Epilepsy Research 122 (2016) 84–90

Contents lists available at www.sciencedirect.com

Epilepsy Research

journal homepage: www.elsevier.com/locate/epilepsyres

Concentrations of carbamazepine and carbamazepine-10,11-epoxide in maternal and umbilical cord blood at birth: Influence of co-administration of valproic acid or enzyme-inducing antiepileptic drugs

Ivana Kacirova[a,b], Milan Grundmann[a,*], Hana Brozmanova[a,b]

[a] Department of Clinical Pharmacology, Faculty of Medicine, University of Ostrava, Syllabova 19, 703 00 Ostrava, Czech Republic
[b] Department of Clinical Pharmacology, Department of Laboratory Diagnostics, University Hospital Ostrava, 17. listopadu 1790, 708 52 Ostrava, Czech Republic

ARTICLE INFO

Article history:
Received 28 July 2015
Received in revised form 3 February 2016
Accepted 28 February 2016
Available online 2 March 2016

Keywords:
Carbamazepine
Carbamazepine-10,11-epoxide
Delivery
Therapeutic drug monitoring
Drug–drug interaction
Epilepsy

ABSTRACT

Background: Carbamazepine is one of the three most frequently prescribed antiepileptic drugs in pregnancy. However, data relating to both carbamazepine and carbamazepine-10,11-epoxide transplacental passage remain sparse.
Material and methods: We have analysed in a cohort of 114 women carbamazepine and carbamazepine-10,11-epoxide levels in maternal and umbilical cord serum at birth during 25 years retrospectively. The carbamazepine maternal apparent oral clearance, ratio of the umbilical cord/maternal level and ratio of the carbamazepine-10,11-epoxide/carbamazepine ratio were estimated. The influence of co-medication with valproic acid or enzyme-inducing antiepileptic drugs was evaluated.
Results: The maternal carbamazepine levels varied from 0.6 to 11.8 mg/L (carbamazepine-10,11-epoxide 0.1–2.5 mg/L) and in umbilical cord between 0.1 and 10.5 mg/L (carbamazepine-10,11-epoxide 0.1–2.2 mg/L). The ratio the of umbilical cord/maternal level of carbamazepine ranged from 0.03 to 2.23 (median 0.80) and of carbamazepine-10,11-epoxide between 0.17 and 2.00 (median 0.83). Concomitant administration with enzyme inducers significantly increased the maternal apparent oral clearance by approximately 50% and co-administration with valproic acid approximately by 70%. Combination with valproic acid significantly increased the rate of carbamazepine-10,11-epoxide to the parent drug both in maternal serum (by approximately 80%) and in umbilical cord (by 100%).
Conclusions: The data showed the wide interindividual variability of the ratio of the umbilical cord/maternal level of both carbamazepine and carbamazepine-10,11-epoxide. It is the first study showing the significant increase of the ratio of umbilical cord/maternal level of carbamazepine-10,11-epoxide and carbamazepine-10,11-epoxide/carbamazepine ratio not only in maternal serum but also in umbilical cord in addition of valproic acid. The present study demonstrates that a concomitant administration of enzyme-inducing antiepileptics and valproic acid increases the maternal apparent oral clearance of carbamazepine significantly.

1. Introduction

1.1. Background

Carbamazepine (CBZ) is an important option for women with focal epilepsy during their childbearing years. It is presently one of the three most frequently prescribed antiepileptic drugs (AEDs) in pregnancy, together with lamotrigine and valproic acid followed by levetiracetam and oxcarbazepine (Kacirova et al., 2010a; EURAP, 2015). The risk of teratogenic effects of CBZ appears to be dose

Abbreviations: AEDs, antiepileptic drugs; CBZ, carbamazepine; Cl, clearance; CLZ, clonazepam; CYP, cytochrome P450; EURAP, European and International Registry of Antiepileptic Drugs and Pregnancy; LTG, lamotrigine; N, number; M, maternal; MCMs, major congenital malformations; PB, phenobarbital; Pbmet, phenobarbital as a metabolite of primidone; PHT, phenytoin; PRM, primidone; TPM, topiramate; UC, umbilical cord; VPA, valproic acid.

