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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.

Table 1
Patients' characteristics.

		N.	Total (%)	Mean	SD	Min.	Max.
Gender	Male	241	54.8				
	Female	201	45.2				
Age (years)		442		29.6	15.76	6.0	79.9
Weight (kg)		442		70.5	23.00	16.9	134.0
Drug (dose per day)	Timox®/Trileptal®	324	73.3	1610	624	225	3450
	b.i.d.	275	62.2	1562	624	225	3450
	t.i.d.	49	11.1	1876	560	750	3000
	Apydan®	118	26.7	1814	665	450	3600
	b.i.d.	116	26.2	1806	663	450	3600
	t.i.d.	2	0.5	2250	849	1650	2850
Number of MHD trough serum conc.	With AEs[a]	29	37.2				
	Without AEs[b]	297	81.6				
MHD serum conc. (μg/ml)	With AEs[c]	78	17.6	27.9	8.55	5.4	57.5
	Without AEs[d]	364	82.4	21.8	7.91	3.3	46.3
OXC dosage (mg/kg)	With AEs[e]	78	17.6	27.1	9.73	8.1	62.3[g]
	Without AEs[f]	364	82.4	25.0	10.83	4.6	62.5[g]

Abbreviations: conc.: concentration, MHD: mono-hydroxy-derivate, OXC: oxcarbazepine, AEs: adverse effects.
[a] Serum conc. was determined as trough level (immediately before drug intake) in 29 (37.2%) of 78 patients with AEs.
[b] Serum conc. was determined as trough level (immediately before drug intake) in 297 (81.6%) of 364 patients without AEs.
[c] lowest measured MHD serum conc. associated with an AE in patients with AEs.
[d] highest measured MHD serum conc. in patients without any AE.
[e] lowest body weight adjusted OXC dosage associated with an AE in patients with AEs.
[f] highest body weight adjusted OXC dosage in patients without any AE.
[g] In total, 9 patients were treated with OXC dosages higher than 50 mg/kg (range 50.3–62.5 mg/kg) of whom 8 were younger patients (<18 years). Seven of the 8 younger patients and the adult patient tolerated these high dosages. Six of the 7 patients without AEs were treated with extended-release formulations and one patient (child) without AEs was treated with an immediate-release formulation.

Fig. 2a and b indicate that younger patients (<18 years) tolerated higher MHD serum levels as well as higher OXC dosages than adults (≥18 years). Furthermore, Fig. 3a and b illustrate that patients treated with extended-release OXC formulation tolerated higher body weight adjusted dosages compared to patients treated with immediate-release formulations, whereas MHD serum levels at which AEs occurred were not dependent on the OXC formulation.

Multivariate GEE including all 893 blood samples confirmed the significant effect of MHD serum levels, pharmaceutical formulation and age (<18 years vs. ≥18 years) on the occurrence of AEs, whereas the body weight adjusted dosage of OXC had no additional significant influence on the probability of the occurrence of an AE (Supplementary Table A).

4. Discussion

In total, at least one adverse effect was reported in 78 patients (17.6%). The reported AEs were asserted and documented by neurologists or epilepsy specialist nurses on the laboratory order form. Compared with other studies [6,11–13], the rate of 17.6% of patients suffering from adverse effects is relatively small. However, in this study only clinical symptoms, predominately central nervous system (CNS) related symptoms, of an OXC overdose were considered, but not lab results, such as hyponatremia, which is also a frequently mentioned AE [6]. Additionally most of the studies are based on OXC as adjunctive therapy and serum levels were assessed for study reasons and not as part of clinical routine [11,13–15].

Table 2
Summary of adverse events in 78 patients.

	No. of patients	Patients with AE (%) ($n = 78$)	Total of patients (%) ($n = 442$)
Dizziness	46	59.0	10.4
Diplopia	25	32.1	5.7
Nystagmus	25	32.1	5.7
Ataxia	11	14.1	2.5
Fatigue	9	11.5	2.0
Nausea	6	7.7	1.4
Headache	5	6.4	1.1
Vomiting	4	5.1	0.9
Others[*]	6	7.7	1.4

Abbreviation: AE: adverse effect.
[*] Drowsiness, xerostomia, concentrating impairment, memory impairment, eczema, dysphasia.

Furthermore, some studies report that side effects of OXC are observed most frequently within the first weeks after changes of therapy or increase of dosage [13,15]. These findings are in accordance with our results. In our study, AEs were reported in 38 (40.0%) of 95 patients with changes of OXC dosage within the past 4 days compared to 23 (24.0%) of 96 patients with changes of OXC dosages between the last 4 and 14 days and compared to 17 (6.8%) of 251 patients with OXC dosages unchanged for more than 2 weeks ($p < 0.001$, Fisher's exact test). Therefore, the high rate of patients on a stable (long-term) treatment with OXC in our study contributes to the relatively low prevalence of side effects compared those reported in clinical studies. Bourgeois and D'Souza [15] also mentioned that clinical studies compared to clinical practice overestimate the rate of AEs though the prevalence determined in this surveillance has to be confirmed or refuted by further real-life data.

