

Pharmacokinetics of the Monohydroxy Derivative of Oxcarbazepine and Its Enantiomers after a Single Intravenous Dose Given as Racemate Compared with a Single Oral Dose of Oxcarbazepine

G. Flesch, C. Czendlik, D. Renard, and P. Lloyd

Novartis Pharma AG, Basel, Switzerland (G.F., D.R., P.L.); and Zentrallaboratorium für den Blutspendedienst, Bern, Switzerland (C.C.)

Received October 6, 2009; accepted March 9, 2011

ABSTRACT:

Oxcarbazepine (OXC) is an antiepileptic drug. In humans, OXC is metabolized via reduction and conjugation. Monohydroxy derivative of OXC (MHD) is the major pharmacologically active component after OXC ingestion. This study was performed to characterize the disposition of the two enantiomers of MHD after oral and intravenous administration and to estimate the bioavailability of MHD after a single oral dose administration of OXC compared to a single intravenous administration of MHD. The study was performed in two parts. In a first pilot study, three intravenous doses were given in an ascending manner (150, 200, and 250 mg of MHD; one subject per dose level) to assess the safety, tolerability, and basic pharmacokinetics. Part two was an open, single-center, ran-

domized, two-way crossover, single-dose trial in 12 healthy adult subjects ($n = 6$ males and $n = 6$ females) given OXC orally (one film-coated 300-mg tablet of OXC) and MHD intravenously (250 mg infused over 30 min). Concentrations of OXC and its metabolites were measured by means of high-performance liquid chromatography methods. OXC given as a tablet is completely absorbed in man under fasting conditions. When MHD is given intravenously, (S)-MHD predominates as free compound in plasma. When OXC is administered orally, the ratio of the area-under-the-curve values of (S)-MHD over (R)-MHD equals 3.8, indicating an enantioselective reduction of the prochiral carbonyl group of OXC.

Introduction

Trileptal [oxcarbazepine (OXC), 10,11-dihydro-10-oxo-5H-dibenz[*b,f*]azepine-5-carboxamide] is an antiepileptic drug registered worldwide by Novartis (Basel, Switzerland). OXC is approved as adjunctive therapy or monotherapy for the treatment of partial seizures in adults and in children. In the United States, OXC is approved as adjunctive therapy in adults and children above 4 years and as monotherapy in adults. The principal biotransformation product of OXC in humans is the biologically active metabolite 10,11-dihydro-10-hydroxy-5H-dibenz[*b,f*]azepine-5-carboxamide (Flesch, 2004). Oxcarbazepine is rapidly reduced by cytosolic arylketone reductases to the monohydroxy derivative (MHD) (Fig. 1) (Schütz et al., 1986; Menge and Dubois, 1983). In humans, formation of MHD is stereoselective, with the two enantiomers formed in a ratio of 80% (S enantiomer of MHD [(S)-MHD]) to 20% (R enantiomer of MHD [(R)-MHD]) (Flesch et al., 1992). After oral administration of radio-labeled OXC, only 2% of total radioactivity in plasma is due to unchanged OXC, and approximately 70% is due to MHD (Schütz et

al., 1986). Minor amounts of oxcarbazepine are transformed in a sulfate conjugate and directly conjugated (Schütz et al., 1986). Minor amounts of MHD are oxidized to the inactive dihydroxy derivative (DHD). The anticonvulsant properties of MHD are possibly mediated through the effects on neuronal ion fluxes and specifically by blocking voltage-dependent sodium channels (Schmutz et al., 1993).

MHD is a potent anticonvulsive agent after oral and intramuscular administration. MHD is more soluble in water than OXC; the partition coefficients in *n*-octanol/aqueous buffer (pH 7.4) at 25°C are 20.4 and 8.8 for OXC and MHD, respectively. Therefore, intravenously administered MHD has been developed for the treatment of partial seizures.

Since after oral administration all absorbed OXC is rapidly and almost completely metabolized to the monohydroxy derivative MHD, an assessment of the absolute oral bioavailability of OXC was performed using MHD as an intravenous reference. The objectives of this study were to assess the tolerability of a single intravenous dose of MHD (racemate), the bioavailability of MHD after single oral administration of a 300-mg OXC tablet compared to a single intravenous administration of 250 mg of MHD, and the disposition of the two enantiomers of MHD in plasma after oral and intravenous administration. Two additional goals were to determine the pharmacokinetics in plasma and urine of the two enantiomers of MHD, as well

Article, publication date, and citation information can be found at <http://dmd.aspetjournals.org>.

doi:10.1124/dmd.109.030593.

ABBREVIATIONS: OXC, oxcarbazepine; MHD, monohydroxy derivative of OXC; DHD, dihydroxylated derivative; (R)-MHD, R enantiomer of MHD; (S)-MHD, S enantiomer of MHD; GLU-(S)-MHD, glucuronide of the S enantiomer of MHD; GLU-(R)-MHD, glucuronide of the R enantiomer of MHD; A_{∞} , total amount of drug eliminated in the urine; LOQ, limit of quantitation; CL_T , the total plasma clearance; CL_R , renal clearance; AUC, area under the plasma concentration-time curve; CI, confidence interval.

