Consumption of Anti-Epileptic Drugs in Primary Health Care in Albania, 2004-2016

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Abstract

BACKGROUND: Epilepsy is a serious neurological condition requiring sometimes lifelong pharmacological treatment, and continuous specialist monitoring.

AIM: To investigate the use of Anti-Epileptic Drugs (AEDs) in epilepsy, with focus on the exposure of AEDs, differences and changes in prescription patterns over time; to evaluate the relation between the consumption data of AED and the level of epileptic morbidity for the period 2004-2016.

STUDY DESIGN: Official data regarding the consumption of AEDs within Albania were collected retrospectively. Every year of the period, 2004-2016 has been considered separately.

METHODS: The data were assembled from Health Insurance Institute (HII) in Tirana, Albania and analysed for the period 2004-2016. The consumption of drugs was expressed as several Defined Daily Dose (DDDs)/1000 inhabitants/day. Also, for all the period under study 2004-2016, we analysed the data of import and domestic production of drugs, which represent the real consumption of drugs in the country. These data were subsequently involved in a comparative analysis with the utilisation data according to the HII, as well as through performing international comparisons of the consumption of AEDs drugs.

RESULTS: Epilepsy morbidity data indicate that there exists a correlation statistically significant between this disease and the trend of consumption of AEDs.

CONCLUSION: The present study suggests that the level of consumption for AEDs in Albania is very low when compared globally; with a decrease in the consumption of classic antiepileptic drugs and a parallel increase in the consumption of new generation drugs.

Introduction

Epilepsy is a group of neurological diseases characterised by a predisposition to recurrent unprovoked seizures [1], [2]. Epileptic seizures are episodes that can vary from brief and nearly undetectable to long periods of vigorous shaking [3]. The human brain is the source of human epilepsy. Although the symptoms of a seizure may affect any part of the body, the electrical events that produce the symptoms occur in the brain. The location of that event, how it spreads and how much of the brain is affected, and how long it lasts all have profound effects. These factors determine the character of a seizure and its impact on the individual.

The cause of most cases of epilepsy is unknown, although some people develop epilepsy as the result of traumatic or vascular injury, brain tumours, infections of the brain, and congenital disabilities [3]. Epileptic seizures are the result of excessive and abnormal nerve cell activity in the cortex of the brain [4]. The mainstay treatment of epilepsy is anti-epileptic medications, possibly for the person's entire life [5]. The choice of anticonvulsant is based on seizure type, epilepsy syndrome, other medications used, other health problems, and the person's age and lifestyle [6]. A single medication is recommended initially; if this is not effective, switching to a single other medication is recommended [7], [8]. Two medications at once are recommended only if a single medication does not work [8].

There are a number of medications available. Phenytoin, carbamazepine and valproate appear to be equally effective in both partial and generalised seizures [9], [10]. The least expensive anticonvulsant is phenobarbital. The World Health Organization gives it a first-line recommendation in the developing world, and it is commonly used there [11], [12].

Adverse effects from medications are reported in 10 to 90% of people, depending on how and from whom the data is collected [13]. Most adverse effects are dose-related and mild [13]. Despite this, treatment is often continued once effective because the risk of untreated epilepsy is believed to be greater than the risk of the medications [14].

The study aimed to assess the out-of-hospital AEDs use in Albania during the period 2004-2016.

Material and Methods

The data were obtained from the HII [15]. All data were collected for the period 2004-2016 and analysed. The analysis included the total number of prescriptions made and quantities of drugs used.

The data about the population were obtained from the Institute of Statistics (INSTAT) [16]. The data about the consumption of drugs were expressed as several Defined Daily Dose (DDDs)/1000 inhabitants/day. All drugs were classified by groups of Anatomic Therapeutic Chemical Classification (ATC).

Data on real consumption (import and domestic production)

For all the period under study 2004-2016, there were collected and analysed data from the import and domestic production of the drugs [17], which represent the real consumption of drugs in the country. It was noted that the increase in consumption from one year to another was small, e.g. the consumption from 2012 to 2016 (i.e. 4 years) was increased by only 2.32%. Consequently, to obtain an updated study, there were chosen the data of import and domestic consumption only for the last three years, 2014, 2015, 2016, and those were involved in a comparative analysis with the equivalent consumption data according to HII. To minimise the effect of variations between consumption and stock inventory balances from one year to another, it was calculated and put to analysis the annual average value of the three chosen years (on the one hand that of the import and domestic consumption, and on the other hand that of HII).

