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Recommendations of the Italian League Against Epilepsy Working Group on Generic Products of Antiepileptic Drugs

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Summary: The availability of generic products of antiepileptic drugs (AEDs) has been increasing in recent years. In view of the importance of the issue, the Italian League against Epilepsy (LICE) set up an ad hoc working group whose task was to assess available evidence on the efficacy and safety of generic AEDs in the treatment of epilepsy and to produce recommendations on their use. A careful review of the literature revealed no adequately powered randomized controlled trials that assessed the risk/benefit ratio of generic substitution. Although there have been reports of loss or worsened seizure control, or appearance of adverse events, following the switch from brand products to generics, a critical assessment of the evidence generally does not allow us to establish a cause–effect relationship between the switch and a change in clinical status. Overall, the working group concluded that generic AEDs meeting current regulatory criteria for bioequivalence represent a valuable choice in the management of epilepsy by allowing a substantial reduction of treatment costs, particularly in patients initiating monotherapy or adjunctive treament and in those with persistent seizures. The working group considered that in patients who achieved seizure freedom a modest change in plasma drug levels, which may occasionally occur even after substitution of products that meet bioequivalence criteria, could in rare cases lead to seizure breakthrough. Therefore, generic substitution is not recommended in patients who achieved seizure remission. Switches between a particular generic and another generic should also be preferably avoided. Finally, sustained-release AED formulations should not be used interchangeably with immediate-release brand or generic products. Patients need to be informed about the stringent criteria that currently govern the approval of generic products and about the implications of the use of generic AEDs, and their opinion should be taken into consideration at the time of prescribing.
Key Words: Antiepileptic drugs—Epilepsy—Generics—Brand Products—Bioequivalence—Italian League against Epilepsy—Recommendations

The Italian League against Epilepsy (LICE) was asked by some of its members and other organizations to provide its assessment on the use of generic products of antiepileptic drugs (AEDs), whose availability has been increasing in recent years. In view of the importance of the issue, which has also been addressed and debated in the international literature (Crawford et al., 1996; Richens, 1997; Besag, 2000; Wilner, 2004; Argumosa and Herranz, 2005; Gonzalez de Dios et al., 2005; Haskins et al., 2005), the LICE Executive Council set up in October 2005 an ad hoc working group whose task was to assess available evidence on the use of generic products in the treatment of epilepsy and to produce recommendations on their prescription. The Group completed its work on January 21, 2006 by reaching consensus on the present document.

GENERAL CONSIDERATIONS

A generic is a pharmaceutical product which is marketed under the International Non-proprietary Name (INN) and meets internationally standardized requirements for "essential similarity" to the originator's product (henceforth called "brand" or "proprietary" product): same qualitative and quantitative composition in terms of active substances, same pharmaceutical form, same strength, same route of administration, and equivalent bioavailability (bioequivalence). Two products are considered to be bioequivalent "if their bioavailabilities after

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administration in the same molar dose are similar to such a degree that their effects, with respect to both efficacy and safety, will be essentially the same (Committee, 2001)."

The bioequivalence of a generic versus the brand product is demonstrated by comparing critical pharmacokinetic parameters after single and/or repeated administration of both products in an adequate number of healthy volunteers and/or patients with the disorder of interest. In order to receive marketing authorization, the 90% confidence interval for the ratios between the pharmacokinetic parameters of the generic and those of the brand product must fall within the 80% to 125% range (Committee, 2001). Although this may be interpreted as implying that plasma drug levels after administration of a particular generic can be reduced by as much as 45% compared with those observed with another generic, in practice such a difference does not occur because the need to maintain the 90% confidence intervals (not the mean value!) within the acceptable range implies that, typically, mean plasma concentrations after administration of the generic do not differ by more than 5–7% from those observed after administration of the brand product. This variability is relatively modest when compared not only with interindividual differences in pharmacokinetics, but also with differences in plasma drug levels observed over time even within subjects under the influence of physiological, pathological, and environmental factors, in addition to variation in compliance (Leppik et al., 1979; Graves et al., 1988; Gatti et al., 2001).

It should also be noted that not even the brand product is exempt from variability over time. In the E.U., for example, differences in content of active principle between lots of the same product can fall within 95% to 105% of the nominal value. In addition, at times the manufacturer of the brand product may modify the production/formulation characteristics to an extent that requires conduction of bioequivalence studies to exclude important pharmacokinetic differences. The acceptability limits for these tests are identical to those applied for the approval of a generic.

METHODS

Assessment of evidence

The working group evaluated published evidence by conducting a Medline search using the following key words: "antiepileptic drugs," "anticonvulsants," "generic," "bioequivalence," "bioavailability," "randomized controlled trial" in addition to the names of individual AEDs. In addition, the members of the working group searched their archives, and some manufacturers of AEDs made available a variety of documents. Colleagues interested in this topic at national and international level were also consulted informally for any additional evidence.

