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Changes in the Disposition of Oxcarbazepine and Its Metabolites during Pregnancy and the Puerperium

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Summary: *Purpose:* To determine potential changes in the plasma concentrations of oxcarbazepine (OXC) and its metabolites during pregnancy and puerperium.

Methods: Five women receiving OXC monotherapy were followed prospectively during pregnancy and the puerperium. Four women were enrolled in the first trimester, and one woman, 2 weeks before delivery. Steady-state concentrations of OXC, its active *R*-(-)- and *S*-(+)-monohydroxy derivatives (MHD), and the additional metabolite carbamazepine-10,11-*trans*-dihydrodiol (DHD) were measured at regular intervals by an enantioselective HPLC assay.

Results. In all samples, *S*-(+)-MHD was the most abundant compound in plasma and accounted almost entirely for the amount of active moiety (defined as the molar sum of OXC, *R*-(-)-MHD, and *S*-(+)-MHD) found in the circulation. The dose-normalized concentrations of active moiety decreased markedly during gestation and, in four of the five patients, increased strikingly after delivery. Plasma concentrations of *S*-(+)-MHD mirrored closely the levels of the active moiety. Plasma concentrations of the parent drug and other metabolites also tended to decrease during pregnancy and to increase after delivery.

Conclusions: During treatment with OXC, *S*-(+)-MHD is by far the most abundant active compound in plasma. The concentration of this metabolite as well as the active moiety may decrease markedly during pregnancy and may increase several-fold after delivery. Because of these striking pharmacokinetic changes, the clinical response should be monitored closely in OXC-treated women throughout pregnancy and the puerperium.
Key Words: Oxcarbazepine—Monohydroxycarbazepine—Pregnancy—Puerperium—Pharmacokinetics—Enantiomers—Therapeutic drug monitoring.

The management of epilepsy during pregnancy may be complicated by clinically significant changes in the pharmacokinetics of antiepileptic drugs (AEDs). In particular, the total plasma concentrations of phenytoin, carbamazepine, phenobarbital, and valproic acid (VPA) may decrease considerably during pregnancy (1); for drugs highly bound to plasma proteins, however, serum unbound concentrations decrease to a lesser extent and, in the case of VPA, may even increase at the end of gestation (1,2). Information about pregnancy-related changes in the pharmacokinetics of newer-generation AEDs is virtually nonexistent, with the notable exception of lamotrigine (LTG), whose serum concentrations decrease prominently during pregnancy and rebound sharply after delivery (3–6). The latter changes are considered to be due to a marked increase in LTG clearance, presumably associated with enhancement of its conjugation with glucuronic acid in the liver (5,6).

In recent years, oxcarbazepine (OXC) has been increasingly used in women of childbearing potential who have epilepsy. Although reports on pregnancy outcomes in these women are starting to emerge (7,8), the possibility of changes in OXC pharmacokinetics during pregnancy has not been explored. Although OXC has anticonvulsant activity of its own, its pharmacologic effects are largely mediated by its active metabolite monohydroxycarbazepine (MHD) (9), which exists in two enantiomeric forms (10). Like LTG, MHD is primarily cleared by glucuronide conjugation, and therefore it is reasonable to hypothesize that its clearance may also increase during gestation. We describe the profiles of OXC, *R*-(-)-MHD, *S*-(+)-MHD, and the inactive dihydrodiol derivative (DHD) in the plasma of five women followed prospectively during pregnancy and

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the puerperium. The findings indicate that pregnancy can be associated with striking alterations in the disposition of these agents.

PATIENTS AND METHODS

Patients

Five women receiving OXC monotherapy gave their informed consent to participate in the study, according to the following inclusion criteria (a) pregnancy; (b) clinical indication to start or continue treatment with OXC, either alone or in combination with other drugs; (c) absence of associated disorders (e.g., renal or hepatic disease) that could lead to pharmacokinetic changes during the study period; and (d) no history of poor compliance. The age range of the patients was 22 to 34 years (mean, 27 years), their body weight at inclusion in the study was 54–62 kg (mean, 58 kg), and the indication for treatment was partial epilepsy in all cases.

