

Increase of Classical Antiepileptic Drug Utilization in Croatia During the Process of Introducing the New Generation of Drugs

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ABSTRACT

During the last decade the process of introducing the new generation of antiepileptic drugs (AEDs) has substantially changed the ways of treating epilepsy. Although a great deal of information about the role of new drugs has been accumulated, much less attention was paid to the impact of the new generation of AEDs on the utilization of classical AEDs. In order to detect the relation between the new and classical AEDs, the data about drug consumption in Croatia in the period 2000–2002 were analyzed. The main results indicated that the growth utilization rate (15%) was more the result of increasing consumption of the classical antiepileptic substances (in almost 2/3). It has been discussed that one of the possible interpretations for this phenomenon could lie in the fact that the continuing process of introducing the new AEDs was accompanied by a great number of educational activities. These activities have led to greater awareness of the facilities in treating epilepsy and consequently to a more active therapeutic approach, which encompassed both generations of drugs, even more the older one.

Key words: epilepsy, drug utilization, therapy

Introduction

At the end of the 20th century, several new antiepileptic drugs (AEDs) were introduced into therapeutic practice. Although the exact role of the new drugs in

some aspects of the therapy is still controversial¹, their introduction has led to substantial qualitative and quantitative changes in the pattern of medication use.

It is clear that the introduction of the new AEDs has led to the substantial expanding of the AEDs spectrum of use, but it is not completely clear whether the consequences on the consumption of traditional remedies could be the result of the introduction of the new drugs. Monitoring the drug utilization could be a useful tool for assessing these changes.

The new AEDs have been registered in Croatia in the following order: vigabatrin (1996), lamotrigine (1999), topiramate (2000) and gabapentin (2002). As the process of gradual introducing of new AEDs is still under way, Croatia could be a useful model for studying the relationship between the traditional (»old«) and new AEDs.

The purpose of this study is to determine the changes in AEDs utilization which could be related to the process of introducing new AEDs into antiepileptic therapy.

Methods

Data obtained from the Croatian Health Institute were used. The original data consisted of the numbers of packs and costs of the drugs for the periods 01/01/2000–31/09/2002. These data were transformed into yearly values, and numbers of packs were expressed as numbers of defined daily doses (DDD), as defined by WHO Collaborating Centre for Drug Statistics Methodology². The drug utilization was also expressed as the number of DDD/1000 people, according to the census carried out in the year 2001³.

Results

In Figure 1 it is shown that the utilization of AEDs in the year 2002 was dominated by carbamazepine and the group of barbiturates (phenobarbital, methylphenobarbital, primidon). The valproates (valproic acid and valpromide) were in the

third place, whereas other AEDs, including the new AEDs, were substantially less often prescribed.

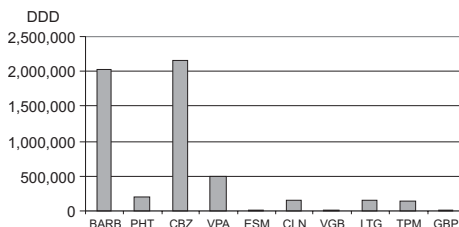


Fig. 1. Frequency of prescribed AEDs in 2002. Abbreviations and DDD values used² (in brackets): BARB – barbiturates: phenobarbital (0.1 g), methylphenobarbital (0.5 g), primidon (1.25 g), PHT – phenytoin (0.3 g), CBZ – carbamazepine (1 g), VPA – valproates: valproic acid (1.5 g), valpromide (1.5 g), ESM – ethosuxinimide (1.25 g), CLN – clonazepam (8 mg), VGB – vigabatrin (2 g), LTG – lamotrigine (0.3 g), GBP – gabapentin (1.8 g).

The trend of growing utilization of AEDs in the three-year period is demonstrated in Figure 2. It can be seen that in the year 2000 3.9 DDD were consumed daily in the population of 1000 people, and in the year 2002 this number reached 4.5 DDD, i.e., the increase was about 15% in relation to the year 2000.

