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The impact of age on lamotrigine and oxcarbazepine kinetics: A historical cohort study

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ABSTRACT

Age as well as estrogen levels may have an impact on the pharmacokinetics of lamotrigine (LTG) and monohydroxycarbazepine (MHD), the active metabolite of oxcarbazepine (OXC). To assess the effects of age and menopause, we evaluated retrospectively a therapeutic drug-monitoring database. Samples from 507 women and 302 men taking LTG and 464 women and 319 men taking OXC were used to develop a population pharmacokinetic model. Data were analyzed using NONMEM software and were compared with a population pharmacokinetic model based on samples of 1705 women and 1771 men taking carbamazepine (CBZ). Age was a significant factor contributing to pharmacokinetic variability in individuals using LTG, OXC, and CBZ with increasing clearance as a function of bioavailability (Cl/F) over age 18, a maximum Cl/F at 33 years (CBZ) and 36 years (LTG and OXC), and a gradual decrease of Cl/F towards older age. We found no effect of perimenopausal age range on LTG and MHD clearance.

1. Introduction

Lamotrigine (LTG) is a commonly used antiepileptic drug (AED), mainly metabolized through glucuronidation [1]. Age, smoking, diet, certain disease states, coadministered drugs, ethnicity, genetic factors, and hormonal effects may influence the pharmacokinetics of glucuronidated drugs [2]. The effect of age on glucuronidation is known in the neonatal period with significant changes during fetal and neonatal development requiring age-adapted drug therapy [2,3]. A recent study showed a 20% lower LTG clearance in older adults on monotherapy compared to younger adults [4]. When assessing the influence of age throughout the lifetime, we also have to consider the possible effects of changing hormonal status on LTG pharmacokinetics. Hormonal effects on LTG clearance caused by concomitant use of oral contraceptives (OCs) are well documented. Several studies showed a pharmacokinetic interaction between LTG and estradiol-containing oral contraceptives (OCs), resulting in an average reduction of ~50% of the plasma level of LTG [5–7]. The elimination of LTG also significantly increases during pregnancy, causing a marked decline in plasma concentrations with potential clinical relevance [8–11]. Steroid induction of hepatic 2-N-glucuronidation, a major route of metabolism for LTG [12], probably causes these changes. Not much is known of the effect of changing perimenopausal hormonal status on LTG kinetics. We found previously a higher mean LTG clearance in postmenopausal women compared with younger women with a regular menstrual cycle [13]. This was surprising considering the low levels of both estrogen and progestogen in postmenopausal women. Data from a retrospective study [14] suggested a transitory decline in LTG clearance in the perimenopausal or early postmenopausal period. If this interpretation is correct, women taking LTG might need dose adjustment to prevent dose-related adverse effects in the perimenopausal period as well as seizure aggravation or breakthrough in the postmenopausal state.

To assess this, we used a drug-monitoring database to explore the effects of age including the perimenopausal age range on the clearance of LTG as well as of monohydroxycarbazepine (MHD), the active metabolite of oxcarbazepine (OXC), which, like LTG, is also predominantly metabolized through glucuronidation. We compared our findings with an analysis of the clearance of carbamazepine (CBZ), an AED predominantly metabolized by cytochrome P450 3A4.

2. Methods

We used the therapeutic drug-monitoring digital database of a tertiary epilepsy center for a retrospective analysis of LTG, MHD, and CBZ

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serum concentrations. Serum concentrations of all available AEDs sampled for therapeutic drug monitoring are kept since 1990. The request form includes weight, length, time of drug intake, and concomitant drugs. Coprescribed oral contraceptives, pregnancies, hormone replacement therapy, smoking habits, and other factors influencing pharmacokinetics are, however, not always recorded. We searched the database for LTG, MHD, and CBZ serum concentrations determined between January 1990 and October 2010. At the time of sampling, individuals had to be over the age of 17 years and on monotherapy. Drug dosage and time elapsed since last drug intake had to be available. Sample concentrations had to be over the lower limit of quantification. Samples taken monthly during pregnancy were excluded.

2.1. Drug assays

Serum concentrations of LTG, MHD, and CBZ were determined by a high performance liquid chromatography (HPLC) method with UV detection after solid-phase extraction [15]. The lower limits of quantification were 0.2 mg/l for LTG, 0.1 mg/l for MHD, and 0.1 mg/l for CBZ.