Study procedures

The study was observational and did not involve any change in routine clinical management, except for the collection of the biologic samples. Heparinized blood samples (10 ml) were to be obtained at least once during each trimester of pregnancy after enrollment, at the time of delivery, and at least once during the 3 months after delivery. Physicians and patients were instructed to keep a constant interval between sampling and the last dose at all study visits (in most cases, samples were taken 12 to 15 h after the last dose). Any changes in drug therapy were recorded. Samples were centrifuged within 6 h, and the plasma was kept frozen at –20°C until assay. The study protocol was approved by Ethics Committees of participating centres.

Assay of oxcarbazepine, its metabolites, and statistical analysis

The concentrations of OXC, *R*-(-)-MHD, *S*-(+)-MHD, and DHD in plasma were determined by using a sensitive and specific enantioselective high-performance liquid chromatography (HPLC) assay, according to a modification of the procedure described by Volosov et al. (11). Because the peaks corresponding to DHD enantiomers were poorly resolved, DHD concentrations were quantitated as racemate. Assays were performed on a Shimadzu HPLC system (Shimadzu Scientific Instrument, Inc., Columbia, MD, U.S.A.), with a Chiralcel ODR column (250 × 4.6 mm i.d., 10 μm; Daicel Inc., Schilling, Milan, Italy) at 40°C and a gradient elution from 18 to 25% acetonitrile in potassium hexafluorophosphate, 37.5 m*M* (flow rate, 0.5 ml/min). The eluate was monitored at 210 nm by using a LaChrom L-7400 (Merck, Darmstadt, Germany) variable-wavelength detector. Carbamazepine-10,11-epoxide was used as internal standard. The quantitation limits of the assay were 0.06 μM for OXC and DHD and 0.12 μM for *R*-(-)-and *S*-(+)-MHD. For all compounds, accuracy ranged between 94% and 116%, and between-assay precision (CV%) was >15% within the working range of the assay.

Individual concentrations of OXC, its metabolites, and the active moiety [defined as the molar sum of OXC, *R*-(-)-MHD and *S*-(+)-MHD] at each study visit were tabulated descriptively. Because in three patients, OXC dosage was modified during follow-up, plasma concentrations were normalized to a 100-mg daily dose by dividing the measured concentration (μM) by the ratio dose (mg/day)/100**.** Repeated measures one-way analysis of variance (ANOVA) was used to compare dose-normalized concentrations in each trimester of pregnancy and the puerperium (when more than one sample was available for each patient, the mean concentration for each period was used in the comparison. Concentrations measured at delivery were considered to belong to the third trimester). For concentration changes before delivery, parametric (*t* test) and nonparametric (signed rank-test) trend analysis also was performed. Statistical significance was set at $p < 0.05$ (two tailed).

RESULTS

Clinical data

All enrolled patients were receiving OXC monotherapy, and the range of daily dosages used ranged from 150 to 1,500 mg/day (Fig. 1) in two divided administrations. As shown in Fig. 1, in three of the four patients who could be monitored from the first trimester of pregnancy to the puerperium, dosages were changed at some point before delivery.

In patient 1, dose was increased from 150 to 300 mg/day at week 20 because of a generalized convulsive seizure; the patient remained seizure free thereafter at a dosage of 300 mg/day.

Patient 2 had partial seizures and secondarily generalized seizures at a frequency of approximately one per day and per week, respectively, and her seizure frequency decreased to one to two per month after her OXC dosage was increased from 600 to 1,200 mg/day at gestational week 21 and from 1,200 to 1,500 mg/day 8 weeks after delivery.

Patient 3 was well controlled until she spontaneously stopped her treatment (OXC, 600 mg/day) at about gestation week 4 after discovering that she was pregnant. She had two partial and four secondarily generalized seizures over a period of 3 days shortly after stopping treatment, and she resumed OXC treatment 2 weeks later (300 mg/day, increased to 600 mg/day on gestational week 12) without further seizures.

