WAS IT NECESSARY TO CHANGE THERAPEUTIC RANGE OF TOPIRAMATE?

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The population-based therapeutic range was defined by the International League Against Epilepsy (ILAE) to 5-20 mg/L.
- The Norwegian National Guidelines decreased the range to 2-10 mg/L based on two older clinical studies and three sets of unpublished personal experiences.

WHAT THIS STUDY ADDS

- Seizure control was poorer in patients with plasma level within 5-10 compared to 10-20 mg/L; further with plasma level <2 mg/L vs 5-10; and 10-20 mg/L.
- Adverse drug reactions (reported in 2.8%) were without relation to plasma level.
- We do not recommend the change of the therapeutic range.

ABSTRACT

Aim: The Norwegian Association for Clinical Pharmacology in their National Guidelines decreased therapeutic range (TR) of topiramate (TPM) from 5-20 mg/L to 2-10 mg/L. The objective of this study is to ascertain which TR produces better clinical outcomes.

Methods: Data source were request forms for routine therapeutic drug monitoring of TPM. Concentration dependent adverse drug reactions (ADRs) were evaluated in 1,721 samples taken pre-dose. Seizure frequency analysis was performed in 294 samples of monotherapy. Statistics: Prism 5.0, GraphPad Instatt: Mann–Whitney U test for median plasma level (PL). χ2-test for seizure frequency and for distribution of PL according to TR 5-20 mg/L and intervals <2, 2-5, 5-10, 10-20, >20 mg/L.

Results: Better seizure control was found in children both in whole cohort (without seizure 49% vs 37% adults), as well as in monotherapy (56% vs 44%), in children with PL 5-20 mg/L vs 5 mg/L (65% vs 44%) and in children with PL 5-10 mg/L vs <2 mg/L. Seizure-free children had higher PL than those with seizure yearly: median (lower, upper quartile) [mg/L]: 5.5 (3.4-6.5) vs 4.7 (4.3-7.95). No difference was found in adults. Seizure control was poorer in all patients with PL <2 mg/L compared to 5-10 mg/L; and 10-20 mg/L; further in PL within 5-10 mg/L vs 10-20 mg/L; and in the period 2003-2005. ADRs reported in 38 samples (2.8%) were without relation to PL.

Conclusions: Change of TR is not recommended.

INTRODUCTION

TPM has been licensed for clinical use since 1995. TPM is used for monotherapy as well as adjunctive therapy in partial seizures and primary generalized tonic-clonic seizures. It is also licenced for seizures associated with Lennox-Gastaut syndrome and for migraine prophylaxis. TPM has multiple mechanisms of action, including inhibition of voltage-sensitive sodium and calcium channels, enhancement of GABA-mediated activity and inhibition of kainite/AMPA-type glutamate receptors [1]. TPM failed an expectation to be managed without TDM. In our region TPM has been used since 2000, while TDM was introduced at our University Hospital in 2003.

The population-based therapeutic range was defined by the International League Against Epilepsy (ILAE) to 5-20 mg/L [2]. Recently published Norwegian National Guidelines [3] decreased the range to 2-10 mg/L based on two older clinical studies and three sets of unpublished personal experiences.

The aim of this study was to evaluate the relationship between seizure frequency and ADRs in both therapeutic ranges of TPM in patients routinely examined under our TDM regiment.

METHODS

Request forms for routine TDM of TPM in the period of June 2003 – May 2018 were used as data sources (AddFile1). Samples taken pre-dose were included into the study. Sample selection is shown in Figure 1. Mean age was 20±16 years and mean body weight 52±27 kg. Information about seizure type and frequency was given in 1,090 cases, 294 in monotherapy.

Between one and 16 samples were taken from each patient. 219 (47%) patients in whole cohort and 101 (62%) on monotherapy were examined only once during the whole period. The seizure types were: generalized tonic clonic seizure in 547 (50%) cases, focal impaired awareness in 159 (15%), focal motor aware in 124 (11%), absence in 25 (2%), pseudoabsence in 23 (2%), myoclonic seizure in 15 (1%), infantile spasms in 15 (1%), febrile seizure in 10 (1%), focal sensorial in 8 (2%), other – not specified in 76 (7%) cases. There were four samples, taken from four patients with psychiatric indications, submitted by the psychiatric department. Samples were divided into four categories: occurrence of seizures daily, monthly, several seizures per year, and seizure free longer than 1 year. The relationship between intervals <2 mg/L, 5-10 mg/L, 10-20 mg/L and >20 mg/L was studied in monotherapy.