Respecting the type of AEs, we found the expected adverse drug reactions typical for OXC, or rather voltage-gated sodium channel blockers (VGSC) in general, which are related to the central nervous system (dizziness, fatigue, diplopia, nystagmus, headache and ataxia) or digestive system (nausea and vomiting), as most frequent [8,11,13,14,16,17].

Furthermore, our findings confirm that AEs of OXC are significantly related to MHD serum levels or OXC dosages in accordance with the results of Barcs et al. or Striano et al. [8,11]. The Kaplan Meier plots indicate especially that at MHD

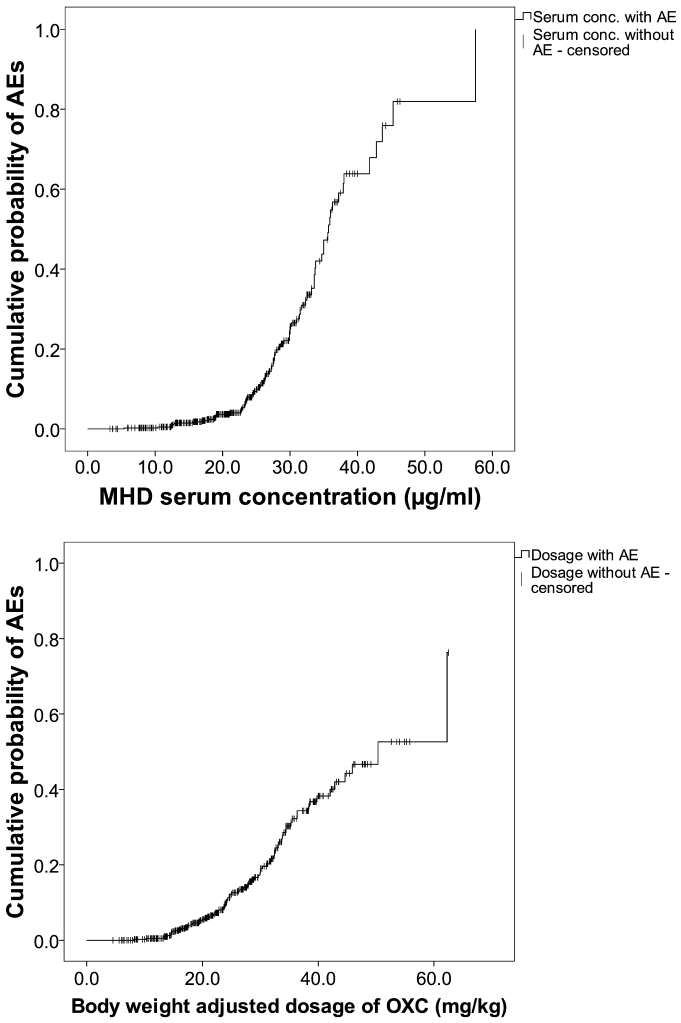


Fig. 1. (a and b) Kaplan–Meier plots of the cumulative probability of adverse effects (AEs) related to MHD (mono-hydroxy-derivate) serum concentration and body weight adjusted dosage of OXC (oxcarbazepine).

serum levels >20 μg/ml the risk of AEs ascends steeply, whereas the relationship to OXC dosage is less distinctive.

In case of AEs, only 29 (37.2%) of the corresponding MHD serum levels were trough levels (blood samples taken immediately before drug intake) compared to 297 (81.6%) corresponding MHD serum levels without AEs. This indicates that most AEs were related to increasing or peak MHD serum concentrations after drug intake. This seems to be true especially for vestibulo-cerebellar AEs including dizziness, diplopia, nystagmus or ataxia. Whereas in case of vestibulo-cerebellar AEs, only 19 (30.2%) of the 63 corresponding MHD serum concentrations were trough levels, this was true for 10 (66.7%) of 15 MHD serum concentrations concerning other AEs, e.g. tiredness, headache ($p = 0.016$, Fisher's exact test).