Patient 4 had been free from seizures for 3 years with no treatment. She had five partial seizures and three secondarily generalized seizures during the second gestational week and, as a result, she was rapidly titrated to

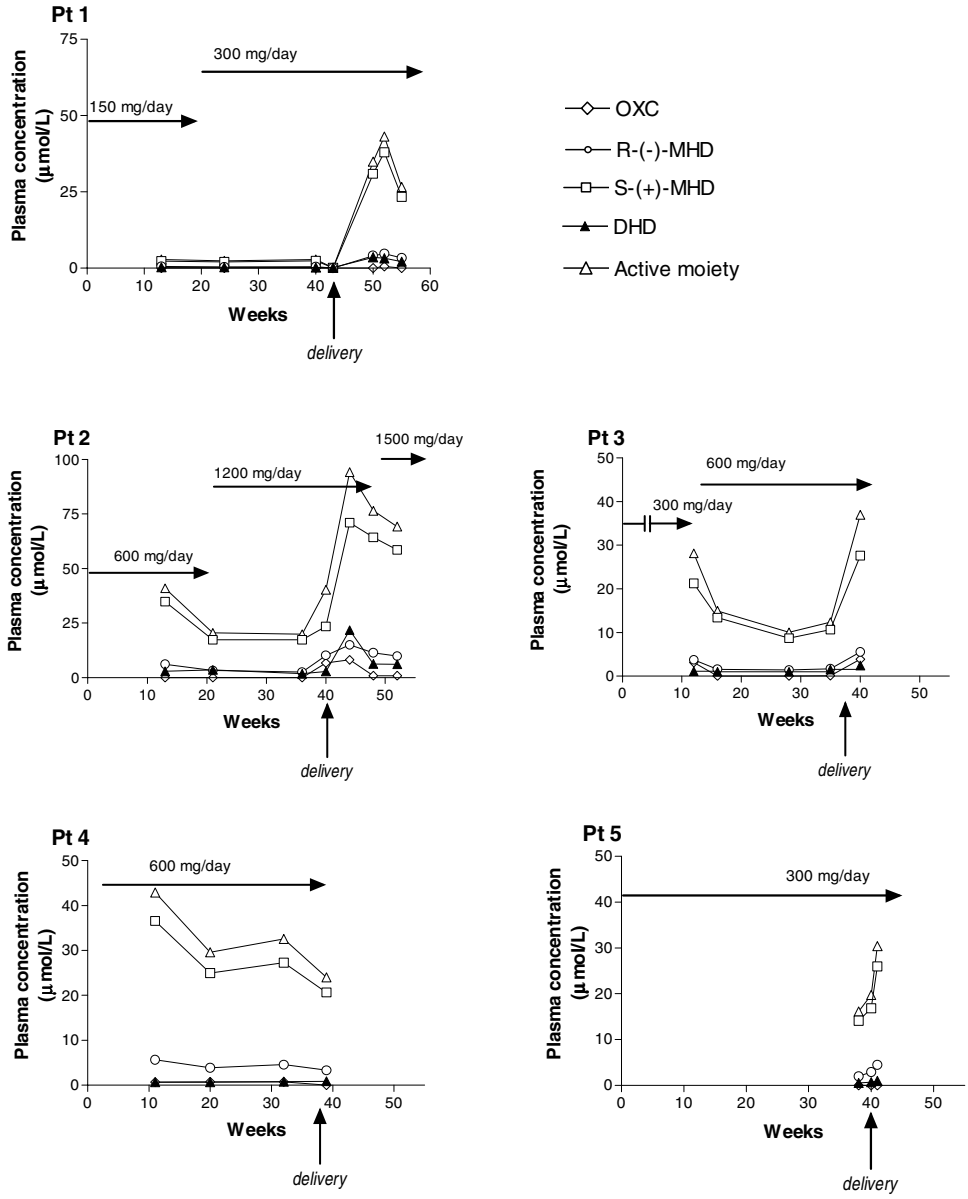

FIG. 1. Concentrations of oxcarbazepine and its metabolites in five women during pregnancy and the puerperium.

600 mg/day OXC, and she had no further seizures during pregnancy.

Patient 5 was enrolled just before delivery, and she reported no seizures during her pregnancy and 1-week follow-up after delivery.

