CORRELATION BETWEEN PRESCRIBED DAILY DOSE, SEIZURE FREEDOM AND DEFINED DAILY DOSE IN ANTIEPILEPTIC DRUG TREATMENT

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Introduction

Epilepsy is one of the most common neurological disorders and it puts a big burden on health care systems, requiring a long-term drug treatment [1].

In 1996, the World Health Organization (WHO) launched the methodology defining the daily dose (DDD), a widely used tool in drug utilization studies [2, 3]. Although DDD is an average maintenance dose in adults by definition [4] and a unit used in drug consumption, notwithstanding, contradictions with prescribed daily dose (PDD) can be observed [2, 5]. Based on prescription data, Hsieh and Huang reported lower or similar PDDs of the most commonly used AEDs in monotherapy compared to polytherapy in a nation-wide drug utilization study. Although significantly higher doses were confirmed between monotherapy and polytherapy groups among carbamazepine (CBZ), valproate (VPA) and gabapentin (GBP) users, in both groups the PDD/DDD ratios were lower than 1.00 [6]. Similar findings were published in a Czech study [7] and in a comparative study based on Swedish and Czech data [8]. Both studies used PDDs of patients' data who had undergone therapeutic drug monitoring (TDM).

Studies have confirmed that combination therapy is used in the minority of cases; notably, the proportion of combination therapy reported in four studies by Brodie et al. [9], Kořístková et al. [7, 8] and Rochat et al. [10] fell in the range of 15-38.2%. Accordingly, there is another contradiction between clinical practice and DDDs of AEDs assigned for combination therapy in the case of AEDs by WHO [4].

DDD is used not only as a simple number to compare different periods and/or regions, it is used, e.g., for the estimation of ever-users' prevalence in the equation of population attributable risk (PAR) [11-13]. Further importance of the DDD has been published by Kwan et al. and Brodie et al. who concluded that effective seizure control could be achieved at 50% or 75% of DDD and could be applied to the definition of drug-resistant epilepsy [14, 15].

Aim of the study

The aim of this study was, first, to determine PDDs of AEDs and to reveal PDD/DDD ratio among seizure free vs. not seizure free patients in everyday clinical practice. Second, to test the applicability of 75% cut-off of DDD to achieve seizure freedom. Furthermore, it was our intention to find out what factors might influence PDD.

Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki declaration of 1964 and its later amendments or comparable ethical standards. For this type of study no formal consent is required. Ethical approval was obtained from the Regional and Institutional Research Ethics Committee (DEOEC RKEB/IKEB: 2584A-2007).

Methods

A cross-sectional retrospective database was compiled from the outpatient files covering the period between November 1992 and December 2011 at the outpatient unit of the department of neurology, at the medical centre of a university [16].

This epilepsy outpatient unit provides care for patients from 16 years of age. As the university is a tertiary referral hospital of the Northern Great Plain and Northern Hungary, the majority (67%) of the patients are from Debrecen and the rest come from 3-4 counties of Hungary.

All the patients in the study were coded with epilepsy diagnoses in accordance with the International Classification of Diseases by the WHO [17]. The data of 1282 patients who had taken AEDs were retrieved from the database and analysed on the basis of gender, age, age at seizure onset, seizure type (generalized and focal), seizure freedom status as an outcome of treatment, and PDD. PDD was calculated on the basis of the proposed dosage regimen of the last follow-up visit. For each patient, DDD% was computed as the percentage of PDD divided by DDD and mean DDD% was calculated in order to compare different groups. The 75% cut-off have been chosen based on Brodie et al.'s suggestion [15]. Current age and age at seizure onset were distinguished for further analysis. Patients aged 16-40, 41-65 and over 65 were included in the former group, and childhood (0-14-year-old), adolescence (15-20-year-old) and adulthood (>21-year-old) were categories in the latter group of patients. According to the definition by the International League Against Epilepsy, in this study, seizure freedom was considered at least three times the interval of the longest previous interseizure duration (determined from seizures occurring within the past 12 months), or 12 months, whichever was longer [18].