It should be noticed that the diurnal fluctuation of the MHD concentration may also have an impact on the tolerability of OXC [18–20]. Even if the daily fluctuation of MHD serum levels is generally described as relatively small in most cases, high individual variations are possible [21]. These considerations correspond to our findings concerning the pharmaceutical formulation of OXC. Our results indicate that of the extended-release formulation higher body weight adjusted doses are better tolerable than comparable OXC dosages of the immediate-release formulations, whereas we found no difference in relation to the tolerated MHD serum level. Similar results have been reported by Steinhoff et al., Leppik and Hovinga and French et al. ([12,18]; Steinhoff and Wendling, 2009; [20]). Even if not directly object of this investigation, studies have demonstrated that intermitted AEs could also be related to fluctuations of OXC levels as prodrug of MHD. These as well could markedly be reduced by using extend-release formulations and therefore also can be a reason for better tolerability of higher doses by avoiding immediate-release formulations [17,20,22].

Furthermore, our results illustrate that younger patients (<18 years) tolerate higher MHD serum levels as well as higher body weight adjusted OXC dosages compared to adult patients (≥18 years). Seven patients tolerated even doses above 50 mg/kg (six on a b.i.d. regimen of the extended-release formulation, one on t.i.d. regimen of an immediate-release formulation) of which 6 have been younger than 18 years of age. So far, several studies investigated the impact of age on pharmacokinetics of MHD, efficacy and tolerability. But only a few studies considered patients on OXC monotherapy and in most cases the compared age groups were defined differently. Further, most studies focused on special groups like younger children or elderly patients. But, in spite of differences in the comparing age groups, our results are in accordance with the finding of various studies [1,23,24] indicating that younger children require higher dosages in order to attain adequate serum levels whilst maintaining tolerability. This was confirmed in our study as well. The calculated MHD level-to-dose ratio (MHD serum concentration/OXC dose/body weight) was about 20% lower for patients aged under 18 years compared to those aged over 18 years (0.79 ± 0.23 [μg/ml]/[mg/kg] vs. 1.04 ± 0.36 [μg/ml]/[mg/kg], $p < 0.001$).

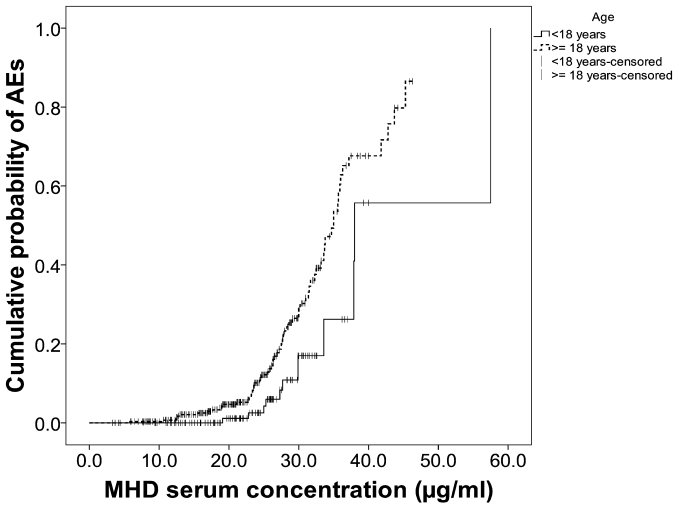
A contrary effect was described for elderly patients [1,25,26] which, however, could not be investigated in this study due to the small number of patients aged over 65 (<2% of the patients).

As far as we know, there have been no investigations concerning gender as a potential influencing factor on tolerability

Table 3
Results of the Log-Rank test for gender, age and pharmaceutical formulation.

	N. of patients	Mean conc. (μg/ml)	Standard error	Sig.	Mean dose per kg (mg/kg)	Standard error	Sig.
Gender							
Male	241	42.7	2.61	0.110	50.6	1.87	0.082
Female	201	34.5	0.96		44.5	2.07	
Age							
<18 years	128	44.3	3.82	0.006	55.8	1.86	<0.001
≥18 years	314	34.8	0.88		38.2	1.29	
Drug							
Timox®/Trileptal®	324	37.4	1.51	0.125	44.1	2.10	0.010
Apydan® extended-release	118	35.0	1.04		53.4	2.38	

Abbreviations: *N*: number of patients, conc.: concentration, sig.: significance, y: years of age.



