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EXPERT OPINION

Is bioavailability altered in generic versus brand anticonvulsants?

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Therapeutic window of anticonvulsants is not a wide one, with phenytoin being one extreme, which can be classified as a narrow therapeutic index drug, since its ratio between the least toxic and the least effective concentration is less than twofold. In order to obtain marketing authorization, a generic anticonvulsant should demonstrate relative bioequivalence with its brand-name counterpart. However, although bioequivalent, generic anticonvulsants still do not have the same bioavailability as brand-name drugs, which may lead to larger fluctuations of steady-state plasma concentrations, and sometimes to loss of seizure control if a patient is switched from brand-name to generic or from generic to generic anticonvulsant. Generic anticonvulsants are effective, safe and affordable drugs for treatment of epilepsy, and patients could be successfully treated with them from the very beginning. It is switching from brand-name to generic anticonvulsant or from one generic anticonvulsant to another that should be avoided in clinical practice, since subtle differences in bioavailability may disturb optimal degree of seizure control to which the patient was previously successfully titrated.

Keywords: anticonvulsants, bioavailability, bioequivalence, interchangeability

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1. Introduction

Generic drugs are precisely defined in regulatory documents of European Union as 'products which have the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies' [1]. Therefore, the accent stays on bioequivalence of a generic and an original drug, that is, generic drug should have virtually the same bioavailability as the original drug. New generic drug application could be submitted to a regulatory Drug Agency only after it was shown in a study on 12 – 24 healthy adult males that 90% CIs of ratios between AUC, maximal plasma concentration and time to maximal plasma concentration of generic and original drug after their administration by the same route are somewhere between 80 and 125%. Exceptions to this rule are drugs with 'narrow therapeutic index' or narrow therapeutic window in general leading to safety concerns whose 90% CIs of AUC ratios with original drugs should fall within much narrower limits – between 90 and 111.11% [1]. However, we should not forget that bioequivalence studies are performed in standardized conditions, in healthy volunteers and while they are fasting. Brand-name and generic drugs could be bioequivalent under fasting conditions, but not after a meal (e.g., case of nifedipine before and after a high-fat meal) [2]; bioavailability of a drug might not be the same in healthy young males and elderly patients with much comorbidity.

The therapeutic window of anticonvulsants is not wide, since their toxicity starts even within the therapeutic range [3]. One of the oldest anticonvulsants, phenytoin even fulfills the criteria for 'narrow therapeutic index' drug, that is, the ratio

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between its the least toxic and the least effective concentration is less than twofold [4]. Regardless of the fact that generic anticonvulsants should satisfy more stringent bioequivalence CI of 90 – 111%, and be tested in bioequivalence trials using semi-replicated or replicated design to account for individual intrasubject variability, there are several reports in the literature on loss of seizure control in certain number of patients after substitution of an original anticonvulsant with a bioequivalent generic copy. Recent case–control study on 9110 patients who switched from original to a generic anticonvulsant has shown that the switching was associated with increased risk of a seizure-related event (adjusted odds ratio 1.27) [5]. Even higher risk of an epilepsy-related event among patients who switched from original to generic anticonvulsant in comparison to those who did not (odds ratio 1.57) was found in another case–control study on 3028 outpatients suffering from epilepsy [6]. The attitudes of both neurologists and patients suffering from epilepsy toward generic anticonvulsants are mostly negative; in a survey among neurologists 67.8% of them said that they had a case with breakthrough seizures after substituting original with generic anticonvulsant [7], and another study showed that patients generally do not understand concept of generic drugs quality control and are therefore hesitant to switch from original to generic anticonvulsant [8]. However, results of these studies could have been affected by low response rate and possible framing effects.

