

The Effects of Brand-Generic Substitution in Antiepileptic Treatment

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Abstract

The chronic character of the disease has a significant impact on expenses borne by individual patients and by the health care system. Patients diagnosed with epilepsy need a long-term treatment, which is often expensive. In order to minimize the costs, doctors are increasingly turning to prescribing cheaper generic drugs. On the one hand, from an economic perspective, such a solution is cost-effective; on the other hand, the choice of an inadequate treatment may have serious consequences for the patient's health. Patients using drugs with a narrow therapeutic index should be careful because of differences in bioequivalence of medicinal products. An inadequate alteration of the treatment for epilepsy, either by replacing the original drug with a generic one or by replacing one generic drug with another, may adversely affect the patient's condition. It is important, then, that therapeutic decisions should not be guided chiefly by considerations of cost reduction for the patient, but first of all by possible future health effects.

Key words: epilepsy, treatment, antiepileptic drugs, generic drugs, generic substitution

Słowa kluczowe: padaczka, leczenie, leki przeciwpadaczkowe, leki generyczne



Ministerstwo Nauki
i Szkolnictwa Wyższego

Przygotowanie i edycja anglojęzycznych wersji publikacji finansowane w ramach umowy 914/P-DUN/2016 ze środków Ministra Nauki i Szkolnictwa Wyższego przeznaczonych na działalność upowszechniającą naukę.

Introduction

Recent years have seen major changes on the pharmaceutical market. These are due to such factors as population aging, easier access to health care in the developing countries and a growing number of therapeutic products no longer under patent protection, with relatively few new drugs being released onto the market [1].

The drugs available on the Polish market fall into two categories: innovator and generic drugs. The former are original products, marketed for the first time under a brand name, which are protected by patents good for many years. They will have passed lengthy and costly clinical trials to prove their effectiveness, quality and safety. The other category, i.e. generic drugs, are substitute drugs produced by pharmaceutical firms upon the expiry of all the exclusive rights and usually registered under a new name of their own. They contain the same amount of the active ingredient and are administered by the same route, and they will have been developed with

a view to ensuring interchangeability with the reference drug product [2].

The innovator and generic medicines should have comparable therapeutic efficacy and should be equally safe. However, some authors question that assumption with regard to medications with a narrow therapeutic index. There are more and more frequent published reports of an increasing incidence of epileptic seizures after the switch from an original product to a substitute drug [3–5]. There have also been cases of deterioration in patients' health after the reverse switch of drugs, or after the substitution of one generic drug for another. It follows from this that in the case of drugs with a narrow therapeutic index the bioequivalence of generic drugs may be different and their evaluation is either insufficient or incorrect. In addition, the acceptable deviations from the confidence interval in the bioequivalence studies of generics, amounting to 20–25%, are considerably larger than those expected of original drugs, which cannot exceed $\pm 5\%$.

Some specialists claim that the research results regarding generic drugs are unreliable on account of extremely small numbers of patients involved. The innovator therapeutic product and the generic contain identical doses of the same active ingredient, so the change should not be perceptible to the patient. The only perceptible difference should be the amount of money saved by the purchase of the generic drug, because of its lower price [6].

Similarities and differences between innovator and generic drugs

Generic drugs are frequently, and not without reason, referred to as substitutes for brand-name drugs. They are defined as such because of the great similarity between the two types of products. They contain the same active ingredient, have the same form, dose, indications and route of administration. They exhibit fundamental similarities in bioavailability and pharmacological effects. They are equally effective and equally safe. However, they may look different. The generic drug may have a different size, shape or colour, but these features have no essential effect on its action. However, what can be a matter of concern is another difference, due to the presence of excipients added to the generic drugs. These are added when there is no risk that they will change the pharmacological properties of the drug or adversely affect its effectiveness [6].

Research on original drugs is a complex and time-consuming process requiring appropriate scientific, technological, organizational and, above all, financial resources. It involves a high risk of failure for the pharmaceutical companies, as only a small percentage of potentially therapeutic compounds are subject to clinical trials, and subsequently only one in five is registered and made generally available. That is why only a very few companies, chiefly international ones, are capable of engaging in drug development [7].

In contrast to the costly and lengthy clinical research (phases I–III) required for an innovator drug, in order to prove the safety and efficacy of a generic drug it is enough to carry out a bioequivalence study. If the substitute drug will be administered under the same regime as the original product, it is only necessary to demonstrate, on the basis of appropriate research, that the two preparations are bioequivalent, that is to say, that their formulas are either equivalent or alternative and, when administered at the same dose of the active ingredient, their bioavailability, i.e. the rate and extent of their absorption, is close enough to ensure the same degree of efficacy and safety [8].

Besides determining the similarities and differences in the properties of drugs and in their production processes, it is also necessary to consider their registration procedures. Whether original or generic, a newly introduced medication has to gain the approval of an administrative drugs agency. In Europe the relevant institutions are the European Medicines Agency (EMA) if the assessment is made at the central level, and the national agencies

when dealing with the individual countries. The Polish institution is Urząd Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych (URPLW MiPB). In the United States the assessment is carried out by the Food and Drug Administration (FDA) [9].