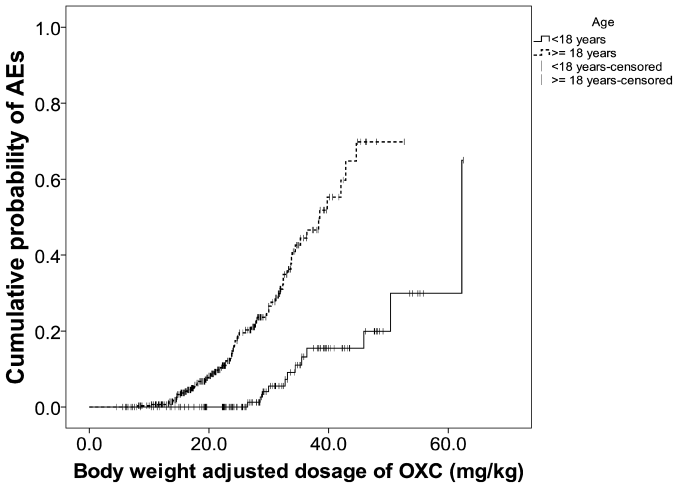
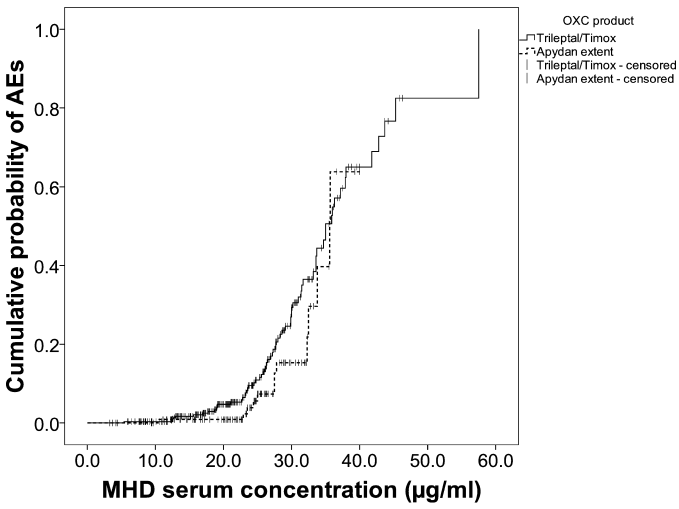


Fig. 2. (a and b) Kaplan–Meier plots of the cumulative probability of adverse effects (AEs) related to MHD (mono-hydroxy-derivate) serum concentration and body weight adjusted dosage differentiated by age groups.



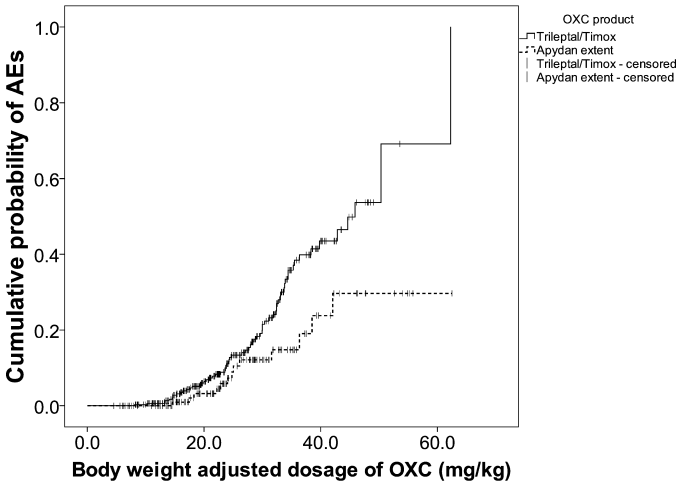


Fig. 3. (a and b) Kaplan–Meier plots of the cumulative probability of adverse effects (AEs) related to MHD (mono-hydroxy-derivate) serum concentration and body weight adjusted dosage differentiated by pharmaceutical products.

of OXC so far. However, our results indicate no significant difference in tolerability of OXC between men and women.

The above discussed effects of MHD serum levels, pharmaceutical formulation of OXC, and age (<18 years vs. ≥18 years) on the tolerability of OXC were confirmed by GEE. Finally, it should be mentioned that due to a different ratio of S- and R-enantiomers these results should not be generalized to patients receiving eslicarbazepine.

4.1. Limitations

Our study has several limitations. First of all, this was a retrospective study, accordingly there was no fixed schedule–neither for the minimum or the maximum dose of OXC nor for the time of taking blood samples. Furthermore, the reporting of AEs was dependent on patient's subjective perception and abnormal lab values were not considered. In some cases, determined serum levels could differ from the actual serum level at first appearance of the AE as blood sampling was lagged. But the number of these cases can considered being small as, apart from five, all patients were inpatients of an epilepsy center and timely blood sampling is part of clinical routine.

5. Conclusion

Our results indicate that the occurrence of adverse effects, especially those related to the central nervous or digestive system was significantly related to the MHD serum level. Children and younger patients tolerated higher body weight adjusted doses of OXC as well as higher MHD serum levels compared to adults. Furthermore, higher doses of the extended-release formulation of OXC seem to be better tolerated than identical doses of immediate-release formulations, probably due to lower diurnal fluctuations of MHD serum levels.

Conflict of interest

The authors have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.seizure.2015.07.018.

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