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Pharmacokinetics of the mono-hydroxy derivative of oxcarbazepine and its enantiomers after a single i.v. dose given as racemate compared with a single oral dose of oxcarbazepine

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Pharmacokinetics of oxcarbazepine and of its main metabolites

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ABBREVIATIONS: OXC, oxcarbazepine; MHD: Monohydroxy derivative of OXC;DHD: dihydroxylated detivative, ((R)-MHD). R enantiomer of MHD; ((S)-MHD). S enantiomer of MHD; O-SUL: O-Sulphate; O-GLU: O-Glucuronide;DHD: dihydroxylated detivative; GLU-(S)-MHD: glucuronide of the S enantiomer of MHD; GLU-(R)-MHD: glucuronide of the R enantiomer of MHD; A_e: Total amount of drug eliminated in the urine; LOQ:limit of quantitation; LOD:limit of detection

Abstract

Oxcarbazepine is an antiepileptic drug. In humans Oxcarbazepine is metabolized via reduction and conjugation. MHD (Monohydroxy derivative of OXC) is the major pharmacologically active component following OXC ingestion. This study was performed to characterize the disposition of the two enantiomers of MHD after p.o. and i.v. administration and to estimate the bioavailability of MHD after single oral dose administration of OXC compared to a single i.v. administration of MHD. The study was performed in two parts. In a first pilot study, three i.v 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, randomized, two-way crossover, single dose trial in 12 healthy adult subjects ((N = 6) males and (N=6) females) given OXC p.o. (one film-coated 300 mg tablet of Trileptal®) and MHD i.v. (250 mg infused over 30 minutes). Concentrations of OXC and its metabolites were measured by means of HPLC 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 AUC values of (S)-MHD over (R)-MHD equals 3.8, indicating an enantioselective reduction of the prochiral carbonyl group of OXC.

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Introduction

Trileptal® (Oxcarbazepine, 10, 11-dihydro-10-oxo-5H-dibenz[b,f]azepine-5-carboxamide) is an antiepileptic drug registered worldwide by Novartis. Trileptal® is approved as adjunctive therapy or monotherapy for the treatment of partial seizures in adults and in children. In the US, Trileptal® 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) (figure 1) [Shuetz et al., 1986; Menge et al., 1983]. In humans, formation of MHD is stereoselective, with the two enantiomers formed in a ratio of 80% ((S)-MHD) to 20% ((R)-MHD) [Flesch et al., 1992]. Following oral administration of radiolabeled OXC, only 2% of total radioactivity in plasma is due to unchanged OXC and approximately 70% is due to MHD [Shuetz et al., 1986]. Minor amounts of Oxcarbazepine are transformed in a sulfate conjugate and directly conjugated [Shuetz 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 following p.o. 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.

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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 were performed using MHD as an i.v. reference. The objectives of this study was to assess tolerability of a single i.v. dose of MHD (racemate), the bioavailability of MHD after single oral administration of a 300 mg Trileptal® tablet compared to a single i.v. administration of 250 mg of MHD, the disposition of the two enantiomers of MHD in plasma after p.o. and i.v. administration. Two additional goals were to determine the pharmacokinetics in plasma and urine of the two enantiomers of MHD, as well as OXC and DHD, and to determine the degree of conjugation of MHD.

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 i.v. 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 p.o. (one film-coated 300 mg tablet of Trileptal®) and MHD i.v. (250 mg infused over 30 minutes). To eliminate carryover effects, a washout period of at least one week duration was adopted between the subsequent study periods based on the elimination kinetics of MHD ($t_{1/2}$ 8 to 14 h). A dose of

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300 mg of OXC was selected for safety and convenience reasons (1 film-coated tablet of Trileptal®). The dose of MHD was chosen taking safety and analytical aspects into consideration. The dose of MHD had to be as high as possible, owing to the slightly lower sensitivity of the enantioselective analytical method [Flesch et al., 1992] compared to the original method for measuring total MHD [Menge et al., 1983].

For determination of MHD concentrations, blood samples were collected before (time point 0) and up to 72 h post single dose drug and up to 12 post final steady state administration. 4 mL of venous blood was drawn into Lithium heparin Vacutainers® (Becton Dikinson) 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 hours post dose, 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 hours 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 minutes at approximately 1500 x gravity. At least 1.5 mL plasma was transferred to a polypropylene screw-cap tube and frozen within 60 minutes 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 of (R)-MHD concentrations, blood and urine samples were collected before drug administration and up to 72 h post dose. Blood samples 5.5 mL of venous blood were drawn into heparinized ®Monovette tubes (Sarstedt AG, Sewelen, Switzerland) at the following sampling points: 0, 1, 2, 3, 4, 6, 8, 10, 24, 32, 48,

56 and 72 h for the p.o. dose and at 0, 5, 10, 15, 20, 25 and 30 minutes as well as 1, 2, 3, 4, 6, 8, 10, 14, 32, 48, 56 and 72 h p.d. after start of infusion. Immediately after blood withdrawal, samples were centrifuged (2200 g for 5 minutes at room temperature), the plasma removed by pipette to plain polypropylene tubes and stored at -80 C until analysis. Urine samples: All produced urine was collected up to 72 h p.d. in the following fractions: 0-3, 3-6, 6-10, 10-24, 24-32, 32-48, 48-56 and 56-72 hours post-dose. During the sampling time, urine was stored refrigerated at + 2 to + 8 C. The weight of each fraction was recorded, an 20 mL aliquot 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 non enantioselective and an enantioselective HPLC method [Menge et al., 1983, Flesch et al., 1992]. In order to determine the urinary concentrations of GLU-(R)-MHD and GLU-(S)-MHD, urine samples (0.5 mL) collected after p.o. and i.v. administration were treated with beta-glucuronidase (110 µL, containing no sulfatase activity Art. 127680 Boehringer Mannheim, in phosphate buffer pH 6.7 at 37ºC for about 15 hours). 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 et al., 1983]. After the internal standard (CGP 23827, mol.wt. 252.27) had been added to the samples, MHD and the internal standard were isolated by automatically performed (ASPEC) liquid-solid extraction from plasma (100 µL) on 50 mg Bond-Elut C18 cartridges. A reversed-phase column (ODS Hypersil, 3 µm particle size, 4 cm x 4.6 mm i.d.) was used with acetonitrile-methanol-0.01 M

potassium dihydrogenphosphate as mobile phase. The eluted compound was detected at 210 nm. The limit of quantitation of the method (LOQ, mean recovery within 80 and 120% and coefficient of variation ≤ 20%) was 0.1 µmol/L.