Pharmacokinetic data

Individual actual and dose-normalized plasma concentrations of OXC and its metabolites are illustrated in Figs. 1 and 2 respectively, and individual dose-normalized concentrations in each trimester of pregnancy and during puerperium are reported in Table 1. In all patients and at all sampling times, the plasma concentration of OXC was lower than the concentrations of the metabolites. At all times, *S*-(+)-MHD was the most abundant compound and accounted almost entirely for the amount of active moiety found in the circulation. As a result, changes in the levels of active moiety mirrored closely the changes in *S*-(+)-MHD concentration.

In the four patients who could be monitored from the first trimester of pregnancy, dose-normalized concentrations of active moiety and *S*-(+)-MHD decreased markedly during the gestational period, the lowest levels being observed after week 20 (Fig. 2). In all five patients except one (patient 4), dose-normalized active moiety and *S*-(+)-MHD increased 1.5- to 13-fold between the last observation during pregnancy and the first observation during the puerperium. In most patients, the plasma concentration of the parent drug, *R*-(-)-MHD, and DHD changed in parallel and in the

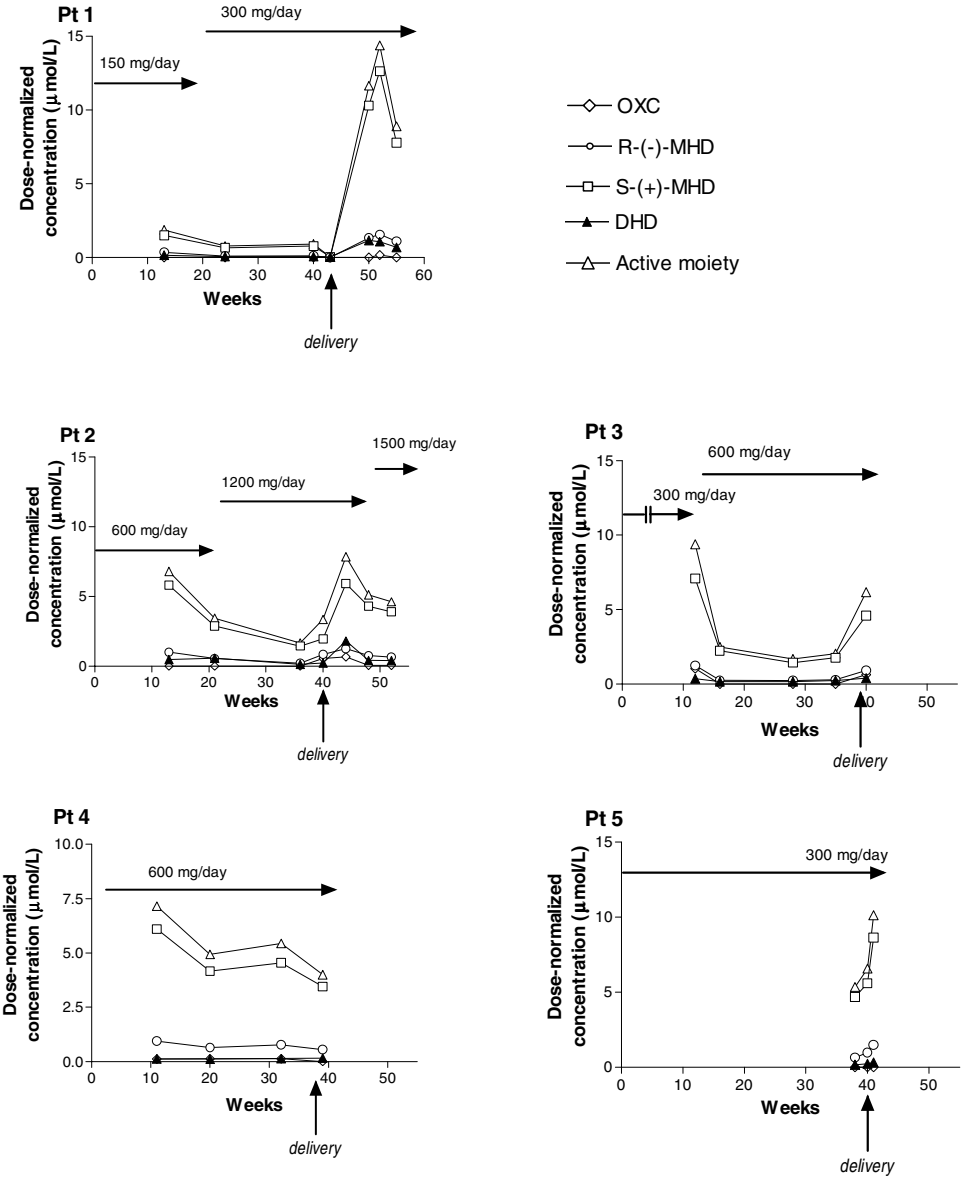

FIG. 2. Dose-normalized concentrations of oxcarbazepine and its metabolites in five women during pregnancy and the puerperium.