2.2. Pharmacokinetic analysis

Population analysis was conducted using NONMEM software (version VI, level 2.0, ICON Development Solutions, Ellicott City, MD, USA) [16]. A one-compartment model with first-order absorption and first-order elimination as implemented in ADVAN2 TRANS2 subroutine was used to fit the concentration–time data. First-order conditional estimation method (FOCE) with interaction was used to derive population pharmacokinetic parameters, the parameter variability (between subjects and occasions), and the residual variability between observed and predicted concentrations. Exponential models were used to describe between-individual and between-occasion variability, while additive, proportional, and mixed error models were tested for residual variability. All available serum concentrations were introduced in the model.

2.3. Covariate model building

To establish the possible relationships between the pharmacokinetics of LTG, MHD, CBZ, and individual characteristics, the following covariates were defined: gender, weight, and age. Effects of age and weight were examined as continuous variables, and gender was examined as a dichotomous variable:

Model 1: $\theta 1 \times \theta 2^{(1\text{-SEX})}$
Model 2: $\theta 1 \times (\mathrm{WT}/71)^{\theta 2}$
Model 3: $\theta 1 \times (\mathrm{AGE}/36)^{\theta 2}$ for AGE $\geq$ 36, and $\theta 1 \times (36/\mathrm{AGE})^{\theta 2}$ for AGE $<$ 36
Model 4: $\theta 1 \times (\mathrm{AGE}/\theta 3)^{\theta 2}$ for AGE $\geq \theta 3$, and $\theta 1 \times (\theta 3/\mathrm{AGE})^{\theta 2}$ for AGE $< \theta 3$
Model 5: $\theta 1 \times (1\text{-PERM}) + \theta 2 \times (\mathrm{PERM})$

in which SEX is 0 for males and 1 for females, and the continuous variables weight (WT) and age (AGE) are related to the population means (71 kg and 36 years old, respectively). In model 4, the median age (36 years) is replaced by θ_3 to model the age with the highest clearance as a function of bioavailability (Cl/F). In model 5, PERM (PERiMenopausal) is 1 for women between 44 and 56 years, the age range at which 95% of women experience menopause [17].

The performance of various models was evaluated using both graphical and statistical methods. A covariate was included in an intermediate model when its addition to the basic model was both statistically significant (Δ objective function > -6.6, $P < 0.01$) and relevant. A stepwise backward elimination procedure was also performed, in which each of the covariates was deleted sequentially. A covariate was only retained in the model when its influence was statistically significant and relevant.

As the collected data used for model building were predominantly trough concentrations, estimation of the volume of distribution (V/F) and absorption rate constant (ka) was not possible. Therefore, V/F was fixed at 1.5 l/kg and ka at 1.3 h^{-1} [18] for LTG. Volume of distribution was fixed at 80 l and ka at 1.0 h^{-1} for OXC [19] and V/F at 1.4 l/kg and ka at 0.224 h^{-1} for CBZ [20].

2.4. Model validation

A bootstrap resampling technique was applied to assess model reliability of the parameter estimates and their 95% confidence intervals (CIs) from the final model [21]. One thousand bootstrap data sets were generated by repeated sampling with replacement from the original data set using Wings for NONMEM (version 6.1.6, http://wfn.sourcefourge.net) [16], and parameter estimates were obtained. Parameter estimates at the 2.5th, 50th (median), and 97.5th percentile were compared with the parameter estimates and their 95% CIs were obtained from NONMEM. The stability of

Table 1
The final parameter estimates and 95% CI from NONMEM and the bootstrap analyses of lamotrigine.

	NONMEM				Bootstrap analysis			
Parameter	Estimated value	95% confidence interval			Median	95% confidence interval		
ka [1/h]	1.3							
V/F [l/kg]	1.5							
Cl/F [l/h]	2.56	2.35	–	2.77	2.56	2.35	–	2.77
θ on AGE	−0.313	−0.471	–	−0.155	−0.305	−0.562	–	−0.070
BSV of Cl/F	43%	36%	–	46%	41%	36%	–	46%
BOV of Cl/F	8%	0%	–	19%	8%	0%	–	19%
Rel. error	13%	0%	–	18%	12%	0%	–	18%
Abs error	1.5	1.1	–	1.8	1.5	1.1	–	1.8

Cl/F = clearance as a function of bioavailability.
l = liter.
h = hour.
ka = rate constant of absorption.
V/F = volume of distribution.
BSV = between-subject variability.
BOV = between-occasion variability.
Rel. = relative.
Abs = absolute.