Presentation of the results and statistical elaboration

The database of HII was modified in Microsoft Office Excel 2007, whereas the statistical elaboration of the obtained results was conducted with the statistical package StatsDirect (version 2.7.2.). A descriptive statistic was used to report all data on drugs consumption and the results obtained were displayed in tabular form as well as through the histogram method.

Average annual values of consumption in the country level and for each district were used as a basis to generate the overviews and the graphics that illustrate the trends of consumption for each class of drugs during the 10 years 2004-2016. The linear regression model was used to evaluate the trends of consumption of drugs relative to the time. A value of p ≤ 0.05 was considered as significant.

To asses, if there exists a correlation statistically significant between the level of consumption of drugs and the level of morbidity, it was applied the Spearman correlation (with a significance level of ≤ 0.05).

Results

The data were expressed as a number of defined daily doses per 1000 inhabitants/day (DDDs/1000 inhabitants/day).
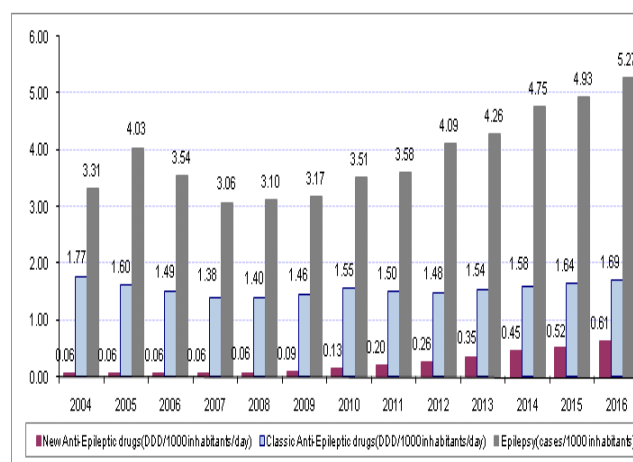

Figure 1: Consumption of different classes of AEDs at national level (DDD/1000 inhabitants/day) versus Epilepsy morbidity (cases/1000 inhabitants) (For the new AEDs: p = 0,0421; strength (with significance level ≤ 0,05) = 53.6%; correlation coefficient statistically significant; for the classic AEDs: p = 0,1618; strength (with significance level ≤ 0,05) = 27.62%; correlation coefficient is not statistically significant).

The consumption of AEDs was 1.82-2.30 DDD/1000 inhabitants/day respectively in 2004-2016. The AEDs most prescribed are the classic or the old

generation with values of 1.77-1.69 DDD/1000 inhabitants/day, 2014-2016. Meanwhile, the new generation of AEDs included in the reimbursement scheme is lamotrigine, gabapentin, levetiracetam and topiramate. Their values of consumption are 0.06-0.61 DDD/1000 inhabitants/day.

Epilepsy morbidity data indicate that there exists a correlation statistically significant between this disease and the trend of consumption of AEDs (P = 0.0034), (Figure 1, and 2).
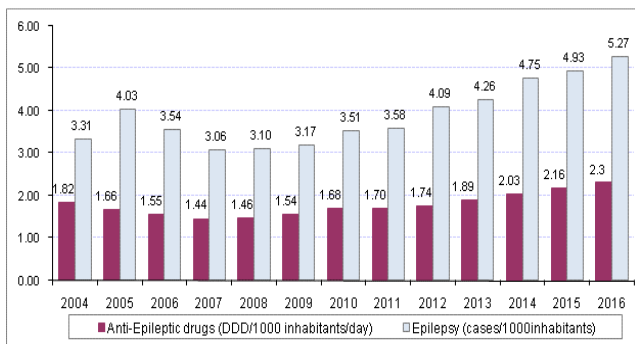

Figure 2: Total consumption of AEDs at the national level (DDD/1000 inhabitants/day) versus Epilepsy morbidity (cases/1000 inhabitants)

