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Relationship between mono-hydroxy-carbazepine serum concentrations and adverse effects in patients on oxcarbazepine monotherapy

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ABSTRACT

Purpose: To evaluate the relationship between serum concentrations of mono-hydroxy-carbazepine (MHD), the main metabolite of oxcarbazepine (OXC), and the occurrence of adverse effects (AE) in a large group of patients on OXC monotherapy.
Methods: An antiepileptic drug (AED) therapeutic drug monitoring (TDM) database was analyzed especially with regard to OXC dosage, MHD serum concentration, and the occurrence of AE. In total, 893 blood samples of 442 patients were included in this retrospective study. The statistical evaluation was performed by means of Kaplan-Meier estimates, log-rank tests and generalized estimating equations (GEE).
Results: At least one AE was reported in 78 (17.6%) of the 442 patients. At MHD serum concentrations of 30.0 μg/ml and 43.7 μg/ml and OXC dosages of 33.1 mg/kg and 62.3 mg/kg, 25% and 75% of patients, respectively, experienced at least one AE. Log-rank tests indicated that younger patients (<18 years) may be able to tolerate higher MHD serum levels ($p = 0.006$) and higher OXC dosages per body weight ($p < 0.001$) compared to adult patients (≥18 years). Furthermore, AEs occurred at higher body-weight adjusted OXC dosages of extended release formulations compared to immediate-release formulations ($p = 0.010$), whereas MHD serum levels at which AEs occurred did not differ significantly between formulations ($p = 0.125$). Multivariate GEE confirmed the results.
Conclusion: The occurrence of AEs is significantly (and non-linearly) dependent on MHD serum level, whereas the dependence of OXC dosage is less distinctive. But, tolerability of OXC seems to depend on age of the patients as well as on pharmaceutical formulation of OXC.

1. Introduction

Oxcarbazepine (OXC) is a second-generation antiepileptic drug (AED) often used for the treatment of focal seizures with and without secondary generalization. It was approved in Europe in 1999 and since 2000 also in the United States, indicated for the treatment of adults and children with focal onset seizures as mono- or adjunctive therapy. In addition to the initially immediate-release formulations as tablet or suspension there are also extended-release formulations available in Germany for several years.

The most common adverse effects are related to the central nervous system, including dizziness, fatigue, headache, diplopia, nystagmus and ataxia [1,2].

After administration oxcarbazepine is rapidly metabolized via reduction to 10,11-dihydro-10-hydroxy-carbazepine (mono-hydroxy-derivate, MHD), it is primary clinically relevant metabolite. There is a linear relationship between the OXC dosage and the MHD serum concentrations [1,3]. Whether there is a significant correlation between MHD concentration in serum and efficacy and tolerability of OXC therapy is still a matter of debate. Different therapeutic ranges of MHD are cited and especially the mentioned upper limits of serum levels showed a considerable variation between 20 and 40 μg/ml [1,4–9].

The aim of this study was to investigate the relationship between mono-hydroxy-carbazepine serum levels and the occurrence of adverse effects in patients on OXC monotherapy.

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Therefore, we retrospectively examined serum levels in a large group of patients treated with OXC as monotherapy with or without adverse effects.

2. Methods

The therapeutic drug monitoring (TDM) database of the Laboratory of the Epilepsy Research Society at the Epilepsy Center Bethel (Bielefeld) was analyzed with regard to OXC dosages, MHD serum concentrations and the occurrence and kind of AEs in patients on OXC monotherapy. As part of clinical routine, serum levels are determined in case of AEs as well as at the beginning or before the end of in-patient treatment. Blood samples have to be accompanied by laboratory order form carrying detailed information about the medication and AEs, in case of occurrence.

In addition, further data were extracted, e.g. the pharmaceutical drug formulation of OXC, date of blood sampling, gender, age and body weight of the patients. MHD serum levels collected for TDM were determined between 2005 and 2010. Almost all patients were inpatients of the Bethel Epilepsy Centre (Bielefeld, Germany), a tertiary reference center for epilepsy. Just five patients were under out-patient care of the epilepsy center.

In total, 990 MHD serum levels under OXC monotherapy were identified by searching the laboratory database. OXC monotherapy as well as all on the laboratory order forms reported AEs were verified by checking patients' medical record and missing information of the above mentioned data was completed, if possible. Cases with an incomplete data set were excluded from further evaluation.

Furthermore, children younger than 6 years of age were excluded as adverse effects reported by children below the age of 6 were assumed as not reliable. Hence, 893 blood samples of 442 patients were included in this retrospective study. The study was conducted in accordance with the Gesundheitsdatenschutzgesetz (GDSG NRW, German law of healthcare data protection).