same direction as the concentration of *S*-(+)-MHD. When repeated-measures ANOVA was used to compare concentrations at each trimester and during the puerperium, changes were statistically significant for *R*-(-)-MHD ($p < 0.02$) and borderline significant for the active moiety ($p = 0.086$). After exclusion of the first trimester of pregnancy from comparisons, significant differences were found for active moiety ($p < 0.05$) and *R*-(-)-MHD ($p < 0.01$) and borderline significant for the *S*-(+)-MHD ($p = 0.06$). Trend analysis for concentration changes over the first, second, and third trimesters revealed a borderline linear trend (parametric testing) for the active moiety ($p = 0.078$), *S*-(+)-MHD ($p = 0.061$), and *R*-(-)-MHD ($p = 0.073$).

Despite modifications in OXC dosages, changes in actual concentrations were qualitatively similar to those observed for dose-normalized concentrations (Figs. 1 and 2).

DISCUSSION

Although OXC pharmacokinetics have been investigated extensively (9), MHD enantiomers have been measured in very few studies (10,12). Our findings confirm previous reports that the formation or elimination or both of MHD is stereoselective, and that the *S*-(+)-enantiomer is the most abundant metabolite in blood (10,12). Therefore the stereoselectivity pattern of MHD disposition during pregnancy appears to be comparable to that in the nonpregnant state. Whereas both the parent drug and *R*-(-)-MHD possess anticonvulsant activity similar to *S*-(+)-MHD (13), the latter enantiomer accounts for the

TABLE 1. *Individual dose-normalized concentrations of oxcarbazepine and its metabolites in each trimester of pregnancy and during the puerperium*

Evaluation period	OXC (μM)				*R*-(-)-MHD (μM)				*S*-(+)-MHD (μM)				DHD (μM)				Active moiety (μM)			
	Trimester				Trimester				Trimester				Trimester				Trimester			
	1st	2nd	3rd	Puerperium	1st	2nd	3rd	Puerperium	1st	2nd	3rd	Puerperium	1st	2nd	3rd	Puerperium	1st	2nd	3rd	Puerperium
Patient 1	ND	ND	ND	0.06[b]	0.37	0.12	0.07[a]	1.34[b]	1.51	0.67	0.41[a]	10.24[b]	0.17	0.09	0.06[a]	0.98[b]	1.88	0.79	0.48[a]	11.64[b]
Patient 2	ND	ND	0.28[a]	0.26[b]	1.01	0.54	0.53[a]	0.89[b]	5.80	2.89	1.70[a]	4.70[b]	0.48	0.57	0.19[a]	0.88[b]	6.81	3.43	2.51[a]	5.86[b]
Patient 3	1.03	ND	ND	0.64	1.26	0.26	0.26[a]	0.92	7.09	2.24	1.61[a]	4.60	0.37	0.16	0.20[a]	0.40	9.38	2.49	1.87[a]	6.17
Patient 4	0.12	0.13	0.13	ND	0.95	0.65	0.77	0.55	6.09	4.16	4.54	3.45	0.12	0.11	0.14	0.15	7.16	4.94	5.44	4.00
Patient 5	–	–	ND	ND	–	–	0.82[a]	1.49	–	–	5.15[a]	8.65	–	–	0.22[a]	0.33	–	–	5.97[a]	10.13
Mean	0.29	0.03	0.08	0.19	0.90	0.39	0.49	1.03	5.12	2.49	2.68	6.33	0.29	0.23	0.16	0.55	6.31	2.91	3.25	7.56
± SD	0.50	0.07	0.12	0.27	0.38	0.25	0.32	0.38	2.47	1.45	2.05	2.94	0.17	0.23	0.06	0.36	3.16	1.74	2.36	3.19

Values are normalized to a 100–mg dose.
Active moiety, OXC + *R*-(-)-MHD + *S*-(+)-MHD; ND, below limit of quantification (ND values were considered equal to zero for calculation of means).
[a]Mean of two values.
[b]Mean of three values.

largest proportion of the active moiety and is therefore considered to be primarily responsible for the drug's effects during prolonged therapy (9).