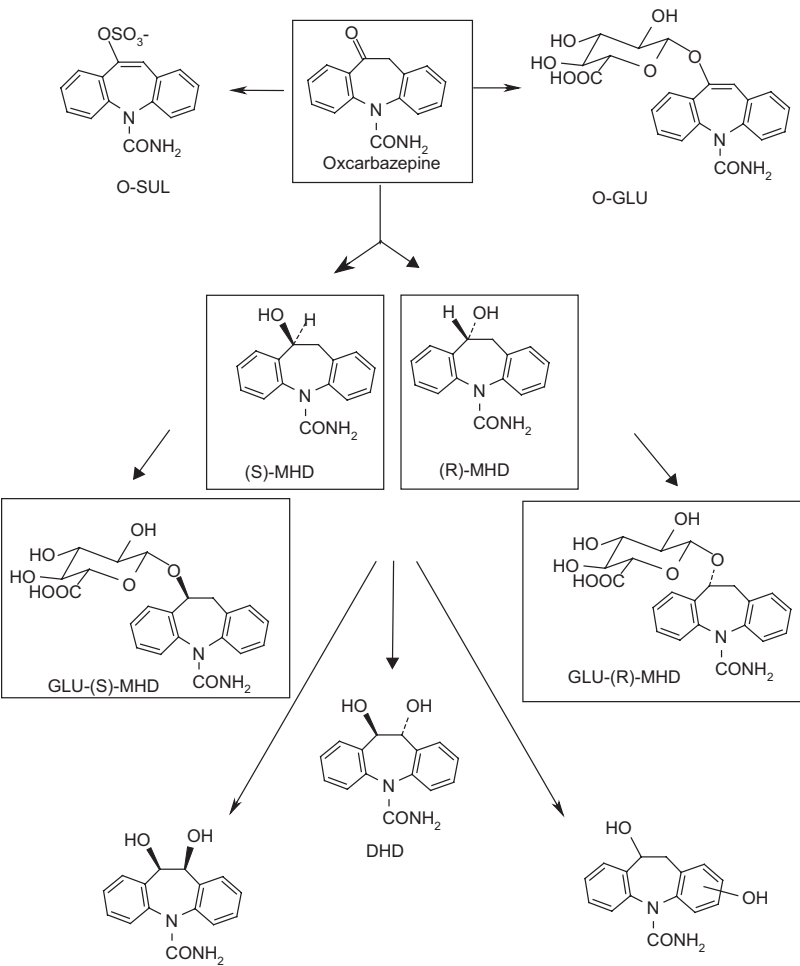


FIG. 1. Metabolism of oxcarbazepine in humans. O-SUL, *O*-sul-fate; O-GLU, *O*-glucuronide.

as OXC and DHD, and to determine the degree of conjugation of MHD.

TABLE 1

Summary of the results of the validation analyses in plasma and urine

Compounds	Medium	LOQ	LOD
		$\mu\text{mol/l}$	$\mu\text{mol/l}$
MHD	Plasma	0.77	0.08
OXC	Plasma	1.05	0.1
DHD	Plasma	0.65	0.07
(<i>R</i>)-MHD	Plasma	0.84	0.08
(<i>S</i>)-MHD	Plasma	0.81	0.08
DHD	Urine	0.47	0.05
(<i>R</i>)-MHD	Urine	1.0	0.1
(<i>S</i>)-MHD	Urine	0.8	0.08

LOD, limit of detection.

Materials and Methods

Study Design and Population. The study was performed in two parts in the Human Pharmacology Department at Ciba-Geigy (Basel, Switzerland). Part one was a pilot study in three healthy adult male volunteers performed to assess the safety, tolerability, and basic pharmacokinetics of single intravenous doses of 150, 200, and 250 mg of MHD (one subject per dose level), as well as sensitivity of the enantioselective analytical method.

Part two was an open, single-center, randomized, two-way crossover, single-dose trial in 12 healthy adult subjects ($n = 6$ males and $n = 6$ females) given OXC orally (one film-coated 300-mg tablet of OXC) and MHD intravenously (250 mg infused over 30 min). To eliminate carryover effects, a washout period of at least 1-week duration was adopted between the subsequent study periods based on the elimination kinetics of MHD ($t_{1/2}$ 8–14 h). A dose of 300 mg of OXC (one film-coated tablet of OXC) was selected for safety and convenience reasons. The dose of MHD was chosen taking safety and analytical aspects into consideration. The dose of MHD had to be as high as possible, because of the slightly lower sensitivity of the enantioselective

TABLE 2

Pharmacokinetic parameters of MHD (first study)

Data show pharmacokinetic parameters of MHD, (*R*)-MHD, and (*S*)-MHD in plasma and urine.

Parameters	MHD/iv	MHD	(R)-MHD	(S)-MHD	MHD	(R)-MHD	(S)-MHD	MHD	(R)-MHD	(S)-MHD
<i>150 mg</i>										
AUC _(0–72 h)	$\mu\text{mol l}^{-1} \text{ h}$	109.2	55.7	69.0	142.4	59.1	92.2	280.1	131.7	191.7
A _e (0–72 h)	% of dose	24.3	N.D.	N.D.	30.7	N.D.	N.D.	42.8	N.D.	N.D.
CL	l h^{-1}	5.4	5.3	4.27	5.52	6.65	4.27	3.51	3.73	2.56
CL _R	l h^{-1}	1.31	N.D.	N.D.	1.7	N.D.	N.D.	1.5	N.D.	N.D.
<i>200 mg</i>										
<i>250 mg</i>										

iv, intravenous; N.D., not determined.

TABLE 3

Mean (S.D.) values of pharmacokinetic parameters obtained after a single 250-mg MHD infusion over 30 min and an oral administration of 300-mg OXC to 12 healthy volunteers

	OXC	DHD	(R)-MHD	(S)-MHD	S/R	GLU-(R)-MHD	GLU-(S)-MHD	S/R
Intravenous								
t_{\max} (h)	0.5* ($n = 4$)	8* ($n = 8$)						
C_{\max} ($\mu\text{mol} \cdot \text{l}^{-1}$)	0.08 (0.13)	0.24 (0.20)						
$\text{AUC}_{(0-48 \text{ h})}$ ($\mu\text{mol} \cdot \text{l}^{-1} \cdot \text{h}$)			105.1 (23.2) [†]	144.3 (30.4) [†]	1.4			
AUC ($\mu\text{mol} \cdot \text{l}^{-1} \cdot \text{h}$)	0.47 (0.76)	7.50 (7.25)	119.5 (25.9)	166.8 (36.5)	1.4			
A_e (% of dose)	nd	3.9 (1.1)	11.9 (1.87)	16.4 (3.07)	1.4	12.7 (3.19)	32.3 (4.05)	2.5
CL ($\text{l} \cdot \text{h}^{-1}$)			4.3 (0.9)	3.1 (0.6)				
CL_R ($\text{l} \cdot \text{h}^{-1}$)			0.9 (0.2)	0.9 (0.2)				
$t_{1/2}$ (h)			9.0 (1.5)	10.6 (2.6)				
V_{ss} (liter)			54.7 (10.9)	45.9 (11.4)				
$t_{1/2 \text{ ur.}}$ (h)			9.0 (1.1)	8.4 (1.7)		14.2 (4.0)	9.9 (1.3)	
Oral								
t_{\max} (h)	1.0* ($n = 12$)	24* ($n = 6$)	3.5	4				
C_{\max} ($\mu\text{mol} \cdot \text{l}^{-1}$)	2.0 (0.7)	0.2 (0.2)	3.0 (0.8)	11.0 (2.2)				
AUC ($\mu\text{mol} \cdot \text{l}^{-1} \cdot \text{h}$)	6.8 (1.9)	5.4 (7.3)	63.9 (19.5) [‡]	241 (54.8) [§]	3.8			
A_e (% of dose)	nd	2.7 (0.5)	4.85 (1.31)	21.8 (4.26)	4.5	5.62 (1.90)	38.8 (6.03)	6.9
CL_R ($\text{l} \cdot \text{h}^{-1}$)			1.0 (0.3)	1.1 (0.3)				
$t_{1/2}$ (h)			15.8 (2.8)	11.2 (1.5)				
$t_{1/2 \text{ ur.}}$ (h)			7.0 (1.9)	8.5 (2.4)		10.3 (2.2)	10.8 (3.0)	

nd, not detected.