Discussion

Epilepsy is a frequent disorder in the western countries occurring in 4-8/1000 inhabitants [30]. The earliest effective pharmacological treatments to prevent epileptic seizures date in 1857, when Locock prescribed for the first-time potassium bromide. However, until 1970, there were in circulation, only a small number of antiepileptic drugs. Since then, the introduction of new antiepileptic molecules in the pharmaceutical market has been highly accelerated, to the point that some new antiepileptic drugs are prescribed even for pain control, psychiatric disorders or migraine prevention [31], [32], [33], [34].
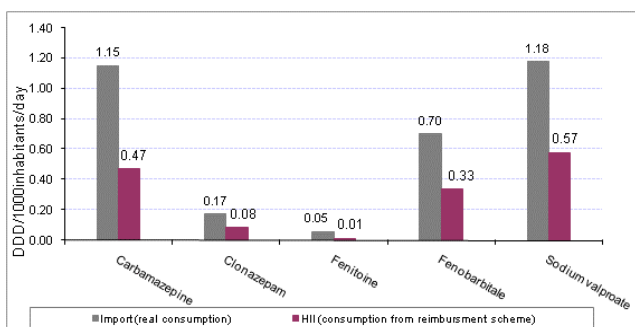

Figure 3: Annual average value of consumption of classic AEDs: consumption-based on import (real consumption) [*] versus consumption based on HII. [*] The "Import" item includes the consumption based on import data as well as the consumption-based on domestic production: this represents the factual consumption

In Figure 1 and 2 can be noted an expressed inconsistency between the level of reported morbidity and the very low consumption of antiepileptic drugs. _First_ of all, in some years it results that more than half of epileptic patients have not taken medication under the scheme. _Secondly_, there is noted refraction in the morbidity trend, going through a significant increase in 2005 and a noticeable decrease in 2006-2007, which is difficult to explain from the medical perspective. The consumption reports do reflect the same trend too, but with slighter refraction and with a decrease in consumption in 2007. However, the consumption for this drugs class, although in low levels compared to the morbidity levels, seems relatively consistent and stable. A reason could be the fact that the main drugs in the treatment of this disease continue to be the classic antiepileptic drugs at low cost and low impact on the HII's budget. As old preparations, they do not attire the interest of pharmaceutical companies, and hence, their promotion and marketing remain low. Another reason could be the fact that new antiepileptic drugs were included under the scheme only in 2009.
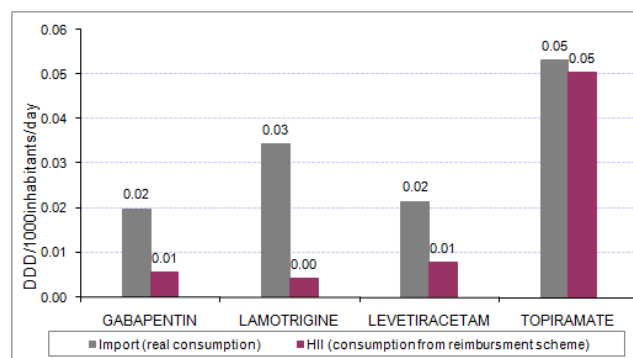

Figure 4: Annual average value of consumption of new AEDs: consumption-based on import (real consumption) [*] versus consumption based on HII. [*] The "Import" item includes the consumption based on import data as well as the consumption-based on domestic production: this represents the factual consumption

To have a better understanding, we have analysed the data of consumption based on imports, comparing them to the analogue consumption data based on HII reports.

As it can be noted in Figures 3, 4 and 5, the consumption of classical antiepileptic drugs is covered in only 57% by the scheme; the remainder of the patients take these drugs without a prescription from the family doctor. It should be considered in this case that such drugs are useable for other purposes apart from for epilepsy, whereas the HII reimburses them only for the treatment of different forms of epilepsy. For instance, sodium valproate is also reimbursed for the treatment of the manic phase of bipolar disorder and is also prescribed for the increase of pain tolerance for chronic pains.
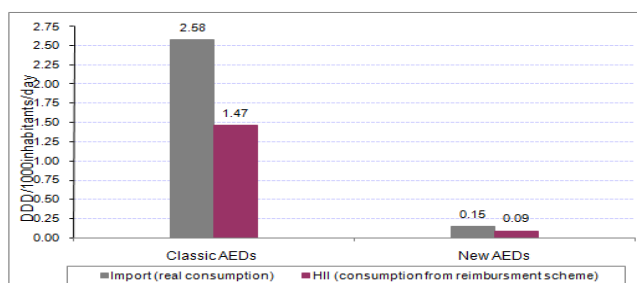
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Figure 5: Annual average value of consumption of both classes of AEDs: consumption-based on import (real consumption) [*] versus consumption based on HII

On the other hand, the consumption of new antiepileptic drugs reported by HII consists in around 60% of their total consumption based on import figures. Some of them, e.g. _gabapentin_, is increasingly indicated by therapeutic guidelines for the treatment of neuropathic pain. However, it is of interest the fact that the total value of consumption of antiepileptic drugs based on import data is very much approximate to the reported values of epileptic morbidity.