In Figure 3 it is demonstrated that the increase of utilization was not only related to the increase of utilization of new AEDs. Actually, what can be seen is the

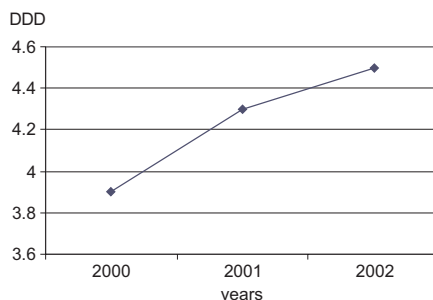


Fig. 2. Number of consumed DDD/1000 population/day.

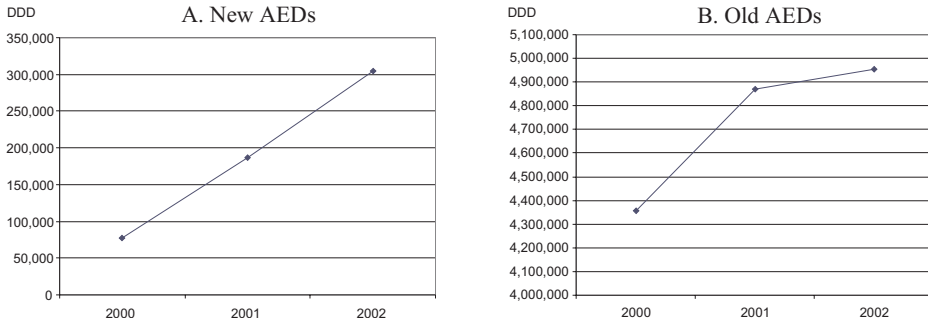


Fig. 3. Increase of AEDs 2000–2002.

fact that in three previous years classical AEDs increased their utilization more than the new ones. The increase of the old AEDs was about 600,000 DDD, and the growth of the new AEDs was about 240,000 DDD.

Discussion

Antiepileptic drug utilization is one of the main markers indicating the level of management for people with epilepsy. The biggest therapeutic gap is in the developing countries, but it has been reported in Europe, too^{4–5}. Consequently, an increase in consumption of AEDs can be generally interpreted as a positive fact.

In the last decade of the 20th century, several new AEDs were introduced into therapy worldwide. Among those widely accepted are vigabatrin, lamotrigine, gabapentin, oxcarbamazepine, felbamate, tiagabine, zonisamide, topiramate, and levetiracetam⁶. These drugs have some advantages: some of them are better tolerated^{7–8}, some of them have fewer interaction capacities^{9–10}, plasma level is not recommended for any of them^{11–12}. Concerning the efficacy of these drugs in comparison to the older ones, they are generally considered to have equal efficacy and in some conditions are slightly more efficacious¹³. In some epileptic syndromes, however, they represent real progress

and a better chance for the cure of epilepsy^{14–21}. Because of the higher cost, the question of the cost-effectiveness is still controversial especially for the poorer, developing countries^{22–24}.

Although a great deal of information about the role of new AEDs in therapy has been accumulated, much less attention was paid to the impact of the new generation of AEDs on the utilization of classical AEDs, such as barbiturates, phenytoin, valproates and carbamazepine. Considering the substantial advantages of the new medicines, one of the possible results of gradual introducing of new AEDs would be the substitution of older drugs for the new, and potentially better AEDs. This hypothesis was tested in this study.

AEDs utilization was studied using the methodology proposed by WHO Collaborating Centre for Drug Statistics Methodology. This methodology is thought to be a useful technique to make it possible for the drug consumption data to be measured and compared, both nationally and internationally^{25–27}.

Our results indicated that the introducing of new AEDs did not result in the simple substitution of classical AEDs for the new ones. In the period of the last three years it was observed that there was a substantial increase of general consumption of about 15% (year 2000 vs.