* median.

[†] $\text{AUC}_{(0-24/48 \text{ h})}$.

[‡] $\text{AUC}_{(0-24/56 \text{ h})}$.

[§] $\text{AUC}_{(0-32/48 \text{ h})}$.

analytical method (Flesch et al., 1992) compared with the original method for measuring total MHD (Menge and Dubois, 1983).

For determination of MHD concentrations, blood samples were collected before (time point 0) and up to 72 h after single-dose drug and up to 12 h after final steady-state administration. Four milliliters of venous blood was drawn into lithium heparin Vacutainers (BD Biosciences, San Jose, CA) at the following sampling points: day 1 predose (morning dose), 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 32, 48, 56, and 72 h postdose; on day 7 predose (evening dose); on day 8 predose (morning dose), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 h postdose. Immediately after blood withdrawal, the tube was inverted gently several times to ensure the mixing of tube contents. Prolonged sample contact was avoided with the rubber stopper. The tube was placed upright in a test tube rack surrounded by ice until centrifugation. The sample was centrifuged at 4°C for 10 min at approximately 1500g. At least 1.5 ml of plasma was transferred to a polypropylene screw-cap tube and frozen within 60 min of venipuncture. The tubes were kept frozen at or below -15°C until assayed.

Drug Analysis. For determination of OXC, MHD, DHD, (S)-MHD, and (R)-MHD concentrations, blood and urine samples were collected before drug

administration and up to 72 h postdose. Blood samples, 5.5 ml of venous blood, were drawn into heparinized Monovette tubes (Sarstedt AG, Sewelen, Switzerland) at the following sampling points: at 0, 1, 2, 3, 4, 6, 8, 10, 24, 32, 48, 56, and 72 h for the oral dose and at 0, 5, 10, 15, 20, 25, and 30 min as well as 1, 2, 3, 4, 6, 8, 10, 14, 32, 48, 56, and 72 h postdose after start of infusion. Immediately after blood withdrawal, samples were centrifuged (2200g for 5 min at room temperature), and the plasma was removed by pipette to plain polypropylene tubes and stored at -80°C until analysis. All produced urine was collected up to 72 h postdose in the following fractions: 0 to 3, 3 to 6, 6 to 10, 10 to 24, 24 to 32, 32 to 48, 48 to 56, and 56 to 72 h postdose. During the sampling time, urine was stored refrigerated at +2 to +8°C. The weight of each fraction was recorded, and a 20-ml aliquot was retained and kept frozen at -20°C for determination of OXC, MHD, DHD, (S)-MHD, and of (R)-MHD before and after enzymatic hydrolysis. Plasma and urine concentrations of OXC, MHD, DHD, (S)-MHD, and (R)-MHD were measured by means of a nonenantioselective and an enantioselective high-performance liquid chromatography method (Menge and Dubois, 1983; Flesch et al., 1992). To determine the urinary concentrations of glucuronide of the R enantiomer of MHD

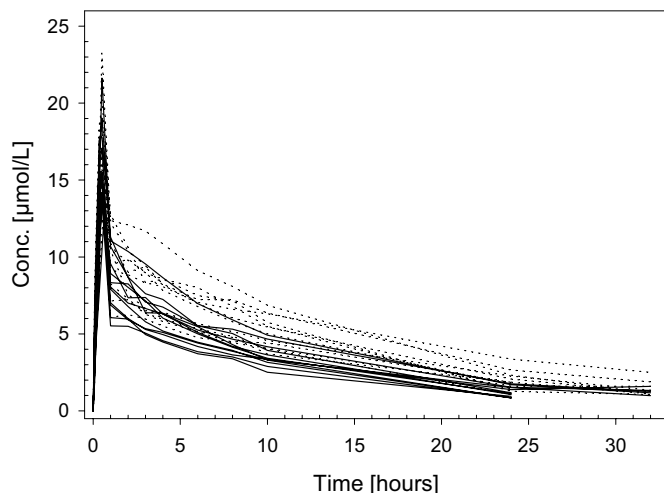


FIG. 2. Plasma concentration-time curves of (R)-MHD and (S)-MHD after 250 mg of MHD administered as an infusion over 30 min to 12 healthy volunteers. Solid line, (R)-MHD; dotted line, (S)-MHD.

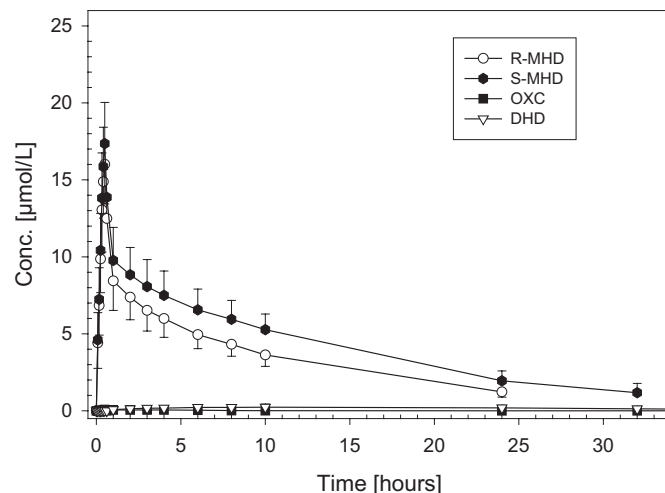


FIG. 3. Mean (S.D.) plasma concentration-time curves of (R)-MHD, (S)-MHD, OXC, and DHD after 250 mg of MHD administered as an infusion over 30 min to 12 healthy volunteers (lin scale).