Concentration-dependent ADRs were evaluated in 1,721 samples. Information was missing in 18% of samples. Statistic were included for fully answered reports – i.e. yes vs none. Clinical outcomes, i.e. frequency of seizure and incidence of ADRs, were evaluated in children i.e. patients <15 years, adults and the whole cohort. The influence of long-term experience with TDM of TPM was compared to the first three years of TDM use. 2003-2005, 2006-2011 and 2012-2018.

Statistics

Prism 5.0 was used for the statistics [4] Mann-Whitney *U-test* was performed for distribution of PL according to frequency of seizure. Chi-square test was used to analyze the frequency of seizure. Because of low ADR incidence, Fisher's exact test was used for the incidence of ADRs with regard to distribution of PL according to the intervals mentioned above. The influence of long-term experience with TDM of lamotrigine was compared to the first four years of TDM of TPM.

Analysis of TPM PL

Analysis of TPM PL was performed using standard validated gas-liquid chromatography [5]. The method participated in externally quality control schemes: Instand e.V., Gesellschaft zur Förderung der Qualitätssicherung in medizinischen Laboratorien e.V.

The Ethics Committee of FN Ostrava approved the study and all protocols on May 28th 2020. Reference number 451/2020.

RESULTS

Higher numbers of seizure-free patients were found in children than in adults, both in monotherapy as well as in the whole cohort (Table 1). Seizures were less controlled in the earlier period (2003-2005) when compared to 2006-2011 (monotherapy as well as whole cohort) and 2012-2018 (whole cohort only).

The relationship between TR 5-20 mg/L and seizure frequency was poor. No levels were above TR in monotherapy. Children had slightly better seizure control in levels within TR, than below TR (Table 1), while no difference was found in adults. Seizure-free children had slightly higher PL than those with seizures yearly: median (range) 5.5 (4.3-8.0) vs 4.6 (3.4-6.5) mg/L, $P<0.05$ (Figure 2). The differences were not significant in adults (Figure 3).

Most PL values were within 2-10 mg/L (Table 1). Children with PL within 5-10 mg/L had better seizure control than those with PL < 2 mg/L, $P<0.05$. No difference was found in adults. In the whole cohort, the seizure control was poorer in PL <2 mg/L when compared to 5-10 mg/L or 10-20 mg/L, $P<0.05$, while more seizure free patients were found in PL within 10-20 mg/L than 5-10 mg/L, $P<0.05$.

Concentration-dependent ADRs were reported in 38 samples (Table 2). They were headache (15), bradypsychism (13), nausea (3), vertigo (2), ataxia (2), dizziness (1), tiredness

and memory impairment (1), anorexia and weight loss (1), somnolence (1), other - not specified (4). In monotherapy, ADRs were reported in 8 adult patients - bradypsychia (3), headache (3), vertigo (1), anorexia and weight loss (1). One child was repeatedly examined within fourteen days. Somnolence was reported at level of 10.8 mg/L, but no ADR were reported at levels of 10.2 mg/L or 11.7 mg/L. No association between TPM PL and occurrence of ADRs was found. TPM PL exceeded 20 mg/L in seven samples. Bradypsychia was reported in one patient at level 40.2 mg/L. No ADRs were reported in 6 patients with PL within 20.4 – 23.9 mg/L, and no information was given on two samples (PL of 20.9 mg/L and 38.7 mg/L).

DISCUSSION

Therapeutic range is defined as the range of drug concentrations associated with the optimal response and low incidence of ADRs, while a reference range was defined as a range of drug concentrations quoted by laboratory with a lower limit for therapeutic response and an upper limit above which toxicity is more likely to occur [2]

In 2008, based on eight clinical studies [6-13], the ILAE defined TR of TPM to be 5-20 mg/L [2] The Update [14] from November 2018 contained no changes for TPM.

In its effort to update and harmonize reference ranges of antiepileptic drugs, the Norwegian Association of Clinical Pharmacology established their own National Guidelines [3] published in February 2018 in which the TR for TPM was lowered to 2-10 mg/L, based on two out of the eight above mentioned studies [12,13] and three of their own, non-published, data sources. At the time of this change, all but three laboratories in Norway were using the TR defined by ILAE [3].