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 et al., 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 p.o. and i.v. dosing was calculated from the concentrations at 6 - 10 h to 24 - 56 hours. CL_T, the total plasma clearance, i.e. the sum of all partial clearances, was calculated from: CL_T=Dose/AUC. V_{SS}, the volume of distribution at steady-state, was calculated as: $CL_T \cdot MRT$. The mean residence time (MRT), a model-independent parameter, was determined by the ratio of AUMC to AUC, where AUMC 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 iv administration corrected by the corresponding doses was used to calculate the fraction of the administered dose which 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 p.o. and i.v. dosing was calculated from the concentrations at 4 - 18 h to

40 - 64 hours. For the determinations of pharmacokinetics 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 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 (i.v. versus p.o.) and enantiomers ((R)-MHD versus (S)-MHD were introduced as factors, and the product of two 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 v 8.2 procedure MIXED. The mean differences contrasting log (R)-MHD and (S)-MHD AUCs were derived with 90% confidence intervals (CI) and back transformed to provide geometric mean ratio estimates R:S with corresponding 90% CI.

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, (S)-MHD. The urine samples were spiked with OXC, DHD, (R)-MHD, (S)-MHD. A summary of the results of the validation analyses in plasma and urine is given in the 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, 280 h(µmol/L) at dose levels of 150, 200 and 250 mg, respectively. Between 24.3 to 42.8 % of the dose was excreted as unchanged from 0 to 72 hours. A complete pharmacokinetic evaluation was not performed. As the 250 mg MHD iv 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 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 (SD) model-independent parameters of R- and (S)-MHD after i.v. administration of MHD over 30 minutes 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 Figure 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 bi-exponential manner. Mean apparent terminal elimination half-lives from plasma of (S)-MHD and (R)-MHD were very similar, 9.0 and 10.6 hours, respectively. Plasma clearance values were 3.1 L/h for (S)-MHD and 4.3 L/h for (R)-MHD. (R)-MHD was characterized by a slightly larger volume of distribution (mean value: 54.7 L) than (S)-MHD (mean value: 45.9 L).

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 Figures 4 and 5. Mean (SD) cumulative urinary excretion curves are shown in Figure 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 (Figure 4) the cumulative urinary excretion of GLU-(S)-MHD did not reach a plateau 72 hours 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 OXC. The mean profiles of the two enantiomers of MHD, as well as OXC and DHD are shown in Figure 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 hours, respectively. This difference might be explained by a difference in the glucuronidation rate of the two enantiomers of MHD, 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 Figures 9 and 10. Mean cumulative excretion curves are shown in Figures 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, the enantiomeric ratio being 6.9. The percentage of the dose excreted as

glucuronides of MHD in urine represents 44 % of the administered dose (45 % after iv dosing), whereas 27 % was excreted as unchanged MHD (28 % after iv 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 i.v. and p.o. 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) 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 Figures 10. The mean elimination half-life of conjugated S- and (R)-MHD was approximately 10 hours. 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 enantioselectivelly conjugated. The mean plasma AUC values of (S)-MHD, (R)-MHD, OXC, DHD, total MHD ain mean pharmacokinetic parameters after p.o. administration of 300mg OXC and i.v. infusion of 250 mg MHD are depicted in Figure 12.

Statistical Analysis

The geometric mean ratios (and 90% C.I.) 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 three-fold increase in the R to S ratio between IV and PO 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 non-enantioselective 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 (SD) f value are summarized in Table 4.

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 GI-tract. Regenerated MHD could later be reabsorbed, explaining the delay in the urinary excretion observed in some volunteers. Other drugs like 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 which is present in all mammalian species [Feldsted et al., 1980]. The formation of the S enantiomer of

MHD can be predicted, using Prelog's rule [Prelog et al., 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, as it has been demonstrated that both enantiomers have similar anticonvulsant efficacy and tolerability [Schmutz et al., 1993; Schmutz et al., 1994].

MHD was given intravenously to humans for the first time in the present study. Systemic adverse experiences associated with an i.v. administration of MHD were similar to those reported after an oral intake of Trileptal® in the present and in a previous study performed in healthy volunteers [2].

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

Intravenous infusion of 250 mg of MHD over 30 minutes 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 treatments 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 as both enantiomers have similar antiepileptic efficacy and tolerability in animals [Schmutz et al., 1993].

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Authorship contributions:

Conducted the clinical studies: Czeslaw Czendlik

Conducted the experiments: Gérard Flesch

Performed data analysis: Gérard Flesch

Performed the statistical analysis. Didier Renard

Wrote the manuscript: Gérard Flesch

Reviewed the manuscript: Peter Lloyd

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Footnotes

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A preliminary account of this work was presented as an oral presentation at the 7th European Congress of Biopharmaceutics and Pharmacokinetics (ECBP) Jerusalem, Israel, April 25-30, 1999 [Flesch et al., 1999]

Legends for Figures

Figure 1 **Metabolism of Oxcarbazepine in humans**

O-SUL: O-Sulphate; O-GLU: O-Glucuronide; (S)-MHD: S-enantiomer of MHD; ®-MHD: R enantiomer of MHD; DHD: dihydroxylated detivative; GLU-(S)-MHD: glucuronide of the S enantiomer of MHD; GLU-(R)-MHD: glucuronide of the R enantiomer of MHD.

Figure 2 **Plasma concentration-time curves of (R)-MHD and (S)-MHD after 250 mg MHD administered as an infusion over 30 minutes to twelve healthy volunteer**

Full line: (R)-MHD; dotted line: (S)-MHD

Figure 3 **Top: Mean (SD) plasma concentration-time curves of (R)-MHD, (S)-MHD, OXC and DHD after 250 mg MHD administered as an infusion over 30 minutes to twelve healthy volunteers (lin scale)**

Figure 4 **Top: Cumulative urinary excretion of (S)-MHD after 250 mg MHD infused over 30 minutes**
Bottom: Cumulative urinary excretion of (R)-MHD after 250 mg MHD infused over 30 minutes

Figure 5 **Top: Cumulative urinary excretion of GLU-(S)-MHD after 250 mg MHD infused over 30 minutes**
Bottom: Cumulative urinary excretion of GLU-(R)-MHD after 250 mg MHD infused over 30 minutes

Figure 6 **Mean cumulative urinary excretions (iv)**

Mean (SD) cumulative urinary excretion of (R)-MHD, (S)-MHD, GLU-(S)-MHD and GLU-(R)-MHD after 250 mg MHD infused over 30 minutes

Full line: (R)-MHD; dotted line: (S)-MHD

Figure 7 **Plasma concentration-time curves of (R)-MHD and (S)-MHD after 300 mg OXC administered orally to twelve healthy volunteer (Top: lin scale; bottom: log scale)**

Full line: (R)-MHD; dotted line: (S)-MHD

Figure 8 **Top: Mean (SD) plasma concentration-time curves of (R)-MHD, (S)-MHD, OXC and DHD after 300 mg OXC administered orally to twelve healthy volunteers (lin scale)**