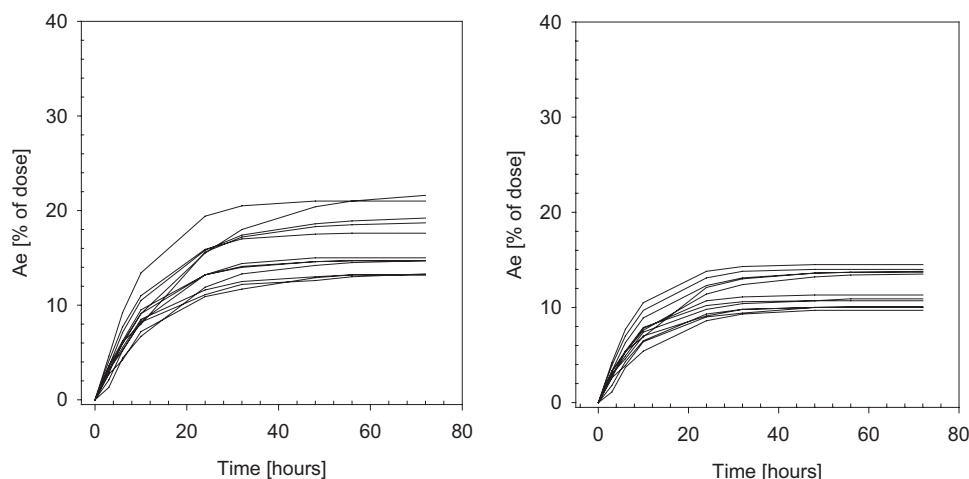


FIG. 4. Left, cumulative urinary excretion of (S)-MHD after 250 mg of MHD infused over 30 min. Right, cumulative urinary excretion of (R)-MHD after 250 mg of MHD infused over 30 min.

[GLU-(R)-MHD] and glucuronide of the *S* enantiomer of MHD [GLU-(S)-MHD], urine samples (0.5 ml) collected after oral and intravenous administration were treated with β -glucuronidase [110 μ l, containing no sulfatase activity (no. 127680; Roche Diagnostics, Mannheim, Germany), in phosphate buffer (pH 6.7) at 37°C for approximately 15 h]. After enzymatic hydrolysis, the samples were handled as described previously. The urinary concentrations of conjugated (S)- and (R)-MHD were calculated from the difference between concentrations after and before enzymatic hydrolysis. Plasma concentrations of MHD were determined using a validated high-performance liquid chromatography method and UV detection (Menge and Dubois, 1983). After the internal standard [CGP 23827 (Menge and Dubois, 1983); mol. wt. 252.27] had been added to the samples, MHD and the internal standard were isolated by automatically performed (ASPEC; Macherey-Nagel AG, Oensingen, Switzerland) liquid-solid extraction from plasma (100 μ l) on 50-mg Bond-Elut C18 cartridges. A reversed-phase column (ODS Hypersil; 3- μ m particle size; 4 cm \times 4.6 mm i.d.) was used with acetonitrile-methanol-0.01 M potassium dihydrogenphosphate as a mobile phase. The eluted compound was detected at 210 nm. The limit of quantitation (LOQ; mean recovery within 80 and 120% and coefficient of variation $\leq 20\%$) of the method was 0.1 μ M.

Pharmacokinetic Evaluation. After oral administration of OXC, the highest observed concentration of the parent or its metabolites was designated C_{\max} , and the time at which this occurred relative to the time of dosing was designated t_{\max} . The area under the plasma concentration-time curve (AUC) was calculated by the linear trapezoidal method (Gibaldi and Perrier, 1982). Slopes of log-linear regression lines from the plasma concentration-time curves were used to calculate half-lives characterizing the concentration decay. The plasma half-life of the terminal phase ($t_{1/2\lambda_2}$) after oral and intravenous dosing was calculated from the concentrations at 6 to 10 h to 24 to 56 h. CL_T , the total plasma clearance (i.e., the sum of all partial clearances), was calcu-

lated from the following: $CL_T = \text{Dose}/\text{AUC}$. V_{ss} , the volume of distribution at steady state, was calculated as $CL_T \cdot \text{MRT}$. The mean residence time (MRT), a model-independent parameter, was determined by the ratio of area under the first moment curve to AUC, where area under the first moment curve is defined as the area under the first moment of the concentration-time curve. The renal clearance (CL_R) of MHD was estimated from the ratio of the amount of unchanged drug excreted in urine (Ae) to the corresponding plasma AUC. The ratio of MHD AUC after oral and intravenous administration corrected by the corresponding doses was used to calculate the fraction of the administered dose that was systemically available (f). Slopes of log-linear regression lines from the urinary elimination curves were used to calculate elimination half-lives. The urinary half-life of the terminal phase ($t_{1/2\lambda_2}$) after oral and intravenous dosing was calculated from the concentrations at 4 to 18 h to 40 to 64 h. For the determinations of pharmacokinetic parameters of MHD, (R)-MHD, and (S)-MHD, only levels above LOQ were used. Because most of the plasma levels of OXC and DHD were below the limit of quantitation, all measured concentrations of these two compounds were used for the evaluation of pharmacokinetic parameters. All urinary concentrations (below and above LOQ) of (R)-MHD and (S)-MHD were used for the estimation of the urinary pharmacokinetic parameters. All DHD concentrations were below the LOQ in the urine. After single and repeated oral administration of OXC, the following pharmacokinetic parameters were determined using the plasma concentrations of MHD, the main metabolite of OXC, and actual sampling times.

Statistical Analysis. The (R)-MHD and (S)-MHD AUCs were subject to analysis of variance after log transformation. Treatment (intravenous versus oral) and enantiomers [(R)-MHD versus (S)-MHD] were considered as factors, and their product was introduced in the model to obtain estimates at each treatment-by-enantiomer combination. The covariance matrix was modeled with a direct-product compound-symmetry structure using the SAS version 8.2

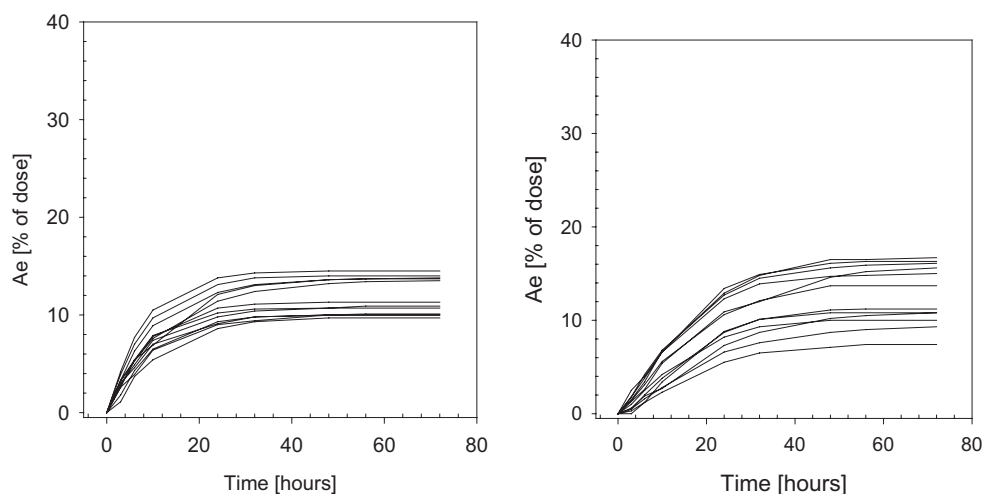


FIG. 5. Left, cumulative urinary excretion of GLU-(S)-MHD after 250 mg of MHD infused over 30 min. Right, cumulative urinary excretion of GLU-(R)-MHD after 250 mg of MHD infused over 30 min.