In the process of registration of an innovator therapeutic product a pharmaceutical company must present the complete record of its detailed clinical and pre-clinical research. The producers of generic preparations face a much easier task at this stage. Since these drugs contain long well-known active ingredients, the proof of their safety, efficacy and quality is based on bioequivalence research only. Such data are much faster and certainly much less expensive to collect than in the case of innovator drugs. Owing to that, the producers of generic preparations are able to save enormous costs as well as gaining time. It is estimated that the mean duration of work on the development of an innovator drug is about 10–12 years, while in the case of a generic drug it is decidedly shorter, from 2 to 5 years [6].

Despite the considerable amounts of time saved in the development of generic drugs, it will be worthwhile to focus on the difficulties encountered by their producers. The main obstacle is of course the 20–25 year patent protection of the original drugs. In fact, innovator therapeutic products can be protected by multiple patents, their number sometimes reaching 20 to 40 or even many more. According to the data of the European Commission, there exists a therapeutic product protected by as many as 1,300 different patents [6, 9].

Another point of difference between the innovator drugs and their substitutes is their price. In Poland, generic products account for almost three quarters of the pharmaceutical market [10]. According to a report entitled *The contribution of the innovative pharmaceutical industry to the Polish economy (Wkład innowacyjnego przemysłu farmaceutycznego w rozwój polskiej gospodarki)* Poland is among the leading European countries in the sale of generics and it has one of the lowest levels of generic drug prices. The average price of a generic in this country is 2.6 times less than the price of a brand-name drug [11]. For comparison, in Holland the factor is 6.5 [11]. Thus the difference in drug prices is very big. The huge gap between the prices of original medicines and their substitutes results first of all from the fundamental differences in their producers' cost structure. The innovator firms invest a large proportion of their money in pre-clinical and clinical research, which need not be done by their competitors who bring generics onto the market [12].

Substitution of generics for brand-name drugs in the treatment of epilepsy

Practically all the branded antiepileptic drugs registered in Poland have generic drugs corresponding to them. However, increasing the application of the latter in the treatment of epilepsy is a matter of much controversy [3]. There are fears related first of all to the fact that

antiepileptic medications mostly have a narrow therapeutic index [4]. Physicians believe that a bioequivalence ranging from 80% to 125% is too broad for this group of drugs. They maintain that such a broad range coupled with other, individual factors in epilepsy sufferers may reinforce small differences in bioequivalence. As a consequence, some epilepsy patients taking generics run the risk of a higher incidence of seizures or other adverse effects [5]. Therefore, it is extremely important to carefully select the right medicine and the right dosage for each individual. It is also important that the physician in charge of the treatment should inform his/her patients, particularly those with a higher risk of seizures, of the possible consequences of taking generic drugs. It is also recommended that the physician should encourage his/her patients to closely monitor their well-being. It is important, too, that pharmacists should participate in the exchange of information concerning changes of therapy, and it is inadvisable to sell substitute drugs to epilepsy patients without the doctor's consent [4, 13, 14].

It is also well known that since antiepileptic drugs are among the medications with a narrow therapeutic index, their application may be particularly dangerous for some patients. This concerns first of all people treated for co-existing diseases and taking many medicines. Other high risk groups include the elderly and patients with renal or hepatic malfunctions, who run an increased risk of drug interactions and therefore should be particularly circumspect [4].

Research has shown that the differences in the composition of original and generic antiepileptic drugs may be minimal, but the difference grows considerably when two generic drugs are compared [15, 16]. Even though all these preparations are considered bioequivalent, in the case of a small percentage of patients variation in the confidence interval in bioequivalence research can have a major effect on their subsequent health and quality of life [15, 16]. It has been reported by both physicians and patients that some epilepsy sufferers experienced seizures much more frequently after a shift from innovator to generic drugs [4]. Some even had to be hospitalized. One example involves a woman who after three years of treatment with an original drug decided to switch to a generic drug; the result was that she suffered breakthrough seizures within three days of the start of the new therapy [17].

A growing number of doctors report with alarm seeing patients whose condition worsened after switching to a cheaper treatment with generic drugs. A report published in a neurological periodical presents a group of 50 people aged 11–64 years, in whom the incidence of epileptic seizures increased as a result of a change of medication. The data were obtained from neurologists who reported on their patients ($n = 69$) who switched from brand-name to generic drugs [18]. The same concerns 4 patients who participated in a case-control study in 2011 [19]. Another cause for concern is the result of an analysis conducted in a group of 187 epilepsy patients, as many as 20–44% of whom (depending on the drug) experienced breakthrough seizures after treatment with generic drugs [20].