Figure 9 **Top: Cumulative urinary excretion of (S)-MHD after 300 mg OXC given orally Bottom: Cumulative urinary excretion of (R)-MHD after 300 mg OXC given orally**

Figure 10 **Top: Cumulative urinary excretion of GLU-(S)-MHD after 300 mg OXC given orally**
Bottom: Cumulative urinary excretion of GLU-(R)-MHD after 300 mg OXC given orally

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

Figure 12 **Mean (SD) plasma AUC values of (S)-MHD, (R)-MHD, OXC, DHD, total MHD after po administration of 300 mg OXC and 250 mg MHD infused over 30 minutes**

Table 1 **Summary of the results of the validation analyses in plasma and urine**

Com-pounds	Medium	LOQ [µmol/L]	LOD [µmol/L]
MHD	plasma	0.77	0.08
OXC	plasma	1.05	0.1
DHD	plasma	0.65	0.07
(R)-MHD	plasma	0.84	0.08
(S)-MHD	plasma	0.81	0.08
DHD	urine	0.47	0.05
(R)-MHD	urine	1.0	0.1
(S)-MHD	urine	0.8	0.08

LOQ:limit of quantitation; LOD:limit of detection

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Table 2 Pharmacokinetic parameters of MHD (First study)

Pharmacokinetic parameters of MHD, (R)-MHD and (S)-MHD in plasma and urine

#: not determined

Doses		150 mg			200 mg			250 mg		
Parameters	MHD/iv	MHD	(R)-MHD	(S)-MHD	MHD	(R)-MHD	(S)-MHD	MHD	(R)-MHD	(S)-MHD
AUC(0-72h)	[µmol.L-1.h]	109.2	55.7	69.0	142.4	59.1	92.2	280.1	131.7	191.7
A_e(0-72h)	[% of dose]	24.3	#	#	30.7	#	#	42.8	#	#
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	#	#	1.7	#	#	1.5	#	#

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Table 3 Mean (SD) values of pharmacokinetic parameters obtained after a single 250 mg MHD infusion over 30 minutes and an oral administration of 300 mg OXC to twelve healthy volunteers

i.v.	OXC	DHD	(R)-MHD	(S)-MHD	S/R	GLU-R-MHD	GLU-S-MHD	S/R
t_{max} [h]	0.5*(n=4)	8*(n=8)	-	-	-	-	-	-
C_{max} [µmol·L^{-1}]	0.08(0.13)	0.24(0.20)	-	-	-	-	-	-
AUC(0-48h) [µmol.L-1.h]	-	-	105.1(23.2)#	144.3(30.4)#	1.4	-	-	-
AUC [µmol.L-1.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 [L·h^{-1}]	-	-	4.3(0.9)	3.1(0.6)	-	-	-	-
CL_R [L·h^{-1}]	-	-	0.9(0.2)	0.9(0.2)	-	-	-	-
$t_{1/2}$ [h]	-	-	9.0(1.5)	10.6(2.6)	-	-	-	-
V_{ss} [L]	-	-	54.7(10.9)	45.9(11.4)	-	-	-	-
$t_{1/2\ ur.}$ [h]	-	-	9.0(1.1)	8.4(1.7)	-	14.2(4.0)	9.9(1.3)	-

p.o.	OXC	DHD	(R)-MHD	(S)-MHD	S/R	GLU-R-MHD	GLU-S-MHD	S/R
t_{max} [h]	1.0*(n=12)	24*(n=6)	3.5	4	-	-	-	-
C_{max} [µmol·L^{-1}]	2.0(0.7)	0.2(0.2)	3.0(0.8)	11.0(2.2)	-	-	-	-
AUC [µmol·L^{-1}·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 [L·h^{-1}]	-	-	1.0(0.3)	1.1(0.3)	-	-	-	-
$t_{1/2}$ [h]	-	-	15.8(2.8)	11.2(1.5)	-	-	-	-
$t_{1/2\ ur.}$ [h]	-	-	7.0(1.9)	8.5(2.4)	-	10.3(2.2)	10.8(3.0)	-

OXC: Oxcarbazepine, DHD: Dihydroxy derivative of Oxcarbazepine; (R)- MHD: R enantiomer of the Mono Hydroxy Derivative of Oxcarbazepine, (S)-MHD: S enantiomer of the Mono Hydroxy Derivative of Oxcarbazepine, GLU-(R)-MHD: Glucuronide conjugate of the R enantiomer of the Mono Hydroxy Derivative of Oxcarbazepine, GLU-(S)-MHD: Glucuronide conjugate of the S enantiomer of the Mono Hydroxy Derivative of Oxcarbazepine,

*: median; @AUC(0-24/56h); &AUC(0-32/48h); nd: not detected

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Table 4 **Mean (SD) f value based on MHD concentrations measured with the non enantiospecific assay after single po administration of 300 mg OXC versus 250 mg MHD infused over 30 minutes**

	OXC/po AUC[h(µmol/L)]	MHD/iv AUC[h(µmol/L)]	f
mean	308	260.6	0.99
SD	66.7	51.6	0.1