RESULTS

Quality of the evidence and interpretation of available data

No randomized controlled trials (RCTs) were identified that compared the effects of generic AEDs and corresponding brand products in a sizeable number of patients with epilepsy. The only identified RCT that enrolled at least 50 subjects was a comparative crossover study of 64 patients assigned to receive in random sequence a generic and a brand product of valproic acid, each for four-week periods. This study, of limited quality for its modest sample size and its short duration, did not detect any difference in seizure control and plasma drug levels between the two treatment periods (Vadney and Kraushaar, 1997).

In contrast to the lack of controlled studies, there are several published reports of loss or worsening of seizure control (Koch and Allen, 1978; Pedersen and Dam, 1985; McDonald, 1987; Wyllie et al., 1987; Sachdeo and Belendiuk, 1987; Hartley et al., 1990; Welty et al., 1992; Jain, 1993; Meyer and Straughn, 1993; Guberman and Corman, 2000; Burkhardt et al., 2004; Wilner, 2004; Haskins et al., 2005) or appearance of adverse events (Finestone and Williams, 1985; Gilman et al, 1993; Brown et al., 1998; Guberman and Corman, 2000; Wilner, 2004; Haskins et al., 2005) following substitution of a brand AED with a generic. Many of these reports date back several years, when regulatory requirements for the approval of generics were not as stringent as those currently in force in major industrialized countries (Richens, 1997; American Medical Association, 2006) and therefore some products of inadequate quality found their way into the market (Bochner et al., 1972; Sansom et al., 1975; Manson et al., 1975; Stewart et al., 1975; Tammisto et al., 1976; Hodges et al.,1986; Mikati et al., 1992; Soryal and Richens, 1992; Meyer et al., 1992; Rosenbaum et al., 1994). In 1988, the U.S. Food and Drug Administration (FDA) set up a special committee to investigate these issues. Between 1988 and 2000, the FDA investigated more than 60 reports of potential inequivalence of generic products, and has been unable to document a single example of therapeutic failure when an FDA-designated therapeutically equivalent generic product, which was manufactured to meet its approved specifications, was substituted for the corresponding brand-name drug listed in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (Henney, 2000).

The frequency with which, disregarding any attribution of cause–effect relationship, the switch from a brand product to a generic (or vice versa) is associated with a change in clinical status cannot be established from anecdotal reports: surveys using questionnaires compiled by patients with epilepsy variably reported frequencies in the order of 11% (Crawford et al., 1996), 14% (Guberman and Coman, 2000), 23% (Haskins et al., 2005), or even 46% (Chappell,

1993), but these estimates are probably influenced by selection bias (the patients who believe to have been affected adversely by the switch are also those who are most likely to return the questionnaire) and by the subjective, retrospective and uncontrolled methodology applied in these surveys. Moreover, reported "problems" do not always refer to a worsening in seizure control: for example, in the survey conducted by Crawford et al. (1996), 11% of patients reported a "validated problem," but only one patient (0.4%) complained of reemergence of seizures after 12 months of complete control and only eight patients (3%) reported "increased seizure frequency." A report on an initiative by the International Bureau for Epilepsy, a patients' organization which expressed concerns about the "risks" associated with generic substitution, estimated that the switch from one product to another may involve a risk of breakthrough seizures in 1 to 2% of cases (Van Emmerink, 2005).

While there is no doubt that in some cases a switch between products can be associated with an alteration in clinical status, a critical assessment of available evidence does not allow us to establish a cause–effect relation, at least for the majority of reported cases. In a disorder such as epilepsy, which is known to be associated with spontaneous fluctuation in the manifestations of the disease, a transient deterioration in seizure control after changing a pharmaceutical product may be due simply to chance or to factors which are unrelated to the product prescribed (for example, a change in compliance). This is well illustrated by the controlled study performed by Vadney and Kraushaar (1997): of 64 patients randomized to generic substitution in this study, 17 had been free from seizures during the 12 months preceding randomization. Two of these patients suffered a seizure recurrence during the study, but in both cases the reemergence of seizures occurred during the period in which the product taken was the same utilized by the same subjects during the 12 months prior to the study!

Some pharmacoeconomic evaluations have been published which suggest that the possible costs of managing the potential disease deterioration or adverse effects resulting from generic substitution may outweigh the savings from the lower price of generics (Jumao-as et al., 1989; Crawford et al., 1996; Argumosa and Herranz, 2005). The working group considered these estimates unreliable, because no unbiased quantitative evidence is available on the possible adverse consequences of generic substitution. By contrast, it is a fact that the difference in price between a brand product and a generic can be substantial, sometimes as much as 10-fold (Vadney and Kraushaar, 1997), even though at times the introduction of a generic may also lead to a reduction in the price of the brand product.