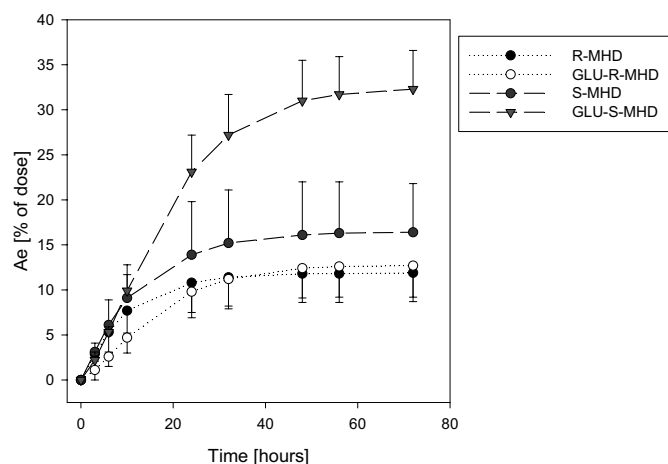


FIG. 6. Mean cumulative urinary excretions (intravenous). Mean (S.D.) cumulative urinary excretion of (*R*)-MHD, (*S*)-MHD, GLU-(*S*)-MHD, and GLU-(*R*)-MHD after 250 mg of MHD infused over 30 min is shown. Dashed line, (*R*)-MHD; dotted line, (*S*)-MHD.

procedure MIXED (SAS Institute, Cary, NC). The mean differences contrasting log (*R*)-MHD and (*S*)-MHD AUCs were derived with 90% confidence intervals (CIs) and backtransformed to provide geometric mean ratio estimates *R/S* with corresponding 90% CIs.

Results

Validation of Analytical Method. The method was validated by analysis of spiked human plasma and urine samples. The plasma samples were spiked with MHD, OXC, DHD, (*R*)-MHD, and (*S*)-MHD. The urine samples were spiked with OXC, DHD, (*R*)-MHD, and (*S*)-MHD. A summary of the results of the validation analyses in plasma and urine is given in Table 1.

Pharmacokinetics Results. A summary of all mean-derived pharmacokinetic parameters from the first study are given in Table 2. The AUC values of MHD increased with the dose; values were 109, 142, and 280 h ($\mu\text{mol/L}$) at dose levels of 150, 200, and 250 mg, respectively. Between 24.3 and 42.8% of the dose was excreted as unchanged from 0 to 72 h. A complete pharmacokinetic evaluation was not performed. Because the 250-mg MHD intravenous dose gave plasma concentrations comparable to those observed previously after an oral dose of OXC of 300 mg, these two doses were selected for the

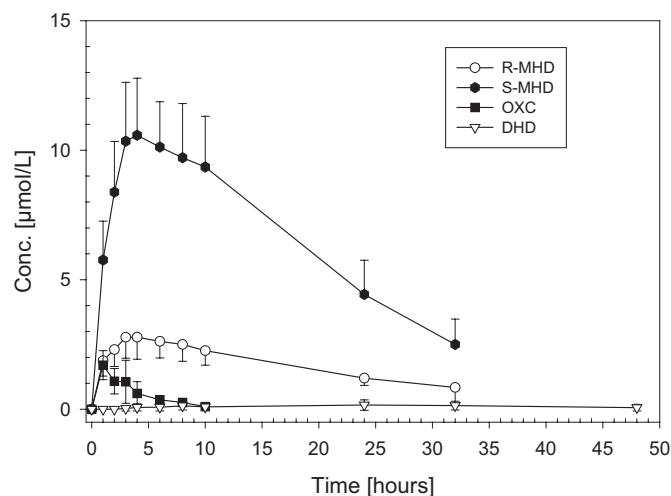


FIG. 8. Mean (S.D.) plasma concentration-time curves of (*R*)-MHD, (*S*)-MHD, OXC, and DHD after 300 mg of OXC administered orally to 12 healthy volunteers (lin scale).

main study. In terms of AUC, the enantiomeric ratio of *S* over *R* was between 1.2 and 1.6, indicating a different disposition between the two enantiomers of MHD. The total plasma clearance values were 5.4, 5.5, and 3.5 l/h at dose levels of 150, 200, and 250 mg, respectively. The renal clearance values of 1.3 to 1.7 l/h indicate that renal excretion is only a minor elimination pathway for free MHD. The mean (S.D.) model-independent parameters of (*R*)- and (*S*)-MHD after intravenous administration of MHD over 30 min are presented in Table 3. Figure 2 shows the individual plasma concentration-time profiles of (*R*)- and (*S*)-MHD. The mean profiles of the two enantiomers of MHD, as well as OXC and DHD, are shown in Fig. 3. The disposition of (*R*)-MHD is different from (*S*)-MHD. The ratio of the mean AUC value of (*S*)-MHD to (*R*)-MHD shows a predominance of (*S*)-MHD (enantiomeric ratio equals 1.4). In plasma, OXC, the oxidized metabolite of MHD, accounted for 0.2% if the sum of the AUC of (*S*)- and (*R*)-MHD is taken as 100%, whereas DHD represented 2.6% of the total AUC of MHD. After the end of the infusion, the plasma concentrations of the two enantiomers declined in a biexponential manner. Mean apparent terminal elimination half-lives from plasma of (*S*)-MHD and (*R*)-MHD were very similar, 9.0 and 10.6 h, respectively. Plasma clearance values were 3.1 l/h for (*S*)-MHD and