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Figure 1

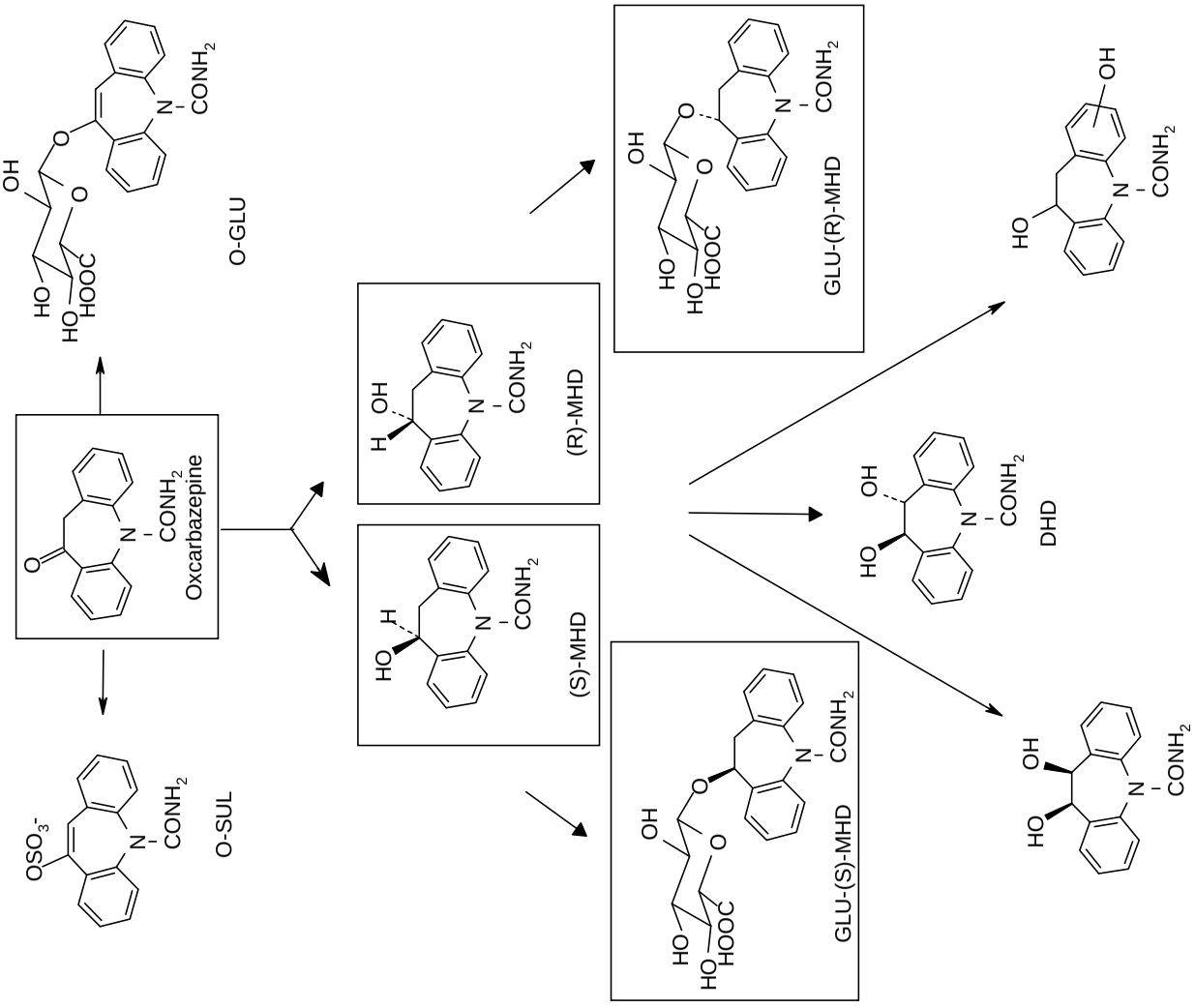

Figure 2

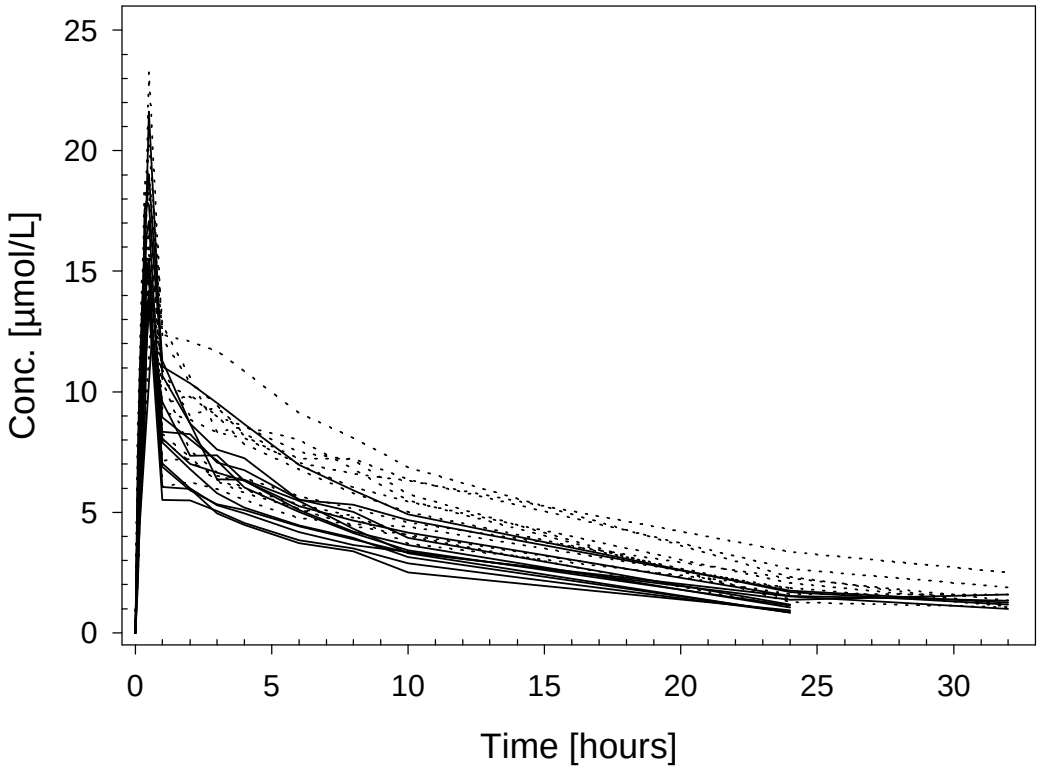

Figure 3

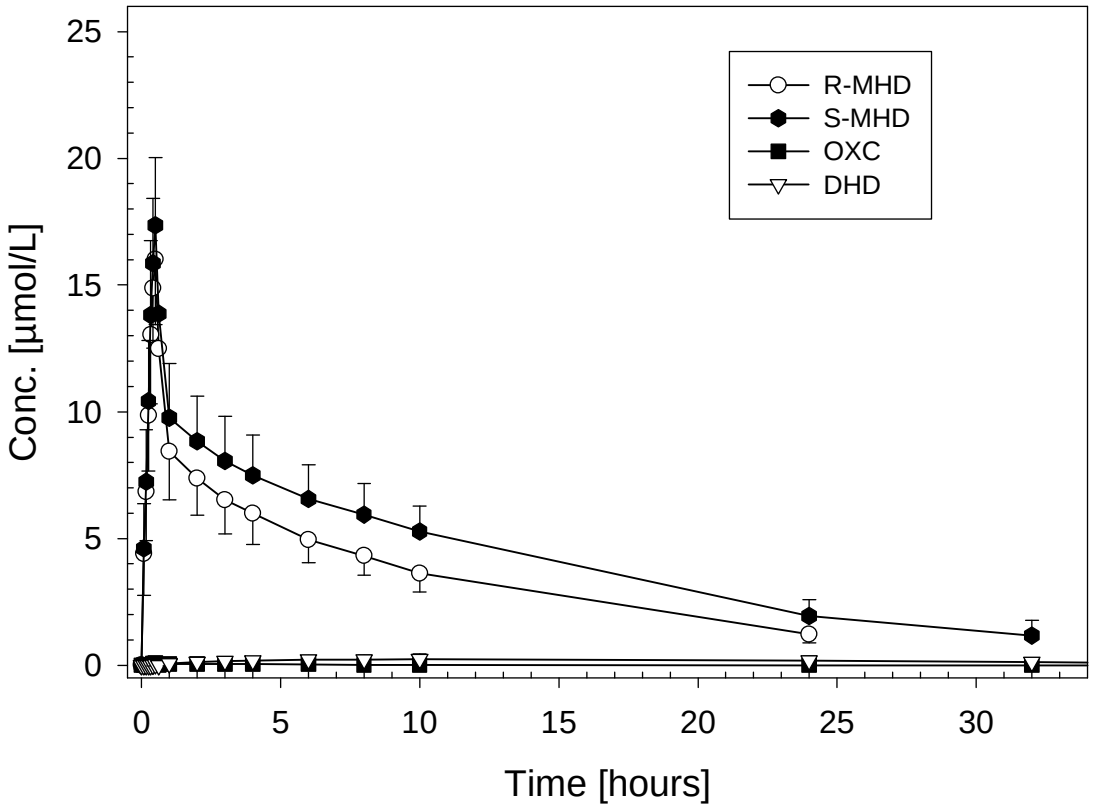