Among the new antiepileptic drugs, the only one that has been part of the list since in 2004, is _topiramate_: 3.08%-5.43%, 2004-2016. Antiepileptic drugs of the new generation have been included in the list only by 2009.

The consumption of antiepileptic drugs in different regions (Figure 6) remain relatively low. The region with the minimum consumption along the years is Vlora, whereas the maximum consumption is in Berat.
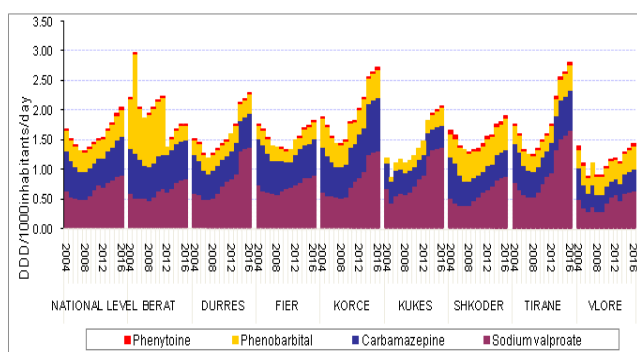

Figure 6: Consumption of AEDs in different regions and at the national level (DDD/1000 inhabitants/day)

A common feature for all regions is the gradual reduction of the consumption in 2006, and especially in 2007 (a year in which the list of reimbursable antiepileptic drugs was the poorest compared to any other year), whereas in subsequent years the list gets re-extended, a fact which is reflected also in the consumption, particularly in the last years of the study.

At the national level, the consumption of antiepileptic drugs undergoes a slight increase (from 1,82 DDD/1000 inhabitants/day in 2004 to 2.30 DDD/1000 inhabitants/day in 2016). This increase in consumption does not reflect the evident increasing morbidity trend of 5.97% (3.31-5.27 cases/1000 inhabitants during 2004-2016). In total, we note a decrease in the consumption of classic antiepileptic drugs and a simultaneous increase in the drugs of the new generation. The clinical trials performed report little evidence that supports the usage of monotherapy with antiepileptic drugs of the new generation or their usage as adjuvants in the antiepileptic treatment, compared to the classic antiepileptic drugs. Furthermore, there is no evidence indicating the priority of usage of an antiepileptic drug over another one [35], [36]. _Levetiracetam_, as well as the other similar antiepileptic drugs of the last generation such as _gabapentin_, _lamotrigine_, _oxcarbazepine_, _tiagabine_ and _topiramate_, are recommended by international therapeutic guidelines to be used as drugs of first choice, in order to reinforce the "on" phenomena and the improvement phase in partial epilepsies at adults, resistant to previous drugs (with partial or generalized seizures) [36], [37], [38].

In general, the data obtained in the clinical efficacy, the security of consumption and the pharmacological tolerance to them, have not been able to demonstrate statistically significant differences between these drugs. As an exception, the comparison between new antiepileptic drugs and placebo has resulted in significant differences in favour of the new generation. However, the clinical trials are generally short-termed, limiting to a certain extent the applicability of the data obtained. New antiepileptic drugs used as monotherapy, may have a favourable efficacy-cost report in the treatment of patients that have incurred severe negative side effects from the old classic antiepileptic drugs, of those where the therapy with classic antiepileptic drugs has failed, or of those cases where the drugs of the old generation have been counter-indicated [39].

From the perspective of the efficacy-cost report, an investigation of the British Sanitary system published in 2005, has indicated that new antiepileptic drugs may be superior in patients with partial or generalised seizures refractory to traditional antiepileptic drugs [39].

Comparisons of consumption at the international level

In international comparisons, the consumption of antiepileptic drugs in Albania remains in very low values (_Figure 7_). The total consumption of antiepileptic drugs in our country in 2016 results 2,36 DDD/1000 capita/day, whereas in the Netherlands the consumption of this class appeared since in 2001 around the value 7,02 DDD/1000 capita/day [40]. A reason can be the lack of combined schemes of therapy and the usage of lower than needed doses. These may be indicators of the under-treatment of this pathology in our country.

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In conclusion, the consumption values of anti-epileptic drugs in Albania are very low. We noted a decrease in the consumption of classic antiepileptic drugs and a simultaneous increase in the drugs of the new generation. Also, an important part of anti-epileptic drugs flows out of the reimbursement scheme.

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