* Corresponding author. Tel.: +420 597 374 389.
E-mail addresses: ivana.kacirova@fno.cz (I. Kacirova), milan.grundmann@osu.cz (M. Grundmann), hana.brozmanova@fno.cz (H. Brozmanova).

http://dx.doi.org/10.1016/j.eplepsyres.2016.02.013
0920-1211/

dependent (Tomson et al., 2011); nevertheless, the mechanism by which CBZ exerts its teratogenicity remains largely unknown (Wlodarczyk et al., 2012).

Ninety-nine percent of CBZ is metabolised by the liver; cytochrome P450 (CYP) isoenzymes 3A4 and 3A5 are the most prominent enzymes that converted CBZ to CBZ-10,11-epoxide, the active metabolite. The epoxide is metabolised to the inactive metabolite CBZ-10,11-diol by microsomal epoxide hydrolase, and it is excreted in the urine. It had been reported that CBZ is metabolised into epoxide in human foetal liver (Piafsky and Rane, 1978; Rane et al., 1975). CYP3A7 was identified as a member of the CYP3A subfamily expressed in foetal liver, and differential expression of this enzyme in the foetus with a switch to CYP3A4/3A5 in the adult was demonstrated (Schuetz et al., 1994; Yang et al., 1994; Wrighton et al., 1988). Clonazepam (CLZ), lamotrigine (LTG) and topiramate (TPM) do not affect the pharmacokinetics of CBZ. Phenobarbital (PB), phenytoin (PHT) and primidone (PRM) enhance the metabolism of CBZ through CYP3A4, and valproic acid (VPA) inhibits the metabolism of the epoxide by inhibition of epoxide hydrolase (Patsalos, 2013a,b). Pregnancy can affect the pharmacokinetics of AEDs at any level from absorption, distribution and metabolism to elimination. However, CBZ seems to be affected only marginally by pregnancy (Tomson et al., 2013). Approximately 70–80% of CBZ (50–60% of epoxide) is bound to plasma proteins in the non-pregnant state. The free fraction of CBZ increases during pregnancy, from 0.23 at baseline to a maximum of 0.32 in the third trimester. However, total and free CBZ and epoxide clearances do not change substantially during pregnancy, and seizure frequency worsening is not associated with decreased concentrations of total or free CBZ (Johnson et al., 2014). These minimal changes do not necessitate measurement of free fractions of CBZ and epoxide during pregnancy.

Measuring the ratio of the umbilical cord/maternal serum drug level at birth is the method often used to assess transplacental transfer (Tomson, 2005). However, the data relating to the CBZ and especially CBZ-10,11-epoxide transplacental passage remain sparse. The CBZ and the epoxide levels were analysed in the amniotic fluid during first trimester by Omtzigt et al. (1993). The umbilical cord CBZ levels were reported as either not significantly different from maternal or lower, with the range of the ratio of the umbilical cord/maternal level of 0.50–1.53 (Bardy et al., 1990; Friel et al., 1987; Fröscher et al., 1991; Kuhnz et al., 1983; Meyer et al., 1988; Nau et al., 1982; Rane et al., 1975; Takeda et al., 1992; Yerby et al., 1985). The ratio of the umbilical cord/maternal level of the epoxide was measured in the study of Kuhnz et al. (1983) ($n = 5$, mean ± SD: 0.75 ± 0.09) and Yerby et al. (1985) ($n = 5$, mean = 0.68). The CBZ levels were also analysed by Pienimäki et al. (1997) in three maternal (3.7–5.0 mg/L) and umbilical cord (2.9–4.3 mg/L) samples, as well as the epoxide levels (0.24–0.53 mg/L in maternal and 0.21–0.54 mg/L in umbilical cord blood), though the ratio of the umbilical cord/maternal level was not reported. The pharmacokinetics of CBZ during pregnancy was studied by Pynnönen et al. (1977) in the foetal tissues at autopsy. The liver and kidney contained high levels of CBZ, whereas brain and lungs had low values; the epoxide was also detected in the foetal circulation (Pynnönen et al., 1977). The influence of co-medication with VPA to the ratio of CBZ-10,11-epoxide to parent drug in the umbilical cord has not yet been studied.