The relationship of PDD to DDD was analysed in 894, 286 and 102 epileptic patients on monotherapy, bitherapy and polytherapy, respectively. The most commonly used AEDs and their role in the outcome of these groups were compared. The attending epileptologist chose the best treatment modality for each patient. The first treatment always was monotherapy; the second choice was either an alternative monotherapy or a combination of the first or second monotherapies together with a second AED, and so on [19-23].

AED doses were prescribed according to the summary of product characteristics (SPC) to a mid-range dose, and were further increased up to the maximally tolerated dose in case seizures occurred repeatedly. When needed, TDM was performed and assessed to guide dosage changes and also to test patient compliance [24]. In case of seizure freedom, the dosage of AED was not increased further. An AED was changed due to lack of efficacy or poor tolerability.

Since newer AEDs are widely available on the Hungarian market, they can be compared with the older ones.

Statistical analysis was carried out using the SPSS for Windows 19.0 (SPSS Inc. Chicago, USA) and Microsoft Office Excel 2007.

Two-sample T test, and F test were used to analyse the patients' data. Categorical variables were assessed with Pearson χ^2 test.

A logistic regression model was created in order to analyse what factors characterised 75% DDD cut-off; the dependent variable was equal to or less than 75% of DDD and more than 75% of DDD. The independent variables included gender, age group, age at the onset of seizure, type of seizure, seizure freedom, other CNS related drugs and number of AEDs.

Differences were considered significant if $p<0.05$.

Results

At the time of the analysis, of the 1282 patients (male: 608 [47.4%] and female: 674 [52.6%]), 894 (69.7%) were on monotherapy, 286 (22.3%) on bitherapy and 102 (8%) on polytherapy. The baseline characteristics of the patients has been assessed in Table 1.

Comparing the number of prescribed old and new AEDs, a significant increase was observed in the proportion of newer AEDs between the mono- versus bitherapy ($p<0.0001$) and bi- versus polytherapy groups ($p=0.0003$; Table 2).

Other drugs acting on the CNS were taken by 279 patients (22%). In the previous study published recently, we found the pooled group of other CNS-acting drugs had an effect on seizure freedom [16]. Twenty-two out of 279 patients took other CNS-acting drugs belonging to ATC N05 and N06. Only bupropion, risperidon and sertraline were identified to have interacted with four AEDs (carbamazepine, lamotrigine, phenytoin and valproate). As only 12 patients might have had these potential interactions we disregarded analysis in this group due to the low case number.

In the study population, the patients did not take more than the maximum recommended doses for AEDs in the SPC.

DDD values, mean PDDs of AEDs and distribution of prescribed AEDs in each group are summarized in Table 2. The mean number of AEDs per patient was 1.4. Using bitherapy the old-old, old-new and new-new type AED-combinations were prescribed for 118 (41%), 133 (47%) and 35 (12%) patients, respectively.

No significant gender differences were confirmed between seizure free and not seizure free groups. The mean antiepileptic dose was higher among males ($p<0.001$) only in the group on monotherapy.

The mean DDD% of all prescribed AEDs increased steadily from monotherapy, through bitherapy towards polytherapy (58.54%±24.04, 74.38%±42.89, 93.68%±54.82, respectively).

The effects of the most commonly used AEDs on seizure freedom status in mono-, bi-, and polytherapy are demonstrated in Figure 1.

CBZ and oxcarbazepine (OXC) showed similar patterns but CBZ was prescribed in less than 75% of DDD, while OXC was prescribed in all scenarios in more than 75% of DDD (Figure 1 C and E).

In the case of VPA, mono- and bitherapy PDDs remained below 75% of DDD but in the group on polytherapy a higher dose did not increase the likelihood of seizure freedom (Figure 1 D).