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Figure 4

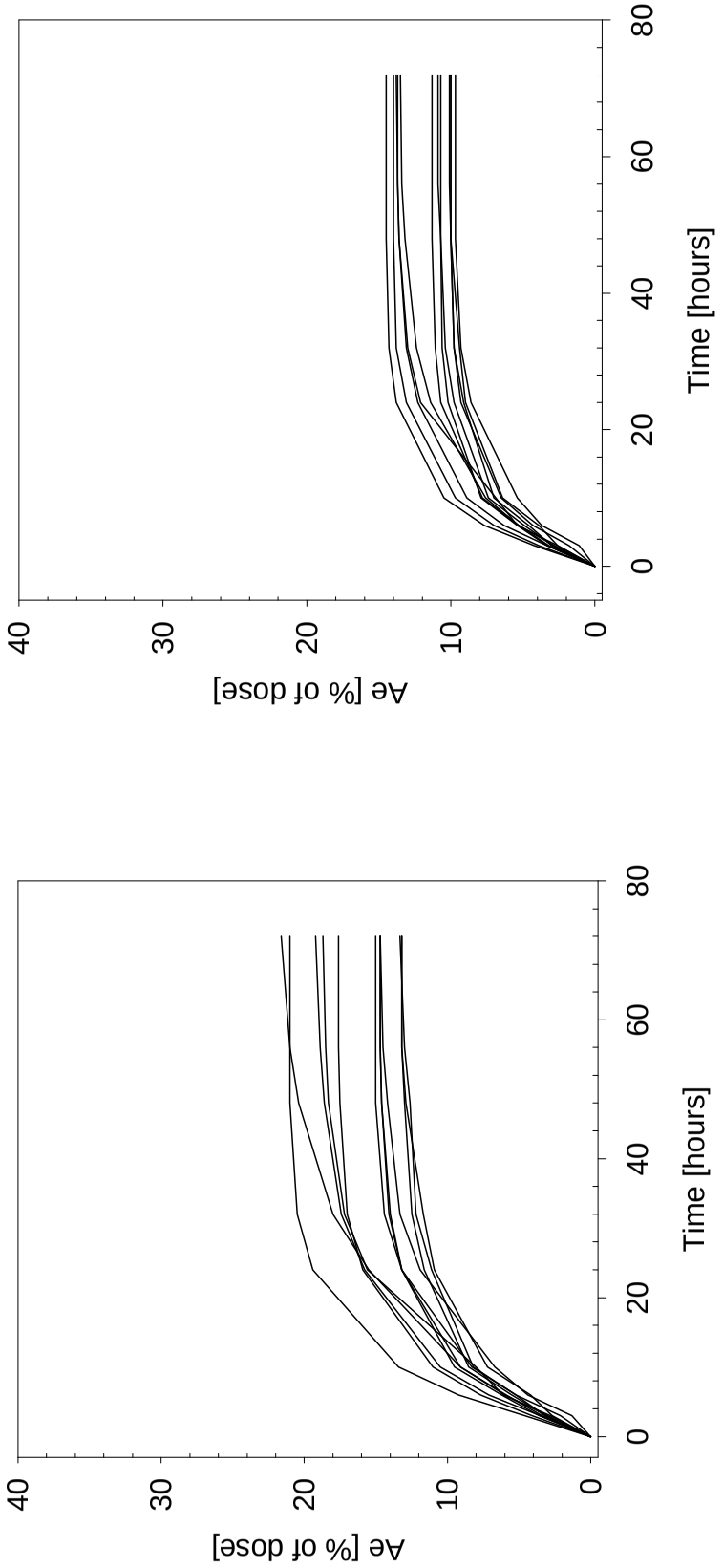

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Figure 5

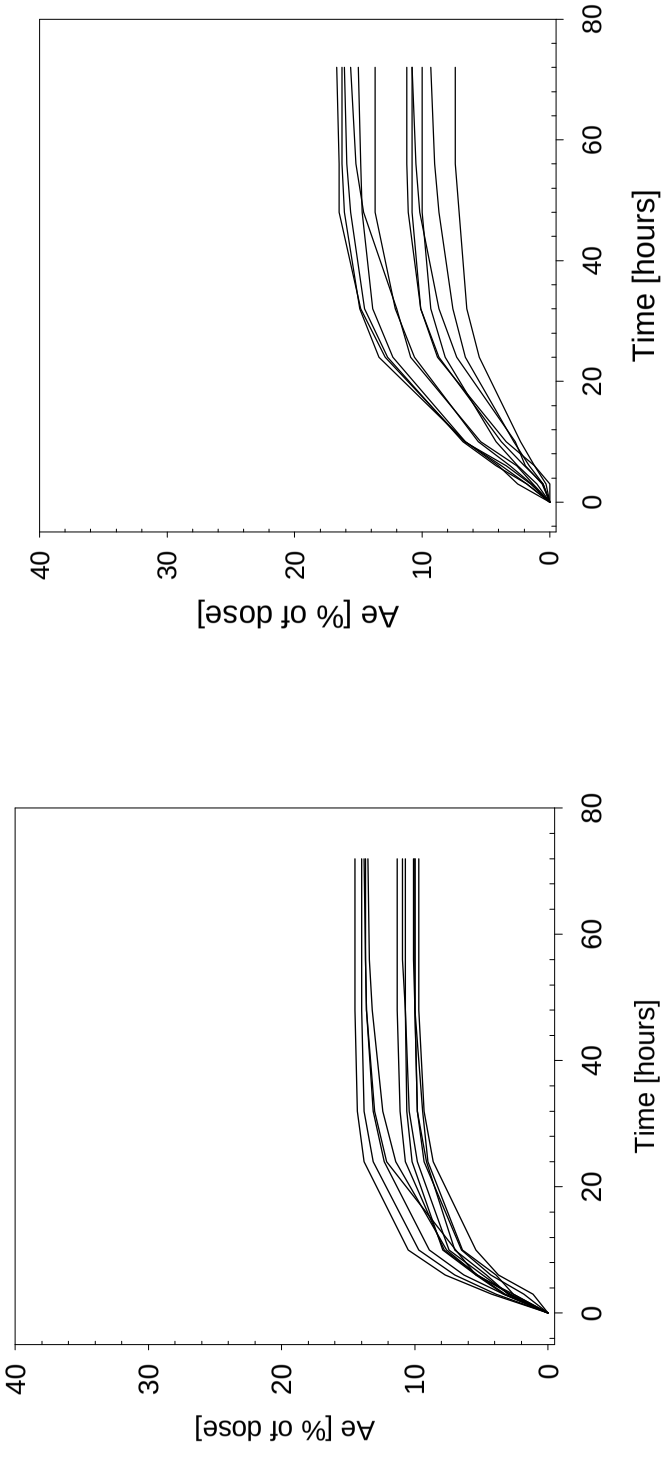