Most of patients in our cohort reached PL within the interval of 2-10 mg/L, but their clinical outcomes could not be considered optimal. Patients with PL within the interval of 10-20 mg/L seemed to have the benefit of lower seizure frequency, compared to those with PL in the 5-10 mg/L range. Altogether, no difference in the incidence of ADRs, that was generally very low, was found in levels within 10-20 mg/L. ADRs were reported in one out of seven patients with PL values above 20 mg/L.

As for the lower limit of TR - PLs below 2 mg/L were shown as less likely to be effective. PL in seizure-free patients ranged from 0.5 mg/L to 13.9 mg/L. Some patients might reach clinical response with PL within 2-5 mg/L but these values cannot be considered as therapeutic in population-based TR.

The difference between terms population-based "reference" and "therapeutic" range seems to be more or less academic. Commonly used laboratory information systems usually do not distinguish between these two concepts. It is generally known that many drugs analysed for TDM are effective in values below the lower limit of TR. E.g. phenytoin [2] or theophylline [15] are effective in PL of 5 mg/L whereas TR is defined as 10-20 mg/L, or 8-20 resp. Amiodarone is effective in values from 0.5 mg/L, while TR is defined as 1-2.5 mg/L [16], etc. There is little information in the literature about confirmation of TR in clinical practise after it was proposed [2] TR of lamotrigine was increased from 1-4 mg/L [18-21], where the correlation with clinical effect was found to be poor, to 3-14 mg/L based on later studies [21, 22] TR of digoxin for patients >65 yr was lowered from 0.8-2.0 ug/L to 0.5-1.2 ug/L after considering both clinical effect in heart failure for levels >0.5 ug/L and lower mortality for levels <1.2 ug/L [23].

In clinical practise, physicians often target the lower margin of TR, as seen also in this study, where median values of PL ranged from 4.4 mg/L to 5.5 mg/L. Morris et al

documented similar outcomes in lamotrigine [22]. In case of TPM some patients may benefit from PL >10 mg/L and the lowering of both the lower and the upper limit of TR of TPM may lead to TPM, by mistake, being rejected as ineffective.

In the use of newer antiepileptics the correlation between clinical outcome and population-based TR is known to be less tight and therefore TDM was not expected to be necessary, unlike in the use of older antiepileptics. TDM of TPM commenced three years after TPM was licensed for clinical use in our country. The first period of our study describes clinical outcomes in patients when TPM dose was chosen empirically and then TPM concentrations were taken. The later periods reflect the routine use of TDM service by clinicians, which allowed them to dose TPM based on TDM feedback. Long-term experiences with routine use of TDM led to decreased frequency of seizures in the period of 2006-2011, compared to the first period, i.e. 2003-2005. Total number of samples declined considerably since 2012 due to the shift towards outpatients testing in newly established private laboratories. The difference in patients characteristics might be another reason for lower proportion of seizure-free patients on monotherapy in this period - most of them were examined in the Epilepsy Centre of our tertiary care hospital.

Improvement in clinical outcomes of patients, despite poor correlation of population-based TR with seizure frequency, suggest that individual TR should be estimated for each individual patient, as also recommended by ILAE guidelines [2] and Landmark et al. [24].

Limitations: Non-adherence of physicians to some questions on the request forms (mentioned also by Morris et al. [22]), especially questions regarding seizure frequency or occurrence of ADRs, represents a difficulty for data evaluation. In the case of ADRs, we cannot distinguish whether they were not reported because they did not occur or because of simple non-

adherence. Considering this fact, we decided to show the percentage of the incidence of ADRs from the whole group, as the statistical significance remained unchanged.

Conclusions: Most of patients in our cohort reached PL within the interval of 2-10 mg/L, but their clinical outcomes were not optimal. Patients with PL within the interval of 10-20 mg/L had the benefit of lower seizure frequency, compared to those with PL in the 5-10 mg/L range. Overall ADRs were generally very low and no difference in the incidence was found in levels within 10-20 mg/L. Lowering of both the lower and upper TR limits of TPM may lead to TPM being rejected without being given a thorough trial. We do not recommend the change of the TR of TPM from 5-20 mg/L to 2-10 mg/L.

CONFLICTS OF INTEREST AND SOURCE OF FUNDING

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FIGURE LEGENDS

Figure 1 Sample selection

Figure 2 Distribution of plasma level (PL) of TPM according to seizure frequency in children. * $P<0.05$

Figure 3 Distribution of plasma level (PL) of TPM according to seizure frequency in adults

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