Monotherapy

Mean PDDs mostly fell in the range between 50-75% of DDDs (Table 2).

With the exception of OXC and GBP, the mean DDD% was higher in the group of not seizure free patients (Table 3). Except for OXC, the vast majority of seizure free patients had taken AED doses in the range of ≤75% of DDDs in monotherapy. Not seizure free patients were treated with higher doses of LTG, and significant differences in means could be seen between seizure free and not seizure free cohorts ($p=0.02$; Table 3 and Figure 1 B).

The mean DDD percentage was equal to or less than 75% in most AEDs used in monotherapy in the group of seizure free patients. A significant difference was revealed only among LTG users ($p=0.032$) in favour of ≤75% of DDD and seizure free patient's group. The mean DDD% exceeded 75% in four cases as follows: clobazam (CLB), OXC, topiramate (TPM) and lacosamide (LCM), 100%, 86.82%, 133.3% and 133.3%, respectively. No preferable AED was confirmed based on general effectiveness ($p=0.65$) in relation to desired seizure free status (Table 4).

Low case numbers (<10 patients or <1%) characterised CLB, clonazepam (CZP), primidone (PRM), sultiame (STM), LCM and TPM prescriptions used in monotherapy. Eighty percent of these patients were seizure free.

Only 30% of the patients took 100% or more of DDD (CLB, LCM and TPM) and all had seizure freedom (Table 3). The majority of seizure free patients were females (75%; $p<0.0001$).

Bitherapy

The mean PDDs of CBZ, VPA, PRM, CLZ, GBP and VGB were within 50-75% of DDD (Table 2).

Significantly higher mean DDD% was observed between seizure free and not seizure free cohorts taking levetiracetam (LEV; $p=0.023$; Table 3 and Figure 1). Slightly higher mean DDD% was revealed among seizure free patients on CLB and PRM (Table 3).

The majority of patients belonged to the group of equal to or less than 75% of DDD (except CLB, OXC, phenytoin [PHT], Table 3).

Despite low case numbers, female dominance was found in the bitherapy group; only three out of the sixteen patients were males. Less than one third of the patients (all females) were seizure free. More than two thirds of the patients had taken 100% or more than the DDD.

Polytherapy

Only PDDs of CBZ, PHT, PRM and CLZ remained under 75% of DDD (Table 2).

The mean DDD% was higher among not seizure free patients but no significance was confirmed (except CBZ $p=0.032$ and GBP $p=0.045$; not seizure free patients taking LEV and TPM had lower values but the differences were not significant; Table 3).

In polytherapy, the use of more than 75% of DDDs was recorded in the seizure free and not seizure free groups receiving LEV, LTG, OXC and TPM (Table 4). The mean DDD% was higher among TPM, PRM and LEV users in the seizure free group.

Among the older types of AEDs, both CBZ and VPA had to be given in a significantly higher mean dose in bitherapy than in monotherapy in the seizure free group and in polytherapy in the not seizure free group. Among the newer types, only LEV and LTG had a significantly higher DDD% series pattern between mono-, bi-, and polytherapy in both groups (except LEV in polytherapy in the not seizure free) group.

The mean DDD% of CBZ and GBP in polytherapy was significantly higher in not seizure free patients than in the seizure free group ($p=0.032$ and 0.045, respectively; Table 3 and Figure 1 C).

There was no identical combination in polytherapy with five AEDs and only two out of seventeen patients shared the same four-drug combination. Among the 79 patients taking three AEDs, 31 patients had an own triplet for controlling epilepsy.

Only one fifth of the patients were seizure free (two thirds of them were females) in the low case number category. Sixty percent of the patients took less than 100% of DDD. Although patients in the polytherapy group took three times the DDD of phenobarbital (PB) they were not seizure free.

Logistic regression analysis

In this model, gender, age group, type of seizure, seizure freedom and number of AEDs all had a significant impact (all $p<0.05$). No link was revealed with age at the onset of seizure or other drugs acting on the CNS.