There are also dissonant voices when comparison of efficacy and safety of brand-name and generic anticonvulsants is in question. In a systematic review and meta-analysis of 16 studies (nine randomized controlled trials, one nonrandomized clinical trial and six observational studies) the efficacy and safety of brand-name and generic drugs were assessed through comparison of results of the 10 clinical trials where brand name or generics were initiated from beginning of therapy, while consequences of switching from brand-name to generic or generic to generic anticonvulsant were estimated through review of the results of six observational studies. The clinical trials demonstrated therapeutic equivalence of brand-name and generic anticonvulsants, while the observational studies did not find change in control of epilepsy after the original-generic or generic–generic switch of the three types of anticonvulsants, but it was noted in observational studies that the patients who changed an anticonvulsant used higher doses and either more frequently visited their doctors or were more often hospitalized [9]. Another, more recent systematic review, has also summarized results of both clinical trials (where either brand-name or generic anticonvulsants were initiated from the beginning) and observational studies (where switching from brand-name to generic or generic to generic anticonvulsant was investigated) [10]. Like in the previous review, clinical trials did not find differences among brand-name and generic anticonvulsants in both efficacy and safety, while qualitative analysis of observational studies (limited to carbamazepine, phenytoin and valproate) showed that switching was associated with increased hospitalization rate and duration of stay in a hospital, while utilization of outpatient services remained similar. The authors of both systematic reviews stressed that included observational studies were methodologically deficient, lacking full accounting for confounders, which together with inherent limitations of their design severely hampers generalizability of their conclusions. Besides, it was recently shown that the dispensation event itself, and not switching from brand-name to generic or from generic to generic anticonvulsant, was associated with tripling risk of having a seizure within 21 days [11].

Majority of published studies that dealt with head-to-head relative bioequivalence testing of generic versus brand-name anticonvulsants have shown compliance with regulatory criteria [12,13], concluding that generics and brand-name products are interchangeable. However, there are reports that documented significant bioinequivalence of generic and brand-name oral forms of phenytoin [14] and carbamazepine [15]. Since relative bioequivalence had to be demonstrated in previous studies of generic anticonvulsants, otherwise marketing approval could not have been obtained, the explanation for demonstrated inequivalence could be later changed in process of manufacturing of the generic drugs. Plausibility of such assumption is supported by the study that demonstrated differences in bioavailability between different lots of the same generic product of carbamazepine [16]. It is worrying that besides general rules of GMP there is no established mechanism for state-level control of eventual changes in the manufacturing process of generic drugs, including anticonvulsants.

On the other side, identification of 'bad guys' among producers of generic anticonvulsants and of their bad products is not the only concern. Even when generic drug is bioequivalent with brand-name drug, it does not mean that their bioavailability is the same. Several studies have shown that bioequivalent anticonvulsants show significant differences in pharmacokinetic parameters which are not routinely used for bioequivalence testing [17]. Time to achieving maximal plasma concentration of topiramate was 42% longer after administration of generic copy than after administration of brand-name drug. These subtle differences may cause larger fluctuations of steady-state plasma concentrations with generic anticonvulsant than with its brand-name counterpart, resulting with loss of seizure control. The same could happen if a patient is switched from one to another generic anticonvulsant, since demonstration of bioequivalence is requested by drug agencies between generic and originator drugs only, and not between generics themselves.

Several years ago it was understood that intraindividual variability of bioequivalence could explain some of seemingly paradoxical reports on results of brand-name/generic or generic/generic anticonvulsants switching [18]. Even with different lots of the same brand-name anticonvulsant some individuals will exhibit high variability of plasma concentrations; when determining bioequivalence of a generic anticonvulsant with its brand-name counterpart we are first to measure

intraindividual variability of study subjects in regard to bioavailability of the brand-name drug, and then to ensure that intraindividual variability with the generic product will not go out of these limits. This could be done by new type of bioequivalence studies accepted by some of the regulatory agencies and named 'scaled-average bioequivalence testing' [19]. With this approach the bioequivalence studies are carried out in three periods on the same subjects (the reference product is administered twice, and the test product once), and the bioequivalence criteria are then scaled to observed variability of the reference product. Whether such approach will enable switchability of brand-name and generic anticonvulsants in the future remains to be seen.