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Figure 6

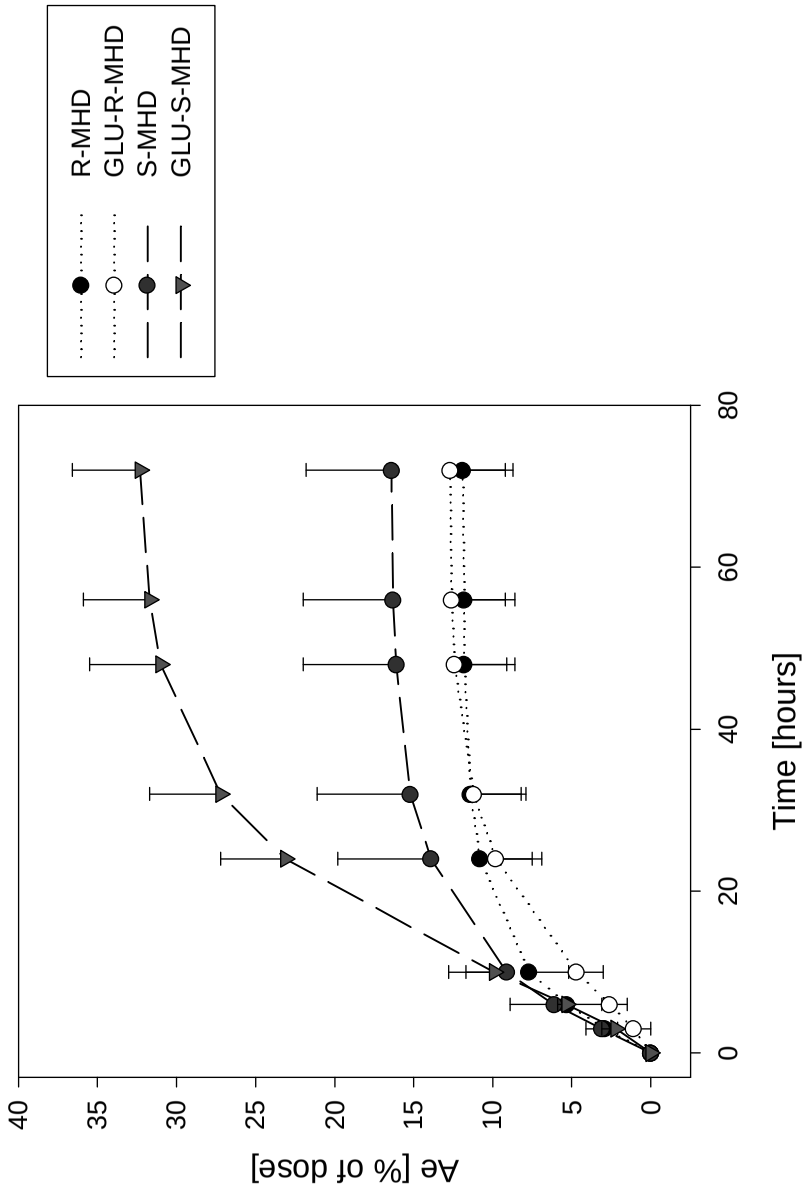

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Figure 7