2.1. Determination of MHD serum concentrations

For the determination of MHD serum concentrations (sum of R- and S-enantiomers) a high-performance liquid chromatographic (HPLC) method with UV detection was used. The serum samples (100 μl) were mixed with the extraction solution, i.e. 200 μl of acetonitrile and methanol (9:1) containing the internal standard ETB = ethyl-tolyl-barbituric acid (all from Sigma–Aldrich, Taufkirchen, Germany). The proteins were precipitated and after centrifuging the supernatant fluid transferred into microvials. The chromatographic separation was carried out on a HP 1090 LC (Agilent, Waldbronn, Germany) apparatus with a Kromasil C18, 5 μm, 250 × 4 mm HPLC column. A gradient elution with acetonitrile and a phosphate buffer (pH 4.5) was used at 75 °C and the wavelength for UV detection was 207 nm. The lower limit of detection was 0.5 μg/ml and the limit of linearity was found with 90 μg/ml for MHD. The coefficient of variation (day to day) of the method was below 3%.

The accuracy of the determination of AED serum concentrations, including MHD, is regularly verified and certified by external quality assessment (participation in interlaboratory comparisons of three different institutes).

2.2. Statistical evaluation

For analyzing the occurrence of AE in relation to MHD serum levels and OXC dosages, Kaplan Meier estimates (mean value, median and standard errors) for the lowest MHD concentration and lowest OXC dosages at which an AE occurred (mean value, median and standard errors) were computed.

In most patients no AE occurred and therefore the (lowest) MHD level or OXC dosage at which AE would occur are unknown. However, in these patients data on the highest MHD level and highest OXC dosage without AE are available and this kind of "censored" data should be considered in the statistical analysis. Therefore, we used methods originally developed for survival analysis (Kaplan Meier estimates, Kaplan–Meier, log rank tests) to describe and analyze the occurrence of AE dependent on MHD levels.

Log-ranks tests were performed to check whether the MHD serum levels or MHD dosages at which AEs occurred were dependent on gender, age of patients and pharmaceutical formulation of OXC. In some patients two or more MHD determinations were assessed; however, for the statistical analyses mentioned above only the highest serum level without AE ("censored" values) or, in case of AE, the lowest serum level at which an AE ("event") occurred was included.

In addition, a generalized estimating equation (GEE) model was used to investigate the effect of MHD serum levels, OXC dosage, pharmaceutical formulation of OXC, gender and age (<18 vs. ≥18 years) on the probability of the occurrence of AE (specifications: binominal distribution, logit link function, independent working matrix structure). Wald-test was used for testing significance of the factors mentioned above. In contrast to usual logistic regression, in the GEE model using a logistic link function repeated measurements of patients may be included. Thus, for GEE all 893 blood samples of 442 patients were analyzed.

More details of the GEE approach of are described, for example, by Fahrmeir et al. [10].

Statistical significance was set at $p < 0.05$ (two-sided, if not mentioned otherwise). For statistical analyzes IBM SPSS for Windows 20.0 was used.

3. Results

The patients' characteristics, daily OXC doses, number of daily drug administrations, number of trough level determinations, mean MHD serum concentrations and OXC doses per kg body weight of patients with AEs ($n = 78$) and without AEs ($n = 364$) are summarized in Table 1. In 251 patients (56.8%) OXC dosage was stable for more than 14 days, in 96 patients (21.7%) dose has been changed between the last 4 to 14 days and in 95 patients (21.5%) dose adjustments have been conducted within the past three days (steady state cannot be assumed in these cases). At least one AE was reported in 78 (17.6%) of the 442 patients. The type of AE is summarized in Table 2.

The relationship between the occurrence of an AE and the related MHD serum levels and OXC dosages per kg body weight, respectively, is illustrated in Fig. 1a and b by using Kaplan–Meier plots. At MHD serum concentrations of 25.3 μg/ml, 30.0 μg/ml, 35.7 μg/ml, and 43.7 μg/ml, 10%, 25%, 50% and 75% of patients, respectively, experienced at least one AE. The corresponding OXC doses were 24.0 mg/kg, 33.1 mg/kg, 50.3 mg/kg and 62.3 mg/kg. The estimated mean and median MHD serum levels at which an AE occurred in 50% of the patients were 37.9 μg/ml (standard error 1.43) and 35.7 μg/ml (standard error 0.70) respectively. Accordingly, the estimated mean and median OXC dose per kg were 47.3 mg/kg (standard error 1.49) and 50.3 mg/kg (standard error 4.05), respectively.

The Log-rank tests (Table 3) indicated that the age of patients (<18 years vs. ≥18 years) had a significant effect on the MHD serum levels and OXC dosages per body weight at which AEs occurred ($p = 0.006$, $p < 0.001$, respectively), whereas the pharmaceutical formulation had a significant effect only on OXC dosages related to AE ($p = 0.010$), but not on MHD serum levels ($p = 0.125$). The effect of gender was not significant.