2002), but the more recent generation of AEDs participated with only about 1/3 of this figure. At first sight, these results seem to be paradoxical, because it appeared that the promotion of new AEDs resulted in an even greater increase of the AEDs which were intended to be replaced.

Apart from the promotional campaign of the new AEDs, some populational factors might have influenced the general increase of AED consumption. However, there were no significant changes in the population number in Croatia during the period of research which could have influenced the prevalence of epilepsy. Moreover, there were no changes in the access to medical care or changes in the reimbursement (all AEDs are free of charge). As a matter of fact, according to the best of our knowledge, there was no increase in AED utilization for other conditions besides epilepsy, and there were no other factors that could have influenced changes in the incidence of epilepsy.

There are no unambiguous answers for the fact that traditional AEDs had a greater share in the general utilization of AEDs. Yet, a plausible explanation for that phenomenon would be that the appearance of new AEDs in Croatia actually resulted in an apparently paradoxical increase in the consumption of the traditional AEDs. We think that it was caused by the intensive promotional campaign, supported by pharmaceutical industries which resulted, among other issues, in a series of meetings dealing with the therapy of epilepsy. Those activities,

at least partly, were designed as educational courses focused on the target population of physicians dealing with epilepsy, especially neurologists and neuropaediatricians*. It seems that the promotional campaign organized in this way, which has been continuing so far, has led to greater awareness of the therapeutic facilities in treating epilepsy. Consequently, the more active and more enthusiastic therapeutic approach has been developed, which led to the greater utilization of all AEDs, both of the new and old generations. As the classical drugs are much more widely used in Croatia, the trend of growing utilization expressed in absolute figures affected the old generation of drugs. If one would accept such an attempt of interpretation, the growing utilization of traditional AEDs could be regarded as a kind of distant secondary effect of the introduction of the new antiepileptics.

In conclusion, it seems that the trend of growing utilization of the standard AEDs could be related to the process of introducing the new AEDs accompanied by a great variety of educational activities. These activities have led to greater awareness of the facilities in treating epilepsy and consequently to a more active therapeutic approach, which encompassed both generations of drugs, even more the older one. Although the above interpretation might sound plausible, similar studies in other countries are indispensable to confirm or reject the hypothesis arrived at in this work.

* In the period 2000–2002 the following meetings and educational courses dealing with the new AEDs were held in Croatia: »The contemporary therapy of epilepsy« – organized by the Croatian league against epilepsy, but with the contribution of the pharmaceutical industries (Zagreb – December 2000, 2001 and 2002), the workshops about Topamax – organized by »Jansen-Cilag« (Zagreb – May 2001, June 2002, and Umag – May 2002)

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PORAST KORIŠTENJA KLASIČNIH ANTIEPILEPTIČKIH LIJEKOVA U HRVATSKOJ TIJEKOM PROCESA UVOĐENJA LIJEKOVA NOVE GENERACIJE

SAŽETAK

Tijekom posljednjeg desetljeća proces uvođenja nove generacije antiepileptičkih lijekova (AEL) znatno je promjenio načine liječenja epilepsije. Premda se došlo do velikog broja informacija o ulozi novih lijekova u liječenju epilepsije, mnogo manje se zna o utjecaju nove generacije AEL na korištenje klasičnih AEL. S ciljem da se ustanove odnosi između novih i klasičnih AEL, analizirani su podaci o korištenju tih lijekova u Hrvatskoj u razdoblju od 2000. do 2002. godine. Rezultati su pokazali da je porast korištenja (15%) više bio izraz porasta potrošnje klasičnih antiepileptika (gotovo 2/3). U raspravi je naglašeno da jedna od mogućih interpretacija tog fenomena može biti u tome što je kontinuirani proces uvođenja novih AEL bio praćen nizom edukativnih aktivnosti koje su dovele do više razine znanja o mogućnostima liječenja epilepsije. Posljedično tome, aktivniji stav pri liječenju doveo je do porasta korištenja obje generacije lijekova, štoviše, u većoj mjeri klasičnih AEL.