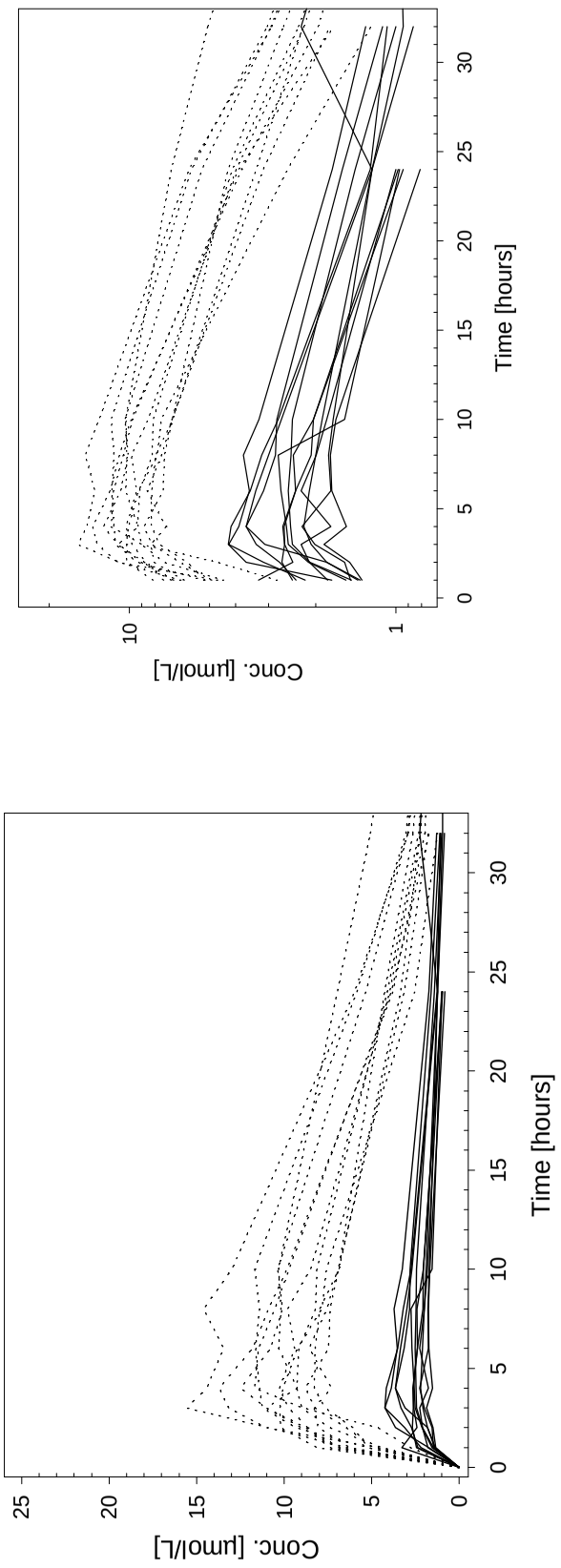

Figure 8

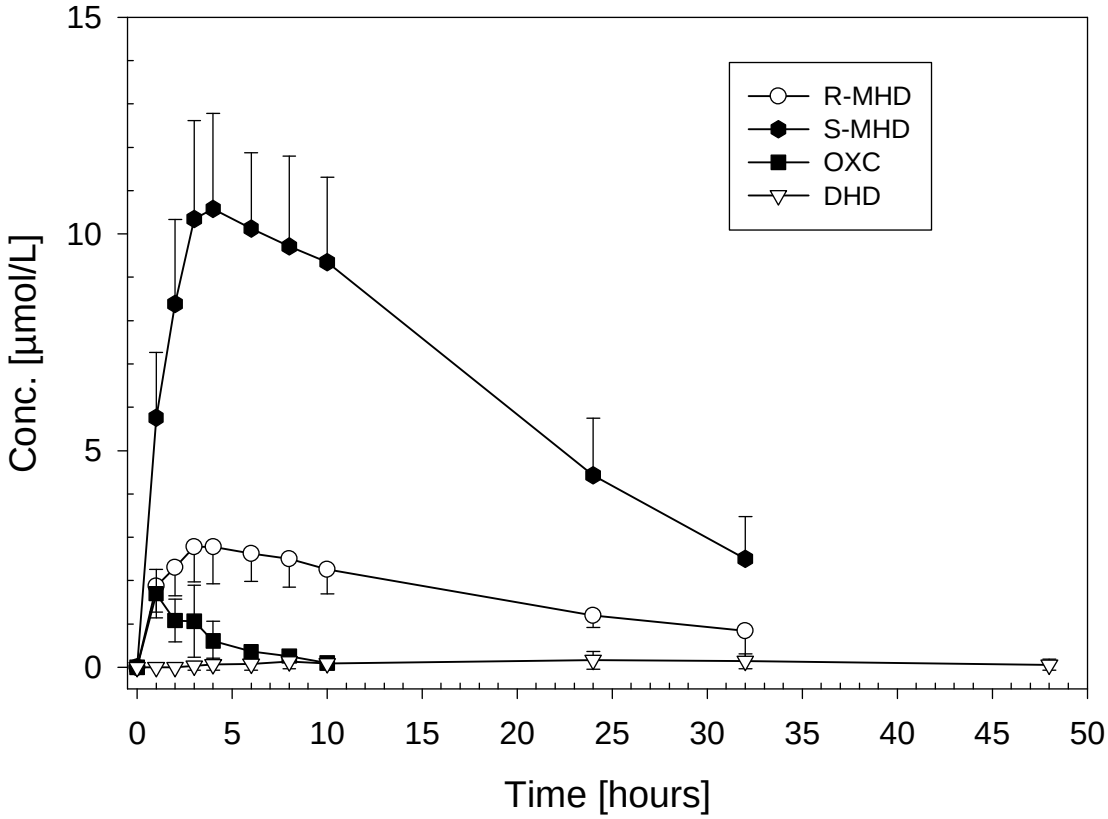

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Figure 9

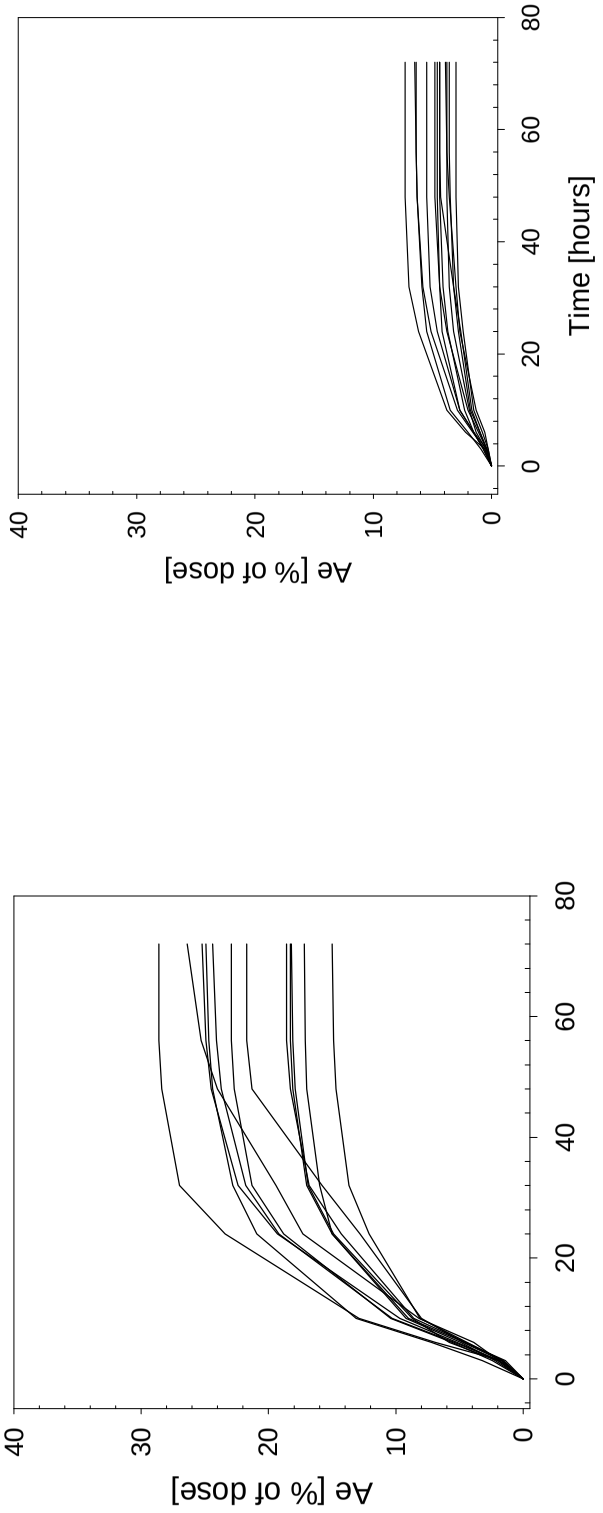