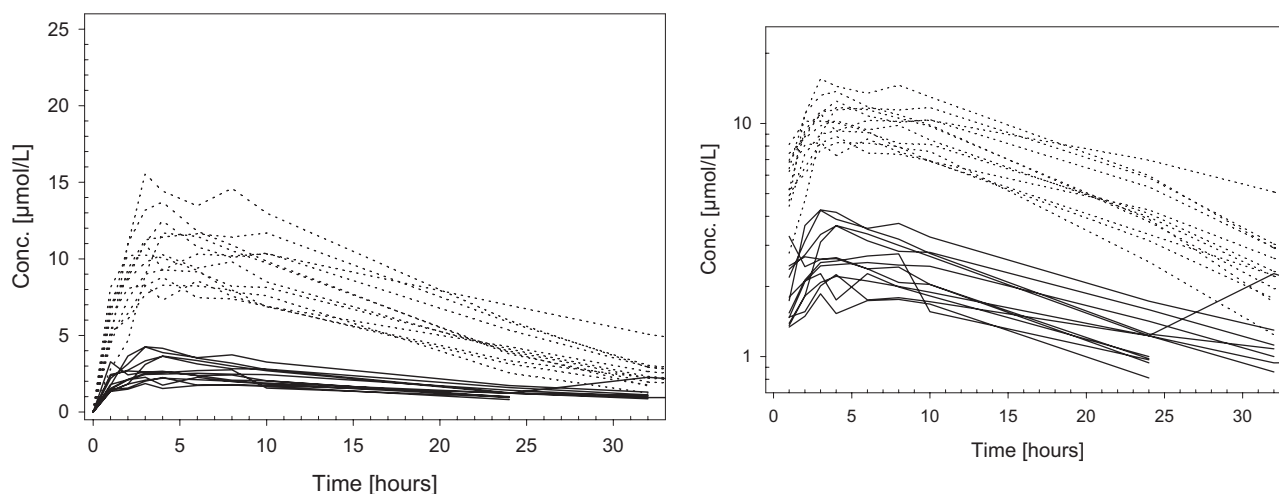


FIG. 7. Plasma concentration-time curves of (*R*)-MHD and (*S*)-MHD after 300 mg of OXC administered orally to 12 healthy volunteers (left, lin scale; right, log scale). Solid line, (*R*)-MHD; dotted line, (*S*)-MHD.

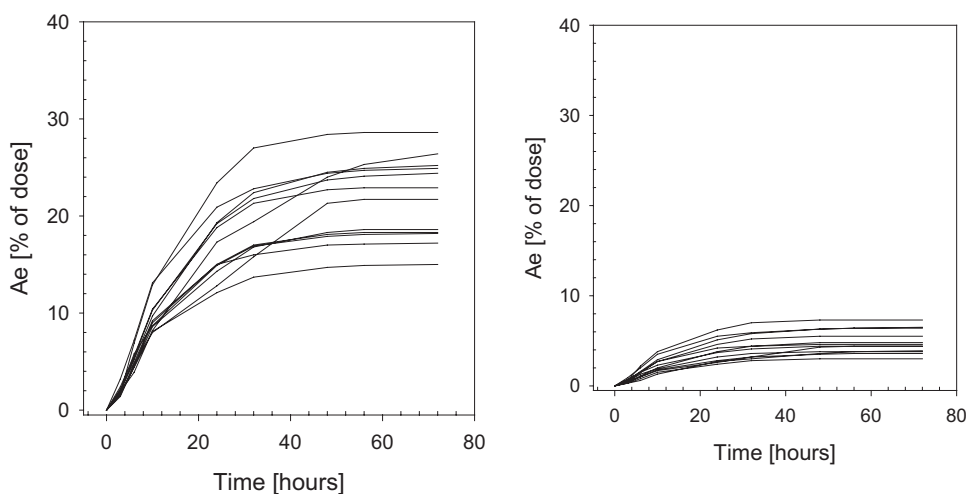


FIG. 9. Left, cumulative urinary excretion of (S)-MHD after 300 mg of OXC given orally. Right, cumulative urinary excretion of (R)-MHD after 300 mg of OXC given orally.

4.3 l/h for (R)-MHD. (R)-MHD was characterized by a slightly larger volume of distribution (mean value, 54.7 liters) than (S)-MHD (mean value, 45.9 liters).

Renal clearance of the two enantiomers was 0.9 l/h, which is consistent with the mean percentage values of the intravenous dose excreted in the urine intact as (S)-MHD (16.4%) and (R)-MHD (11.9%). The cumulative urinary excretion profiles of MHD [(S)- and (R)-MHD], as well as their corresponding glucuronide conjugates, are represented in Figs. 4 and 5. Mean (S.D.) cumulative urinary excretion curves are shown in Fig. 6. The total urinary excretion of (S)- to (R)-MHD (enantiomeric ratio equals 1.4) reflects the situation in plasma. The data are consistent with the extensive metabolism of MHD, which is mainly associated with the conjugation of free MHD (O-glucuronidation). Both glucuronides were detected in the urine, but with a high predominance of GLU-(S)-MHD to GLU-(R)-MHD (enantiomeric ratio equals 2.5). The percentage of the dose excreted as glucuronides of MHD in urine represents 45% of the administered dose, whereas 28% was excreted as unchanged MHD. Only traces of OXC were detected in urine, and 3.9% of the dose was excreted as DHD. All identified compounds in urine (parent compound plus metabolites) represent more than 77% of the administered dose. In some of the volunteers (Fig. 4), the cumulative urinary excretion of GLU-(S)-MHD did not reach a plateau 72 h after dosing. When MHD is administered intravenously, the (S)-MHD predominates as free compound in plasma and as free and conjugated MHD in urine.

Plasma. Figure 7 shows the individual profiles of (S)-MHD and (R)-MHD after oral administration of 300 mg of OXC. The mean profiles of the two enantiomers of MHD, as well as OXC and DHD, are shown in Fig. 8. A summary of the AUC values of (S)-MHD,

(R)-MHD, OXC, and DHD after both oral administration of OXC and parenteral administration of MHD are shown in Table 3. After oral administration of OXC, MHD is the major metabolite detected in plasma, and only low amounts of OXC and DHD were detected in the plasma, 2.2 and 1.8%, respectively, when the sum of the AUC values of (R)-MHD and (S)-MHD is taken as 100%. Mean apparent terminal elimination half-lives from plasma of (S)-MHD and (R)-MHD were 11.2 and 15.8 h, respectively. This difference might be explained by a difference in the glucuronidation rate of the two enantiomers of MHD, with the S-enantiomer being conjugated faster than its antipode.

