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Special contribution

The use of generic medication in epilepsy: A review of potential issues and challenges

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ABSTRACT

Changing from brand name to generic antiepileptic drugs (AEDs) is increasingly being advocated by the authorities, principally for budgetary reasons. However, caution should be exercised since AEDs may have a narrow therapeutic margin, the regimen with AEDs may be complex, the consequences of uncontrolled seizures may be severe, and risk of side effects is relatively high, particularly when seizures are difficult to control. This article focuses on the possible problems that can arise from the substitution of AEDs formulations, such as loss of seizure control and emergence of new side effects. We would advise that patients stay on the same formulation of the first AED, whether a brand name or generic AED. Switching AED formulations should always be done with the necessary caution and under the physician's supervision. Closer follow-up during the transitional period is necessary, and dosage adjustment may be required. The patient should be given full and correct advice about risks involved in switching AED formulations.

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1. Introduction

Epilepsy is a common and chronic disorder with a prevalence of between 0.5% and 1%.[1] Lifelong treatment is often required.[2] Around 70% of patients obtain seizure remission with the help of antiepileptic drugs (AEDs), enabling them to lead a normal life.[1] Caution must be exercised when considering the generic substitution of AEDs in patients who are stabilized on their treatment.[2] This article discusses the potential risks of generic substitution of AEDs in the treatment of epilepsy.

2. Generic products – definitions

A *generic product* is described as "a product which has 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" (Directive 2004/27 of the European Parliament; Directive 2001/83).

Bioavailability can be described as "the rate and extent to which the active ingredient becomes available at the site of

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drug action".[3,55] Most bioavailability studies are based on plasma drug concentrations.[4] In practice the area under the curve (or AUC) (which is equivalent to the quantity of drug available to the body) and the peak concentration (Cmax) are usually measured to compare the bioavailability of different products.[5,58]

3. Generic products – pharmacological considerations

For bioequivalence to be demonstrated the area under the curve (AUC) must lie within 80% and 125% of the reference preparation with 90% reliability.[6] When bioequivalence of the generic agent with the brand name drug is established, usually in single-dose studies, it is generally assumed that the generic product also has therapeutic equivalence in clinical use, although these bioequivalence studies are conducted in healthy volunteers and usually in a limited number of study subjects.

In patients with epilepsy the bioavailability of a drug can vary markedly as a result of differences in age, comorbidities, and the simultaneous use of potentially interacting medications. As a result the bioavailability of a given drug in patients with epilepsy can vary from 74 to 142%.[5] It is important to note that an even greater variation in pharmacokinetic parameters can occur when patients switch between different generic formulations than when a generic is substituted for the brand name drug or *vice versa*. It is theoretically possible for a patient to have a 50% increase in serum concentration when changing from a generic with low bioavailability (e.g. 80% of that of the brand name drug) to a generic with high bioavailability (e.g. 120% of the brand name drug) (see Fig. 1).[6] In the same example, switching the generic with high bioavailability of 120% to one with low bioavailability of 80% will result in a 33% fall in serum concentration.[6]

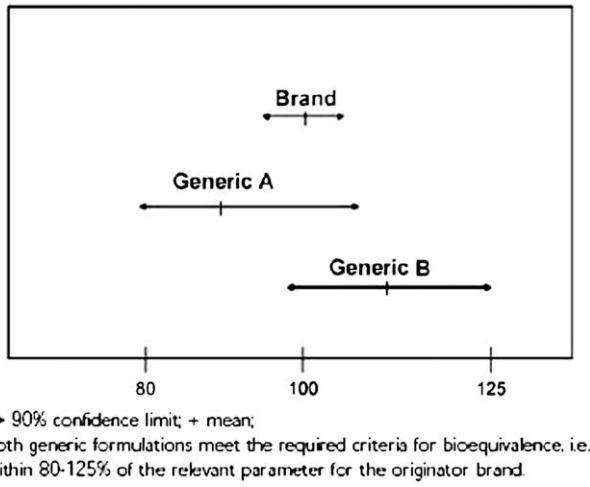

Fig. 1 – Illustration of a brand name and two generic drugs that meet the criteria of bioequivalence. Reproduced with permission: Feely et al. Risk management in epilepsy: generic substitution and continuity of supply, EJHP Science, Volume 11, 2005, issue # 4, Pharma Publishing & Media Europe bvba.

Particular attention is warranted if the original brand name drug has a narrow therapeutic index or a non-linear pharmacokinetic profile, such as phenytoin.

4. Generic products – considerations

Generic medication can also differ in other ways from the original brand name product, such as shelf life[5] or general appearance (color, form and taste). This can result in confusion and concern in the patient.[1,7]

Generic products can also use a different salt or ester of the active substance.[8] Different salts, esters, isomers, mixtures of isomers, complexes or derivatives of an active substance are considered to be the same active substance, unless they differ significantly with regard to safety or efficacy (Directive 2004/27 of the European Parliament; Directive 2001/83).[9] Nevertheless, different salts of the same active substance can exhibit different chemical and biological properties. Also, excipients in the tablet may not always be considered as inactive or inert, and can differ from one generic to another[4] and affect the pharmacokinetics of the active substance.

Different manufacturers market different generic equivalents of the same brand name drug.[1] It is possible, therefore, that patients receive a different generic preparation each time with the same prescription if the drug is prescribed on the basis of the generic name of the AED.[6]

5. Other formulations of brand name drugs – a similar problem

The problem of substitution does not just arise with generic forms of AEDs. The same problem can occur when a company markets a different formulation of the original antiepileptic, as happened with oxcarbazepine (Trileptal®). A new formulation of oxcarbazepine (Trileptal®) resulted in acute side effects such as diplopia, dizziness, dysarthria and ataxia in patients who had been taking oxcarbazepine for years without any side effect. The new oxcarbazepine formulation was absorbed more rapidly and had a higher bioavailability than the old one and resulted in a mean increase in the oxcarbazepine concentration of more than 400%. Oxcarbazepine is a prodrug of the monohydroxy derivative (MHD). The mean serum concentration of MHD increased by more than 40% following the introduction of the new formulation. We, therefore, argue for the same approach to new formulations of brand name drugs as to generics.[10] In this case, however, the new formulation was not bioequivalent with the previous formulation.

6. Risk categories

On the basis of these facts it has been proposed to exclude certain patient groups from generic substitution.[11] This concerns disorders in which patients have a higher risk of an unfavorable outcome, in which potentially serious complications can occur, polymedication is administered, and medication with complex dosage regimens, a narrow

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