associated with high costs that affect individuals and society. Costs differ across centers in relation to the characteristics of patients and the extent of use of more expensive, second-generation AEDs [9]. While generics are widely available across all drug categories, special concern has been voiced regarding their use in the treatment of epilepsy [2].

Indeed, some authors argue about the therapeutic equivalence of branded and generic antiepileptic drugs in patients with epilepsy, who may be at increased risk for problems with brand-to-generic switching. However, in general, few patients experience seizure exacerbations or tolerability issues with product switching [10].

We report a prospective chart review study over a 6-month period after compulsory switch from branded to generic levetiracetam, noting a switchback rate of 3.4 %. Generic levetiracetam was associated with higher switchback rate in only two patients who had previously experienced either seizure exacerbation or AEs on brand-name levetiracetam. Our experience demonstrated that the abrupt switch from branded levetiracetam to generic levetiracetam is not associated with any significant change in efficacy, tolerability and compliance of treatment. In our study there was no difference for switchback regarding age and gender of the patients, and seizure type. This is apparently in contrast with the view that AEs are determined more by individual susceptibility, type of AEDs used, and physicians' skills, rather than to number of prescribed AEDs and AED load [11]. A possible reason for this finding may be due to the fact that patients requiring polytherapy often experience more severe forms of epilepsy and can be sensitive to slight variations in drug bioavailability that occur with generic compounds [12]. In particular, the generic drug used in our study is levetiracetam, Matever 500 mg, manufactured by Ecupharma—Milano (Italy) and its oral bioavailability is close to 100 %. Each tablet of the generic drug used contains as active ingredient: levetiracetam 500 mg, and as excipients: sodium acetate trihydrate, glacial acetic acid, sodium chloride, water for injections.

Previous studies [4, 13–15] obtained opposite results; they showed that when moving from branded AEDs (lamotrigine, levetiracetam, phenytoin) to generic AEDs, patients had a worsening in terms of clinical response and appearance of side effects, in particular patients who showed a high seizure count before the switch [16].

A recent (2011) retrospective cohort study showed that brand-to-generic switching of other AEDs (lamotrigine) was not associated with more clinical events, confirming our results and suggesting no adverse outcomes after the switch [17].

After reviewing the limited series and studies available, the Italian League against Epilepsy (LICE) working group concluded that there are no adequately powered randomized controlled trials that assess the risk-to-benefit ratio of generic AEDs and that the safety of switching between branded and generic AED formulations is therefore unknown. They recommended against generic substitution in patients who achieved seizure remission, and against switches between generics. They felt that generic AEDs should be limited to monotherapy initiation, adjunctive treatment and use in patients with persistent seizures despite the use of a brand-name product [18].

Due to the fact that generics are similar to, but not the same as, the brand name, and even less similar to each another, these differences could be clinically significant when a patient is switched. Identically, our study support the idea that if a patient could always remain on the same formulation from the same manufacturer, whether brand or generic, then this would eliminate such concerns [19]. Noteworthy, the relationship between levetiracetam serum concentration and its clinical effect have not been fully established [20], also due to the unknown saturation threshold of levetiracetam molecular target, i.e., SV2A protein.

A major strength of our study is its prospective nature compared with previous retrospective trials [1, 5, 6, 17]. Moreover, our patients were followed up and evaluated constantly and frequently by our staff. Some limitations of this study include the relatively small sample size and the lack of blood drug monitoring. On the other hand, previous trials evaluating clinical consequences of generic AEDs included larger patient populations, and they also evaluated the serum levels of the drug used [21–24]. Moreover Italiano et al performed a study on generic olanzepine for the treatment of schizophrenia, and the authors concluded that significantly lower serum olanzapine concentrations were found after switching from brand-name to generic olanzepine. Although these modifications did not significantly compromise schizophrenia symptoms control, it cannot be excluded that a longer exposure to lower olanzapine serum

concentrations may result in relapse of schizophrenic symptoms [25].

5 Conclusions

In summary, our pilot study showed that the overnight switch from brand-name levetiracetam to generic levetiracetam is easy and safe in patients with epilepsy. Taking into account that concerns have been raised about the safety and effectiveness of switching between brand name and bioequivalent generic versions of AEDs, further studies enrolling a larger number of patients are eagerly warranted to provide 'real-life' evidence for the safety of generic products of AEDs.

Compliance with ethical standards

Funding No sources of funding were used to conduct this study.

Conflicts of interest All authors declare no conflicts of interest that are relevant to the content of this study.

Ethical approval The study was approved by Ethics Committee of the participating centers.

Informed consent All patients provided written informed consent.

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