Urine. The cumulative urinary excretion profiles of MHD [(S)-MHD and (R)-MHD], as well as their corresponding glucuronide conjugates, are represented in Figs. 9 and 10. Mean cumulative excretion curves are shown in Fig. 11. The total urinary excretion of (S)-MHD to (R)-MHD equals 4.5. These data are consistent with extensive conjugation of MHD, which is mainly associated with the glucuronidation of free MHD (O-glucuronidation). Both glucuronides were detected in the urine, but with a high predominance of GLU-(S)-MHD to GLU-(R)-MHD, with the enantiomeric ratio of 6.9. The percentage of the dose excreted as glucuronides of MHD in urine represents 44% of the administered dose (45% after intravenous dosing), whereas 27% was excreted as unchanged MHD (28% after intravenous dosing). These results indicate a similar excretion pattern of the two enantiomers of MHD, although they are present in a different ratio in plasma after intravenous and oral administration. The renal clearance value of the two (R)- and (S)-MHD was 1.0 to 1.1 l/h. Only traces of OXC were detected in urine, and 2.7% was excreted as DHD. All compounds identified in urine (parent plus metabolites)

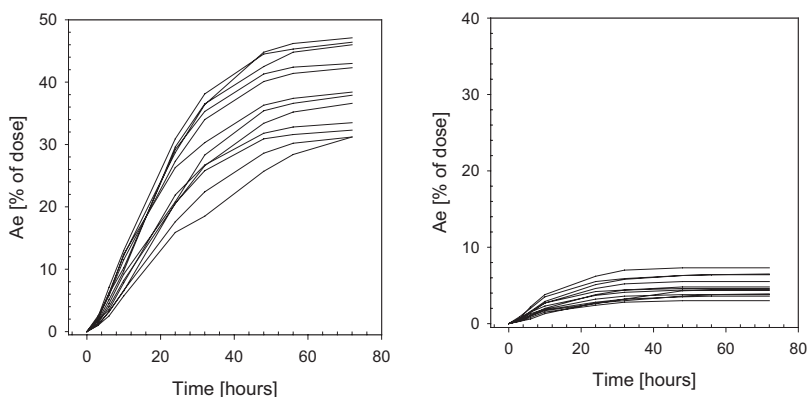


FIG. 10. Left, cumulative urinary excretion of GLU-(S)-MHD after 300 mg of OXC given orally. Right, cumulative urinary excretion of GLU-(R)-MHD after 300 mg of OXC given orally.

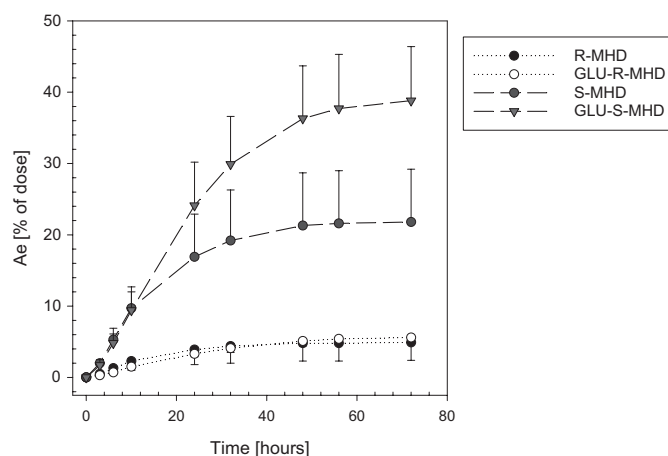


FIG. 11. Mean (S.D.) cumulative urinary excretion of (*R*)-MHD, (*S*)-MHD, GLU-(*S*)-MHD, and GLU-(*R*)-MHD after 300 mg of OXC given orally.

represent more than 73% of the dose. The mean excretion rate curves of (*S*)-MHD, (*R*)-MHD, GLU-(*S*)-MHD, and GLU-(*R*)-MHD are depicted in Fig. 10. The mean elimination half-life of conjugated (*S*)- and (*R*)-MHD was approximately 10 h. OXC is cleared from the human body entirely by metabolism. After a stereoselective reduction of the prochiral carbonyl group, the (*S*)-MHD metabolite is predominant and is enantioselectively conjugated. The mean plasma AUC values of (*S*)-MHD, (*R*)-MHD, OXC, DHD, and total MHD and mean pharmacokinetic parameters after oral administration of 300 mg of OXC and intravenous infusion of 250 mg of MHD are depicted in Fig. 12.

Statistical Analysis. The geometric mean ratios (and 90% CI) of the AUC values of *R* versus *S* were 25.9% (22.3%, 30.0%) for peroral administration and 71.6% (65.4%, 78.3%) for intravenous infusion. This almost 3-fold increase in the *R*-to-*S* ratio between intravenous and oral administration was highly statistically significant, as evidenced by the lack of overlap between the confidence intervals.

Absolute Bioavailability. The absolute bioavailability of OXC was assessed from plasma data of MHD. Using the nonenantioselective assay corrected for the administered dose, bioavailability was 0.99. These data confirm that OXC given as a solid oral formulation is completely absorbed in man. Mean (S.D.) *f* values are summarized in Table 4.

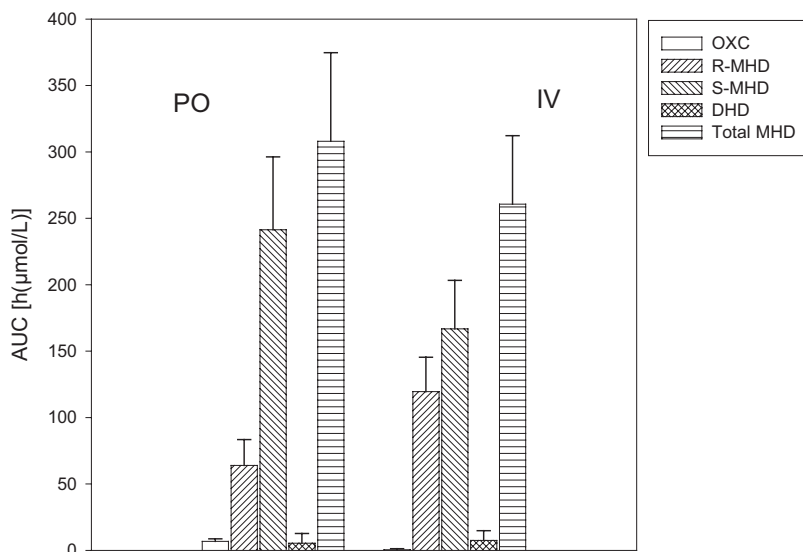


FIG. 12. Mean (S.D.) plasma AUC values of (*S*)-MHD, (*R*)-MHD, OXC, DHD, and total MHD after oral (PO) administration of 300 mg of OXC and 250 mg of MHD infused over 30 min. IV, intravenous.