Before our work, no information was available on OXC disposition during pregnancy. Our study has limitations, because only a few patients were assessed, no prepregnancy (baseline) measurements were available, and only a few samples could be collected from each woman during and after pregnancy. Although these limitations should be kept in mind, in the absence of any indication of inadequate compliance in our patients, our findings provide evidence that OXC pharmacokinetics may exhibit prominent changes during pregnancy and the puerperium. Although interpretation of concentration profiles was complicated by dose changes, plasma MHD levels are linearly related to dose (8), and therefore dose-normalized concentrations provide a reliable estimate of pharmacokinetic changes associated with pregnancy. In all women assessed from the first trimester, the dose-normalized concentrations of *S*-(+)-MHD and the active moiety decreased during pregnancy, reaching the lowest levels at different times after week 20. In four of the five women, the concentration of the active moiety and *S*-(+)-MHD increased 1.5- to 13-fold after delivery; although in patient 4, this increase was not observed, its occurrence could not be excluded because this was the only subject who had no samples collected during the last 6 weeks of gestation and no follow-up beyond 1 week after delivery. In a previous single-case report, Bulau et al. (14) did not detect a change in serum MHD (racemate) over the 5 days after delivery in an OXC-treated woman. Although our sampling schedule did not allow estimation of the precise time course of the change in the active moiety and *S*-(+)-MHD after deliver, in at least two cases (patients 3 and 5), an increase in their concentration was already detected after 8 and 7 days, respectively. Because pharmacokinetic data were not available before conception, it cannot be established whether the concentrations measured during the puerperium reflect a return to preconception levels or an overshoot above baseline. Although the latter possibility cannot be excluded (consistent with the observation that in two patients, active moiety and plasma MHD concentrations decreased moderately after reaching a peak a few weeks after delivery), it is clear from individual profiles that the active moiety and *S*-(+)-MHD levels did decrease during pregnancy. Findings for other AEDs also suggest that the increase in serum drug levels during the puerperium reflects a return to preconception levels (1,2,5).

Because MHD binding to serum proteins is quite modest, 40% (9), important modifications in the unbound fraction cannot be anticipated for this metabolite, and the changes in its serum concentration (and those of parent drug and other metabolites) are most likely due to increased metabolic clearance, presumably secondary to the hormonal changes associated with pregnancy (15). The

changes in the active moiety and *S*-(+)-MHD levels in our patients during pregnancy and the puerperium resemble closely those reported for LTG (3–6), an important similarity in view of the fact that both MHD and LTG are cleared primarily by glucuronide conjugation (2). Interestingly, LTG clearance has been shown to be increased markedly by intake of oral contraceptive steroids (16–18), and it would be of interest to investigate whether a similar interaction also occurs with OXC.

Our study was designed to investigate pharmacokinetic aspects, and details on possible changes in clinical response were sparsely recorded. However, evidence was obtained that in at least two patients (cases 1 and 2), low plasma concentrations of the active moiety were associated with emergence of seizures, whose control improved after a dose increase. A clinical correlate for the observed pharmacokinetic changes also is suggested by a recent report from the EURAP Registry on 1,956 prospective pregnancies in 1,882 women with epilepsy (19). In that cohort, seizure deterioration after the first trimester and increases in AED number or dosage during pregnancy occurred more frequently in women taking OXC than in women receiving other treatments; increases in AED number or dosage were also significantly more common in women treated with LTG. When interpreted in the context of the data from this study, it is reasonable to recommend that clinical response and, possibly, plasma MHD concentrations be monitored carefully in women receiving OXC during pregnancy and the puerperium. Moreover, further studies on OXC pharmacokinetics during pregnancy are indicated to confirm these findings in a large population.

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