Still unresolved issue of brand-name/generic anticonvulsant switchability resulted with additional regulatory actions of some of the drug agencies worldwide. For example, Swedish drug agency made a list of interchangeable drugs, which does not contain phenytoin and carbamazepine, but other anticonvulsants could be found there, like topiramate, lamotrigine and so on. None of the available anticonvulsant drugs is considered interchangeable in American states of Hawaii, Kentucky and Tennessee. This measure seems logical, since it is switching from one to another anticonvulsant, which puts patient under risk to lose seizure control, not the use of a generic anticonvulsant by itself. Avoidance of switching from brand-name to generic anticonvulsant eliminates unnecessary utilization of health-care resources, including hospitalizations. On the other hand, avoidance of switching by no means precludes use of generic anticonvulsants in clinical practice.

2. Conclusion

If a physician and his or her patient decide to use a generic anticonvulsant as more affordable option in treatment of epilepsy, they should do this from the beginning, choosing drug whose presence on the market is stable and foreseeable in the future. Switching from brand-name to generic anticonvulsant or from one to another generic product should be avoided unless there are very good reasons. However, if switching is inevitable, it should be done with due care and precautions, in order to minimize possibility of injuries or other adverse consequences of temporary loss of seizure control.

3. Expert opinion

The studies investigating bioequivalence and interchangeability of brand-name and generic anticonvulsant drugs are not frequent, and their results are conflicting. Those that confirmed bioequivalence were limited to testing whether standards of regulatory agencies are satisfied, and studies that showed inequivalence actually discovered cases of advertent breach of GMP. Only a few studies investigated what happens with seizure control and steady-state plasma concentrations in patients taking bioequivalent generic anticonvulsants after switching from brand-name drugs or from one to another generic drug, which is in fact the central question in this field of research.

Steady-state plasma concentrations of anticonvulsants and their fluctuations are directly linked to seizure control, so any study that intends to explore therapeutic equivalence of brand-name and generic anticonvulsants should include multiple points measurements of steady-state plasma concentrations and estimates of time spent in the therapeutic range, which is already defined for majority of anticonvulsants. Multiple point measurements during the steady state are necessary since only with such data we could make reliable reconstruction of plasma concentration course during the dose interval and estimate true degree of protection against seizure occurrence. Besides, we should investigate influence of intraindividual variability on bioequivalence through repeating measurements in the same subjects after administration of different lots of the same product; introduction of scaled-average bioequivalence testing design is an important step forward in this direction.

Studies designed for obtaining multiple-point measurements of anticonvulsant plasma concentrations are not easy to conduct, since there are two inherent difficulties: compliance of the patients with prescribed regimens should be ensured and the patients are exposed to unpleasant and complication-prone repeated blood sampling during a 24-h period. Such studies are resources-demanding, and it is difficult to find an interested party to fund this research. However, if we are apt to finally resolve the issue of bioequivalence and interchangeability of brand-name and generic anticonvulsants, studies involving steady-state patients should be requested by regulatory drug agencies for drugs with narrow therapeutic window, like anticonvulsants. Such legal requirements would stimulate producers of anticonvulsants to provide necessary funding for this kind of bioequivalence studies. In the meantime, an interesting modeling approach with Monte Carlo simulations was successfully used to test how differences in pharmacokinetic parameters of brand-name and generic anticonvulsants influence their bioequivalence [20].

This editorial gives an updated insight into bioequivalence and switchability issues of brand-name and generic anticonvulsants, pointing to new developments in this area, like scaled-average bioequivalence testing and recognition of a need for the studies based on multiple points measurements of steady-state plasma concentrations with estimation of the time spent in the therapeutic range. It also provides clinicians with useful recommendations for prescribing anticonvulsants to the patients with epilepsy who are either starting to take therapy or in a situation to switch from brand name to generic or from one to another genetic anticonvulsant.

Declaration of interest

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with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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