In the logistic regression model, gender served as a significant predictor ($p=0.001$; Exp(B) [exponentiation of the B coefficient]= 1.456, 95% CI [Confidence Interval]: 1.169-1.813) if it was equal to or less than 75% of DDD among men.

Current age showed significant difference in the model of ≥75% of DDD in the over 65-year-old group ($p=0.022$; Exp(B)= 1.449, 95% CI: 1.055-1.989).

The odds were higher for focal seizures in more than 75% of DDD group ($p=0.002$; Exp(B)= 0707, 95% CI: 0.568-0.881) and equal to or less than 75% of DDD in generalized seizure.

There was no higher chance for seizure freedom if more than 75% of DDD was prescribed ($p= 0.027$, Exp(B)= 0.773, 95% CI: 0.616-0.971).

As a result of increasing the number of AEDs, a higher portion of more than 75% of DDD could be achieved in the logistic regression model.

Discussion

The treatment of epileptic patients is complex. Of course, there are conditions (drug interactions, individual differences in drug metabolism, age, comorbidities, etc.) that emphasise the importance of individual treatment in finding the proper dosage of AED. However, evidence including DDD, clinical trials or TDM is important when choosing the best AED treatment for the patient.

The study by Hsieh and Huang retrieved prescription records for all patients, prescribed AEDs and calculated PDD/DDD ratio [6], but this was not related with the outcome. Meanwhile Kořístková et al. [7, 8] and Lammers et al. [25] considered TDM data besides the PDD/DDD ratio. Serum level monitoring of AEDs is not widely available for every AED, and serum level does not always reflect clinical status.

In our study, a new, clinically important, well-defined and feasible approach was tried in order to determine the correlation between PDD and PDD/DDD ratios based on seizure freedom as an outcome of AED treatment. One of our goals was to see whether PDD/DDD could play a role in seizure freedom as an outcome measure in

epilepsy; no significant unfavourable impact of the lower ratio of PDD/DDD on the outcome of achieving seizure freedom could be confirmed.

Further decrease in the number of AEDs was confirmed (1.4) when we compared the data of our recent study with those by Guelen et al. [26], Lammers et al. [25] reporting 3.2 and 1.7 AEDs per patient, respectively.

The majority of patients (894 [69.7%]) took only one AED and just 102 (8%) patients took more than two AEDs. In a Danish study including 3756 patients, almost the same distribution was published in 2001 [10]. Kořístková et al (2006) described a similar monotherapy cohort among patients involved in therapeutic drug monitoring in a Czech and Swedish University Hospital [8]. Hsieh and Huang reported only 51.9% monotherapy rate in a randomly sampled population of 167 377 patients, which was less than the catchment area of our study [6].

Most of the patients (764 [85.4%]) in the monotherapy group were treated with three AEDs (CBZ, VPA and LTG). Newer AEDs were prescribed for more than a quarter of the patients which is higher than in a study conducted in Taiwan, where the prescription rate of newer AEDs was under 10% [6]. However, according to our data and similar to publications by others [7-10], AEDs – including more newer type ones – are prescribed in monotherapy for more and more patients, but while DDDs of AEDs refer to combination therapy. Therefore, references of monotherapy DDD values are needed for appropriate calculation. The more precisely DDD is quantified the more accurate calculation of other derived values (e.g. DDD/1000 inhabitants/day, prevalence of drug use, population attributable risk) it would provide, which could also play an important role in decision-making in health care.

A significant increase was observed in the proportion of newer AEDs in our database. Probably these data were obtained with due consideration to the different modes of action of AEDs and their favourable ADRs in bitherapy and polytherapy.

In our outpatient setting, the mean PDDs of AEDs were inconsistent with the DDD. Previous investigations were of the same opinion [8, 10, 27].