Researchers from the American Academy of Neurology have expressed the position that there are concerns associated with the change of therapy in epilepsy. Still, no steps have been taken so far to improve the situation of patients [17]. The American Food and Drug Administration maintains that the existing requirements concerning drug bioequivalence are so rigorous that there is only a small risk that the generics that meet them might lead to therapeutic problems [21]. FDA believes that a change of treatment does not increase the risk of relapse or undesirable effects [5]. Interestingly, one of the advisory bodies to FDA stated in its opinion that such a broad confidence interval (80–125%) was not optimal in the case of antiepileptic drugs, and yet FDA has issued no special recommendations in the matter [15]. FDA has also announced that there is no sufficient scientific evidence to suggest that the therapeutic range assumed at the time was too general for medications with a narrow therapeutic index [10]. FDA persists in the opinion that all changes in antiepileptic therapies are equally safe for all sufferers [12].

There is plentiful evidence that treating epilepsy with generic drugs does not produce satisfactory results. Despite that, institutions engaged in bioequivalence research claim that all drugs are equally safe and effective [4]. That view is borne out by several reports showing that no disturbing changes have been found in the patients under observation. One example concerns the results of a meta-analysis of randomized trials on a sample of 204 patients, where no difference in seizure frequency was found between patients given brand-name drugs and those given generics. However, that study was carried out over a very short period and covered a small population of patients. There is a need, then, to undertake detailed research on a large population. Unfortunately, such analysis can be costly and time-consuming, so at this point we have to answer the question whether such work will really be effective from the perspective of public health [22].

Taking generics is often unavoidable for economic reasons, as their price is much lower than that of brand-name drugs. The market is very competitive, so pharmaceutical companies are forced to bring down their prices, a very welcome effect from the patient's point of view. In addition, the low price of medicines can motivate patients to pursue regular and uninterrupted treatment, which is of great importance in the case of epilepsy sufferers [12]. What is more, some insurance companies offering extra insurance simply require their clients to be treated with generic drugs. We must also remember that many generic preparations are made on licence from the original producer upon expiry of the patent; thus the quality of the generic ought to be very good [23, 24].

For all the advantages of treatment with generics, however, we need to analyze the cost of the switch from innovator drugs, taking it into account that some groups of epileptic patients are particularly sensitive to even the minutest changes in bioequivalence. Those are the patients most frequently suffering from a relapse of seizures, which lead to hospitalization and thereby generate extra costs to the system [25]. The savings made by the switch of medicines can be less than the costs generated

in the other areas of health care, such as the purchase of additional medical products and hospital or outpatient services [19]. Another result of therapy switch may be a worsened quality of life for the patient [12]. The available data show that some epilepsy sufferers have been instrumental in causing serious traffic accidents because of sudden seizures. Some have lost their jobs because of a relapse of the disease or have had to spend more time visiting doctors' surgeries or hospitals. In view of the above, we have to note that the wrong change of therapy entails social as well as economic costs [17, 26].

A questionnaire-based survey conducted by Wilner [30] among 301 neurologists revealed that after a shift from an original drug to a generic one as many as 81.4% of doctors observed an increase in the number of seizures (67.8%) or toxic symptoms (56%) in their patients. In the case of a shift from one generic to another the percentages were 32.5% and 26.6%, respectively. Such adverse effects following a change of medication required additional consultations, visits to a surgery or an emergency department, and hospitalization. The costs incurred amounted to \$675,004, with the following breakdown: 46 hospitalizations (\$12,154 each), 166 additional visits to a doctor's surgery (\$120 per visit) and 1,128 emergency department visits (\$570 per visit). These results show that the substitution of generics for brand-name drugs is not always profitable.

Summary

The European pharmaceutical industry currently spends some 30 billion euro per year on clinical research and development of new technologies [27]. Despite the enormous amount of medical knowledge and the availability of medications, doctors are sometimes still helpless in their fight against some diseases. Therefore, it is necessary to pursue systematic clinical research on new substances to meet the growing requirements of therapy. This long-term painstaking research holds out hope for safer and more effective therapies and for the discovery of new medications to treat as yet incurable diseases [28].

Original products go through a long development process, owing to which they will have been examined more thoroughly. Generic drugs should be bioequivalent to the original ones, and their prices are much lower. That enables individual patients, and also the health care system as a whole, to make considerable financial savings. We cannot say that a generic preparation is one hundred per cent identical to the original drug, but we can certainly say that they are similar. It is remarkable that with most patients the change from one to the other may pass unnoticed, but for some, the effect of the two therapeutic products on their organism may be somewhat different [29]. Therefore, we cannot state unequivocally which of the two types of drugs is better.

In the case of epilepsy, the treatment of which requires long-term application of drugs, every change of medication may be dangerous. In view of that, the choice of therapy always requires consultation with a doctor so that the patient and the doctor might jointly agree on a regi-

men best suited to the patient's needs. It is important that when changing a therapy one should not be guided solely by the current price of the medication selected, but also by the costs the given group of patients might incur in future, and above all by the clinical condition of the patient.

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