1.2. Aim

We followed CBZ and CBZ-10,11-epoxide transport through the placenta and analysed maternal and umbilical cord serum levels, its ratio, the maternal apparent oral clearance of CBZ and the influence of co-medication with enzyme inducers (PRM and PHT) and VPA. Relationships between birth weight (and length) and daily dose, dose related to the body weight and maternal and umbilical cord CBZ levels were also analysed.

2. Material and methods

The retrospective study was composed of 114 pregnant women with epilepsy receiving either CBZ in monotherapy or combination with neutral drugs (LTG, CLZ, TPM; $n = 82$), combination with enzyme-inducing AEDs (phenytoin and primidone; $n = 18$) or combination with valproic acid ($n = 9$). One woman used both phenobarbital and valproic acid. Maternal and umbilical cord serum were collected at birth and analysed in our department between the years 1990 and 2014 (CBZ-epoxide in a subgroup of 83 women between 1997 and 2014). Request forms for routine therapeutic drug monitoring were used as the data source. Therapeutic ranges used in our department are 4–9 mg/L for CBZ alone and <12 mg/L for the sum of CBZ + CBZ-10,11-epoxide. The basic characteristics of the mothers and their infants are given in Table 1 (maternal age and weight, infants birth weight, birth length and gender). For the treatment characteristics, see Tables 2 and 3 (total daily dose and daily dose related to the body weight). Total serum levels of VPA were measured by gas chromatography (Brozmanova and Grundmann, 1985), and total serum levels of other AEDs were

Table 1
Basic characteristics of mothers and their infants.

Mothers	Age (years)	*Weight (kg)
n	114	104
Mean ± SD	25 ± 4	76 ± 12
Range	17; 38	48; 108

Infants	*Gender	*Birth weight (kg)	*Birth length (cm)
n	Female = 48/male = 51	93	83
Mean ± SD		3.3 ± 0.4	49 ± 2
Range		2.3; 4.2	43; 54

* Values have not been recorded in all cases.

Table 2
Dosage and maternal apparent oral clearance (Cl) of carbamazepine (CBZ) in monotherapy and/or combination with neutral drugs (lamotrigine, clonazepam and topiramate) versus combination with enzyme inducers or valproic acid (VPA).

	*Weight (kg)	*Dose (mg/day)	*Dose (mg/kg)	*Maternal Cl (mg/L)
CBZ monotherapy + neutral drugs				
n	78	75	70	70
Median	76	600	6.8	1.67
Mean	75	511	6.7	1.82
SD	12	206	2.8	0.89
Min	48	150	1.6	0.56
Max	108	900	12.3	5.92
CBZ + inducers				
n	16	17	16	16
Median	78	800*	7.5	2.57**
Mean	78	671	8.7*	2.83
SD	13	254	3.6	1.26
Min	60	200	3.3	1.16
Max	96	1000	13.7	5.33
CBZ + VPA				
n	9	8	8	8
Median	77	600	9.3	2.82+
Mean	78	600	8.1	3.32
SD	12	212	2.8	1.70
Min	63	300	3.6	1.63
Max	104	900	10.8	6.30

* Values have not been recorded in all cases.
* $p < 0.02$: CBZ monotherapy + neutral drugs versus CBZ + inducers.
** $p < 0.001$: CBZ monotherapy + neutral drugs versus CBZ + inducers.
+ $p < 0.002$: CBZ monotherapy + neutral drugs versus CBZ + VPA.