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Figure 10

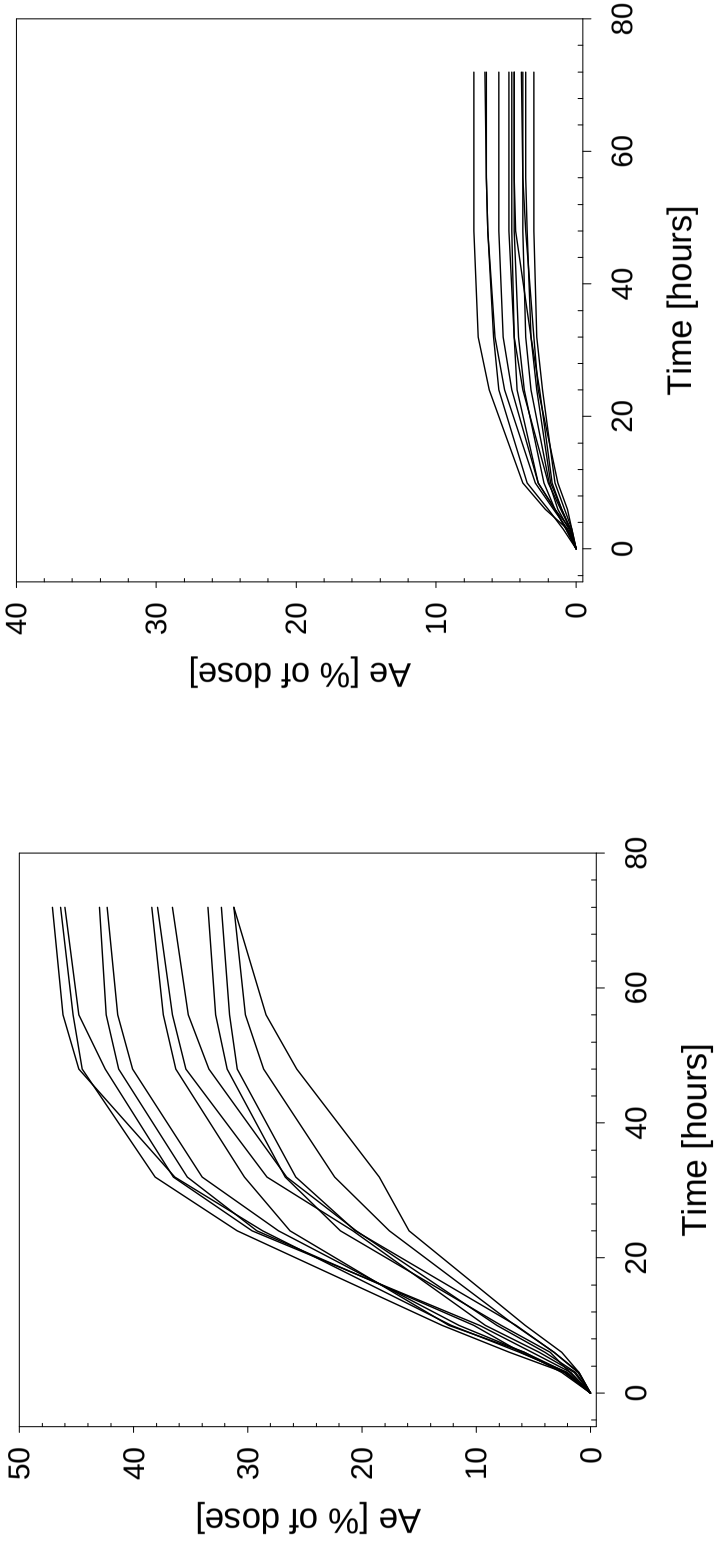

Figure 11

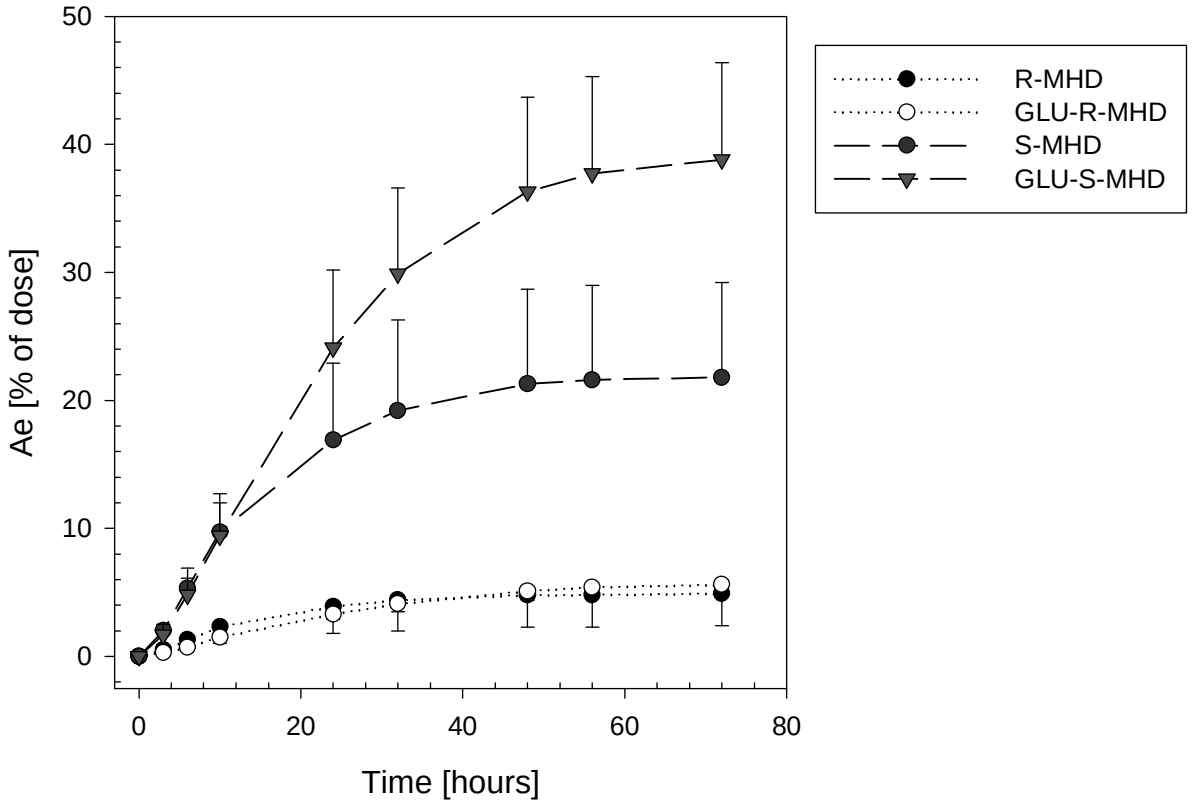

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Figure 12