Based on the considerations summarized above, the working group concluded that, in agreement with the assessment made recently by the U.K. National Institute for Clinical Excellence (2004a,b), there is no reliable scientific evidence about risk/benefit and cost/benefit ratios associated with the use of generic products of AEDs. The working group, in any case, considered appropriate to summarize briefly recommendations made by other scientific organizations and to formulate some of its own, which reflect the opinions of its members based on their expertise and an accurate assessment of available documentation.

Recommendations from other scientific organizations

A number of scientific organizations published recommendations, based on the opinion of experts. As illustrated by the examples below, there is considerable heterogeneity in these recommendations:

- The Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology (1990) advises against substituting pharmaceutical products, particularly in the case of phenytoin and carbamazepine, unless this is necessary for medical reasons. The subcommittee recommends that plasma drug levels be monitored closely "at the time of any known or suspected switch" in the product taken by the patient.
- The German Section of the International League against Epilepsy requested that AEDs be excluded from regulations allowing "automatic" substitution of brand products with generics (Kramer et al., 2002). More specifically, the document recommends not to substitute products in seizure-free patients, while generic substitution in patients with persistent seizures may be acceptable provided that plasma drug levels are monitored during the switch. If a physician elects to prescribe a product which does not belong to those ranking in the lower third in terms of price in a patient who needs to start treatment with any given AED, this would have to be specifically justified.
- The committee responsible for the guidelines published by the U.K. National Institute for Clinical Excellence (2004a,b) "did not consider that it had adequate evidence to make recommendations on the use of generic products in the treatment of epilepsy."
- The guidelines of the Scottish Intercollegiate Guidelines Network (SIGN) for the treatment of epilepsies in adults state that "formulations of AEDs are not interchangeable and generic substitution should not be employed" (Scottish Intercollegiate Guidelines Network, 2003). However, a more recently produced version of the SIGN guidelines focused on the treatment of epilepsies in children states that "with the exception of phenytoin, there is no good evidence of significant differences in bioavailability between proprietary and generic AEDs" (Scottish Intercollegiate Guidelines Network, 2005). The pediatric guidelines, however, also mention that difficulties of ensuring a consistent supply of a single formulation

of a particular generic AED "could militate against the use of generic AEDs in those situations where frequent changes of formulation may be inevitable."

Considerations of the working group

The working group reached consensus on the following considerations:

- There is an important lack of information in the public about the properties of generics. This situation is complicated by the fact that messages released by the media on this topic are not invariably correct;
- Generic products of AEDs that comply with existing regulatory requirements must not be considered inferior to the corresponding brand products in terms of efficacy and safety in the treatment of epilepsy. Generic products offer undeniable advantages in terms of cost and allow a better allocation of resources within the National Health Service;
- Most AEDs have a narrow therapeutic index, i.e., their therapeutic dose is often close to the dose that causes toxicity. It is plausible that a modest reduction in plasma drug levels, for example in the order of 20%, may be sufficient to cause recurrence of seizures in rare patients who had been well controlled. Such a reduction might be observed occasionally after switching from one product to another, even when both products meet regulatory criteria for bioequivalence. This principle is recognized in some countries by regulations which do not permit, for narrow therapeutic index drugs, "automatic" generic substitution by the pharmacist (Guberman and Corman, 2000);
- Differences in bioavailability may have particularly important implications for phenytoin, which exhibits Michaelis–Menten (saturation) kinetics. For phenytoin, a modest difference in amount absorbed may lead to amplified changes in plasma drug levels at steady state;
- Because of the psychological, social and regulatory (driving license) implications of seizure recurrence in previously well-controlled patients, it is desirable that all reasonable steps be taken to minimize the risk of relapse in patients who achieved complete seizure remission.

RECOMMENDATIONS

Based on the assessments and considerations summarized above, the working group reached consensus on the following recommendations:

- At the time treatment is initiated (initial monotherapy, switch to alternative monotherapy, or adjunctive therapy), it is desirable to inform the patient about the availability of generic products that offer advantages, sometimes substantial, in terms of cost. These products represent a valuable choice in patients starting treatment;
- In patients already treated with a brand product who have incomplete seizure control, it may be rational, after discussion with the patient, to substitute the brand product with a generic. During the substitution, monitoring plasma drug levels, if possible, may be useful;
- Whenever generic products are prescribed, it is desirable to inform carefully the patient and, when necessary, his/her family or tutor about the nature and the characteristics of these products and the stringent regulations that govern their presence in the market. This is important to improve compliance and to relieve the anxiety that may be associated with receiving a prescription of these products;
- In patients who achieved complete seizure remission, switching pharmaceutical products is not recommended;
- In patients treated with a generic, it is preferable to avoid its substitution with products (including other generics) from different manufacturers. Therefore, it is desirable to specify in the prescription the type (producer) of the generic selected and to add that the product should not be substituted. If substitution is necessary, it may be useful to monitor, whenever possible, the plasma levels of the drug;
- Modified-release formulations are available for some AEDs. These formulations cannot be used interchangeably with immediate-release brand or generic products.

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