TABLE 4

Mean (S.D.) *f* value based on MHD concentrations measured with the non-enantiospecific assay after single oral administration of 300 mg of OXC versus 250 mg of MHD infused over 30 min

	OXC/po	MHD/iv	<i>f</i>
	AUC[h(μmol/l)]	AUC[h(μmol/l)]	
Mean	308	260.6	0.99
S.D.	66.7	51.6	0.1

po, oral; iv, intravenous.

Discussion

Pharmacokinetics. When MHD is administered intravenously, the (*S*)-MHD predominates as free compound in plasma and as free and conjugated MHD in urine. This difference in disposition of the two enantiomers of MHD could either be explained by different formation clearance for the glucuronide conjugates of (*S*)-MHD and (*R*)-MHD (enantioselective conjugation of (*S*)-MHD and/or by a back oxidation to OXC with inversion of the absolute configuration of MHD from *R* configuration to *S*). The glucuronides of MHD may also be partly secreted by the bile and hydrolyzed in the gastrointestinal tract. Regenerated MHD could later be reabsorbed, explaining the delay in the urinary excretion observed in some volunteers. Other drugs such as indomethacin undergo enterohepatic circulation (Kwan et al., 1976). Less than 20% of the administered dose is excreted as free MHD (unchanged) in urine, and MHD is cleared extensively from the human body by metabolism (glucuronidation).

When OXC is administered orally, the ratio of the AUC values of (*S*)-MHD over (*R*)-MHD equals 3.8 (or an estimate of 3.9 with 90% CI = [3.3, 4.5] based on the statistical analysis), indicating a presystemic enantioselective reduction of the prochiral carbonyl group of OXC, with the (*S*)-MHD predominant in plasma. OXC is reduced by a carbonylreductase that is present in all mammalian species (Felsted and Bachur, 1980). The formation of the *S* enantiomer of MHD can be predicted, using Prelog's rule (Prelog, 1964). This rule states that if a ketone is projected in a plane with the largest group to the left, the resulting alcohol will predominantly have the configuration with the hydroxy group above the plane. These differences in the pharmacokinetics of the two enantiomers of MHD should not be clinically relevant, because it has been demonstrated that both enantiomers have

similar anticonvulsant efficacy and tolerability (Schmutz et al., 1993, 1994).

MHD was given intravenously to humans for the first time in the present study. Systemic adverse experiences associated with an intravenous administration of MHD were similar to those reported after an oral intake of OXC in the present and in a previous study performed in healthy volunteers ($n = 2$).

Locally, short-lived sensation of pressure, ache, or burning at the arm of the infusion site was reported by 13 of 15 volunteers treated with intravenous doses of MHD. In no instance were the symptoms prohibitive for continuation of the infusion, nor were they associated with any local findings.

Intravenous infusion of 250 mg of MHD over 30 min was not associated with any clinically relevant changes in ECG or vital signs based on recordings performed during the infusion and at various time intervals thereafter. Also, an oral intake of 300 mg of oxcarbazepine did not display any untoward influence on ECG or vital signs. Neither treatment showed any clinically relevant influence on clinical laboratory variables measured in the study.

The differences in the pharmacokinetics of the two enantiomers of MHD should not be clinically relevant because both enantiomers have similar antiepileptic efficacy and tolerability in animals (Schmutz et al., 1993).

Acknowledgments

We are indebted to F. Hell and F. Ehrhart for the competent analysis of plasma and urine concentrations.

Authorship Contributions

Conducted experiments: Czendlik and Flesch.

Performed data analysis: Flesch and Renard.

Wrote or contributed to the writing of the manuscript: Flesch and Lloyd.

References

- Felsted RL and Bachur NR (1980) Mammalian carbonyl reductases. *Drug Metab Rev* **11**:1–60.
- Flesch G (2004) Overview of the clinical pharmacokinetics of oxcarbazepine. *Clin Drug Invest* **24**:185–203.
- Flesch G, Francotte E, Hell F, and Degen PH (1992) Determination of the R-(–) and S-(+) enantiomers of the monohydroxylated metabolite of oxcarbazepine in human plasma by enantioselective high performance liquid chromatography. *J Chromatogr* **581**:147–151.
- Flesch G, Czendlik C, Ehrhart F, Hell F, and Lloyd P (1999) Pharmacokinetics of the monohydroxy derivative of oxcarbazepine and its enantiomers after a single i.v. dose given as racemate compared with a single oral dose of oxcarbazepine. *Eur J Pharm Sci Abstr* **8**:2.
- Gibaldi M and Perrier D (1982) *Pharmacokinetics*. Dekker, New York.
- Kwan KC, Breault GO, Umbenhauer ER, McMahon FG, and Duggan DE (1976) Kinetics of indomethacin absorption, elimination, and enterohepatic circulation in man. *J Pharmacokinetic Biopharm* **4**:255–280.
- Menge G and Dubois JP (1983) Determination of OXC in human plasma by high-performance liquid chromatography. *J Chromatogr* **275**:189–194.
- Prelog V (1964) Specification of the stereoselectivity of some oxidoreductases by diamant lattice sections. *Pure Appl Chem* **9**:119–130.
- Schmutz M, Ferrat T, Heckendorn R, Jecker A, Protet C, and Olpe HR (1993) MHD, the main human metabolite of oxcarbazepine (Trileptal®) and both enantiomers have equal anticonvulsant activity. *Epilepsia* **34** (Suppl 2):122.
- Schmutz M, Brugger M, Gentsch C, McLean MJ, and Olpe HR (1994) Oxcarbazepine: preclinical anticonvulsant profile and putative mechanisms of action. *Epilepsia* **35** (Suppl 5):S47–S504.
- Schütz H, Feldmann KF, Faigle JW, Kriemler HP, and Winkler T (1986) The metabolism of ¹⁴C-oxcarbazepine in man. *Xenobiotica* **16**:769–778.

Address correspondence to: Dr. Gérard Flesch, Modeling & Simulation, WSJ-027.6.69, Novartis Limited, CH-4002 Basel, Switzerland. E-mail: gerard_jp.flesch@novartis.com