The mean DDD% was equal to or less than 75% for the most commonly prescribed AEDs used in monotherapy in the seizure free group. In contrast with our findings, Hsieh and Huang (2009) did not reveal more than 100% of DDD [6]. One of the explanations might be that older AEDs were prescribed more circumspectly due to their well-known ADRs. At the same time, the ADR profiles of new AEDs were considered more beneficial. In case of two newer types of AEDs (LTG and LEV) a significant rise in doses between mono-, bi-, and polytherapy was detected, by other AEDs a wide variety of mean DDD% supposes individual treatment regimen. Still CBZ and

VPA are widely prescribed in the clinical practice due to reliable effectiveness and their broad-spectrum. These drugs can be used in low and moderate doses, too.

Our findings suggested that doses equal to or less than 75% of DDD in monotherapy were effective in seizure control and the same quantities were confirmed in bi-, and polytherapy. However, a higher DDD% did not guarantee seizure freedom which emphasises the importance of individual therapy.

It must be remarked that despite the low case numbers of some AEDs (e.g. CLB, CZP, PRM, STM, LCM and TPM) which were statistically unfit for analysis the majority of the patients on these agents were seizure free. These findings highlighted the importance of carefully choosing drugs carefully, i.e. tailored to the individual e.g. in the treatment of special epileptic syndromes.

Prescribing newer AEDs in bitherapy drug combinations has become an established practice now. This research has revealed the spread of newer type AEDs in epilepsy treatment but they are used not only in combinations, but also in monotherapy among patients on AEDs. The findings of this study suggest that individual therapy in epilepsy must be emphasised but 75% of DDD may also be used as a measure in case of seizure freedom. Just under 60% of patients took at least one newer AED in this study, in contrast with the findings by Hsieh and Huang (2009) who reported 13.2% in their polytherapy group (they used this term for patients taking two or more AEDs) [6]. New-new combinations were given to 38 (12.2%) patients on bitherapy and 133 (46.5%) patients took old-new combinations. In choosing the second and third AEDs it may have played an important role whether or not the specific AED had an enzyme-inducing or enzyme-inhibiting effect on the liver's enzyme system.

Dominance of equal to or less than 75% of DDDs could be found in the bitherapy group. A statistically significant, higher DDD% was confirmed between seizure free and not seizure free groups only when LEV was administered.

With logistic regression analysis, gender, age, type of epilepsy and the number of AEDs were found to have had a significant impact on the value of 75% DDD. These were the factors what influenced PDD. These might be limiting factors when making conclusions in studies using DDD.

The present study confirmed that the DDD of prescribed AEDs was equal to or less than 75% of DDD instead of being over 75% among elderly patients. It was in accordance with well-known pharmacokinetic and pharmacodynamic changes in older ages and due to comorbidities and co-medications.

It must be mentioned that, similarly to Kwan et al. [14] and Brodie et al. [15], our findings also emphasise individual therapy and the importance of 75% of DDD.

This study has several limitations as it is an observational study and not a randomized, controlled trial, that is why selection bias could have affected the results. Nevertheless, the advantage is detailed information on all subjects can be regarded as an important advance in this field. Further strength of this study may be the real-life data sets leading to a better understanding of real-life clinical settings and the outcome of routine epilepsy treatment. In this study, seizure freedom was chosen as a measure of outcome. Nevertheless, in everyday clinical practice, reduction in seizure frequency by 50% is an acceptable or good outcome in certain cases despite the fact that the patients are not seizure free.

Conclusion

In conclusion, no significant unfavourable impact of the lower ratio of PDD/DDD on the outcome of achieving seizure freedom has been confirmed. The findings of this study suggest that 75% of DDD may be used as a measure of seizure freedom, but individual therapy in epilepsy must be emphasised. Gender, age, type of seizure, seizure freedom and the number of AEDs have a significant impact on the 75% cut off value of DDD. References for monotherapy DDD values are needed, in order to help with decision-making in health care using appropriate calculations.

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Conflict of interest

The authors declare that they have no conflict of interest.

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