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Serum levels of lamotrigine during delivery in mothers and their infants

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Summary
Purpose: We followed up lamotrigine transport through the placenta and analyzed maternal and umibilical cord concentrations, its ratio and maternal lamotrigine clearance in monotherapy and in combinations.
Methods: Maternal and umbilical cord concentrations were analyzed during delivery in a cohort of 63 women between 2001 and 2009. The request forms for routine therapeutic drug monitoring were used as the data source. Maternal concentrations were used for the estimation of apparent oral clearance and paired infant and maternal concentrations for estimation of the infant (umibilical cord)/maternal serum concentration ratio.
Results: The lamotrigine infant/maternal serum concentration ratio ranged in monotherapy from 0.40 to 1.38 (median 0.91). The ratio in monotherapy showed a possible distribution to two subgroups. Concomitant administration of valproic acid significantly increased both maternal and infant lamotrigine concentrations and significantly decreased lamotrigine clearance by about 65%. Co-medication with carbamazepine increased lamotrigine clearance non-significantly. Highly significant correlations were found between maternal and umbilical cord lamotrigine concentrations, both in monotherapy and in the lamotrigine + valproic acid combination. Infant concentrations of valproic acid were found to be about 30% higher and infant concentrations of carbamazepine were found to be about 20% lower than maternal concentrations.

Abbreviations: AEDs, antiepileptic drugs; UGT, uridine 5′-diphosphate glucuronosyltransferase; M, maternal; I, infant; *I/M* ratio, infant (umbilical cord)/maternal serum concentration ratio; CBZ, carbamazepine; LTG, lamotrigine; VPA, valproic acid.

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Conclusions: Our data from the large cohort showed the interindividual variability of umbilical cord/maternal serum concentration ratio in lamotrigine monotherapy caused probably by the different activity of the placental lamotrigine metabolizing enzymes UGT1A4 and 2B7 associated with genetic polymorphism. The potential teratogenic effect of lamotrigine combination with valproic acid could be associated with the higher lamotrigine and valproic acid concentrations in the fetus.

Introduction

Lamotrigine (LTG) is one of the so-called new generation of antiepileptic drugs (AEDs) and it has become one of the major drugs in the treatment of pregnant women with epilepsy (EURAP, 2008). In our previous study we found that only carbamazepine is prescribed during pregnancy more often than lamotrigine (Kacirova et al., 2007). The decline in LTG plasma concentrations during pregnancy was observed with a considerable interindividual variability in the effect of pregnancy on LTG kinetics (Tran et al., 2002; Pennell et al., 2008). Increased seizure frequency in the second trimester was associated with a lower ratio of current LTG concentration to baseline target concentration, and a ratio <0.65 was a significant predictor of seizure worsening (Pennell et al., 2008). Frequent LTG level monitoring during pregnancy and after delivery is necessary to optimize treatment in women taking LTG in this period of instable kinetics. The data on the LTG transplacental transfer and the risk of exposure to the fetus remain sparse and only a limited number of studies have actually measured the umbilical cord blood levels. Two case reports and three studies with four–six patients have reported cord LTG plasma levels very similar to maternal plasma concentrations, which is compatible with a free transplacental passage (Tomson et al., 1997; Ohman et al., 2000; Myllynen et al., 2003; de Haan et al., 2004; Fotopoulou et al., 2009). This observation was further supported by in vitro human placental perfusion studies (Myllynen et al., 2003). The results of some authors suggest interindividual variation in cord plasma/maternal plasma LTG concentration ratio (Ohman et al., 2000; Fotopoulou et al., 2009).

In our study we followed up LTG transport through the placenta in a larger study group and analyzed maternal and umbilical cord serum levels, its ratio, maternal clearance of LTG and the influence of co-medication with carbamazepine and valproic acid during delivery.

Methods

This retrospective study comprised of 63 pregnant women with epilepsy receiving either monotherapy of lamotrigine ($n = 51$) or combinations of LTG with valproic acid ($n = 7$) or carbamazepine ($n = 5$). Blood samples from the mothers and from the umbilical cords were collected at delivery and analyzed in our department between the years 2001–2009. Request forms for routine therapeutic drug monitoring were used as the data source. The basic characteristics of the mothers and their children are given in Table 1 (age and weight of mothers; birth weight, birth length and gender of the children). For the treatment characteristics see Tables 2 and 3 (total daily dose and daily dose related to the body weight in patients with LTG monotherapy versus LTG combinations with other antiepileptics drugs). LTG and carbamazepine (CBZ) concentrations in the serum were measured by high-performance liquid chromatography (Budakova et al., 2008), valproid acid (VPA) by gas chromatography (Brozmanova and Grundmann, 1985).

Maternal LTG serum levels were used for the estimation of LTG apparent oral clearance calculated as: LTG clearance = daily dose (mg/kg)/serum LTG concentration (mg/L). Paired infant (i.e. umbilical cord) and maternal serum LTG levels were utilized for estimation of the infant (umbilical cord)/maternal serum concentration (*I*/*M*) ratio. The D'Agostino and Pearson omnibus normality test, the Mann–Whitney test and the Pearson correlation test were performed using GraphPad Prism version 5.00 for Windows, GraphPad Software, San Diego California USA, www.graphpad.com. A value of $p < 0.05$ was considered statistically significant.

Table 1 The basic characteristics of the mothers and their infants.

	Mothers	
	Age (years)	Weight (kg)
n	63	63
Mean ± SD	27 ± 5	76 ± 14
Range	18; 41	43; 113

	Infants		
	Gender = female (F)/male (M)	Birth weight[a] (kg)	Birth length[a] (cm)
n	F = 27/M = 28	54	51
Mean ± SD		3.3 ± 0.5	49 ± 2
Range		2.2; 4.6	41; 54

[a] Values of birth weight and birth length has not been recorded in all cases.