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DISPOSITION OF ENANTIOMERS OF SULPIRIDE IN HUMANS AND RATS

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ABSTRACT

Pharmacokinetics of sulpiride enantiomers after intravenous administration of (±)-, (+)-, and (−)-sulpiride was examined in humans and rats. Pharmacokinetic profiles were similar in (+)- and (−)-enantiomers after intravenous administration of (±)-sulpiride. Metabolic inversion at a chiral centre was not observed after intravenous administration of each enantiomer in rats.

KEY WORDS Sulpiride Enantiomer Stereoselective disposition Human Rat

INTRODUCTION

Most drugs containing chiral centre(s) are marketed as racemic mixtures mainly for economic reasons. Because of the dramatic progress in analytical technology in recent years, attention has been focused on the implications of stereoselectivity and stereochemistry of drugs in relation to pharmacokinetics and pharmacodynamics.[1–5]

Sulpiride (Figure 1) has one chiral centre at its pyrrolidine ring, although it is clinically used as the racemate. Jenner *et al.*[6] reported that apomorphine- and amphetamine-induced stereotyped behaviours in rats were antagonized by (−)-sulpiride but not by the (+)-enantiomer. Additionally, they reported that

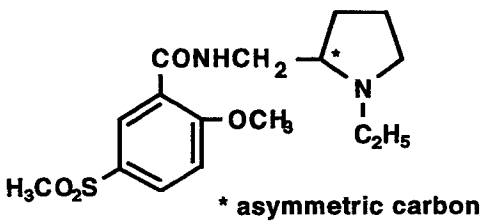

Figure 1. Chemical structure of sulpiride

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(−)-sulpiride induced an increase in striatal and mesolimbic homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic acid (DOPAC) concentrations, while (+)-sulpiride exhibited no effect on HVA or DOPAC in either area. Mizuchi *et al.*[7] also reported that (−)-sulpiride is 40 times more active than (+)-sulpiride in D_2-receptor inhibition.

Pharmacokinetic evaluations that do not employ a chiral assay will be misleading if the disposition of the enantiomers differs. Thus, we investigated the pharmacokinetic behaviour of sulpiride enantiomers after administration of the racemate and each enantiomer of sulpiride in humans and rats.

MATERIALS AND METHODS

Reagents and materials

The (±)-, (+)-, and (−)-sulpiride were kindly supplied by Fujisawa Pharmaceutical Co. (Osaka, Japan). Optical purity of the sulpiride enantiomers was greater than 99·9%. All reagents were of analytical reagent grade and purchased from Wako Pure Chemical Industries (Osaka, Japan).

Human study

Seven depressed patients and 25 schizophrenic patients participated in the study after giving their informed consent either from patients or from their guardians. The study was conducted according to the Declaration of Helsinki. They ranged in age from 19 to 75 years old and weighed between 36·5 and 71·5 kg. Their BUN and serum creatinine values were within the normal ranges. They received sulpiride at a dose of 600–1200 mg day^{-1} for at least 1 month and they also chronically received several kinds of phenothiazines and antiparkinsonism agents. Blood samples were collected 2 h after oral administration. Urine samples were collected the following morning.

Animal study

After male Wistar rats (body weight 250–300 g) were anaesthetized with pentobarbital at an i.p. dose of 50 mg kg^{-1}, their jugular veins and urinary bladders were cannulated with polyethylene tubing. No additional pentobarbital was used during the study. The (±)-, (+)-, and (−)-sulpiride were dissolved in an isotonic buffer (0·263 M citric acid–0·123 M Na_2HPO_4, pH 5·0) at a concentration of 12·5 mg ml^{-1}. The solution was injected into the femoral vein (25 mg kg^{-1}). Blood samples were collected from another jugular cannula at 0, 0·25, 0·5, 1, 2, 3, 4, 6, and 8 h after administration. Urine samples were also collected for periods of 0–1, 1–2, 2–3, 3–4, 4–6, 6–8 h after administration. Blood samples were centrifuged and the serum portion was separated. All samples were immediately frozen at −20 °C until analysis.

Assay

Sulpiride was extracted from the serum and urine according to a solid extraction method. Adsorbex RP18 (400 mg, Merck, Darmstadt, Germany) was used as a column for extraction, which was conditioned by 10 ml each of 0·1 N sodium hydroxide, 0·1 N hydrochloric acid, and methanol. To a 0·2 ml portion of serum or urine in a column, 10 ml of distilled water was added to remove interfering substances. After aspiration of distilled water, 5 ml of methanol was used to desorb sulpiride. The methanol solution was evaporated to dryness using a rotary vacuum evaporator. The residue was dissolved in 50 μl of methanol and 25 μl aliquots of the resulting solution were injected into the HPLC system to separate the optically active sulpirides. The chromatographic system consisted of a LC-6A pump (Shimadzu, Kyoto, Japan) and a variable-wavelength UV detector (Shimadzu) set at 250 nm. For chiral separation of sulpiride enantiomers in serum and urine, a Chiralcel OJ column, 250 mm × 4·6 mm i.d. (Daicel Chemical Ind., Tokyo, Japan) was used. The mobile phase (hexane : isopropanol = 85 : 15 containing 0·1% diethylamine) was pumped at a flow rate of 0·5 ml min^{-1}. Endogenous substances and/or other drugs were eluted at retention times similar to those of the enantiomers. Thus, a double HPLC procedure described below was employed to quantitate the optically active sulpirides. The column effluents of each enantiomer were collected in a 10 ml test tube on the basis of the retention times of the racemic sulpiride standard sample. Each effluent was evaporated to dryness under vacuum. The residue was dissolved in 50 μl of methanol and 25 μl aliquots of a resulting solution were injected into a second HPLC system. The second system comprised a UV detector set at 239 nm and a Nucleosil C-18 column (250 mm × 4·6 mm i.d., Chemco, Tokyo, Japan) held at 45 °C for quantitation of sulpiride enantiomers. Linear calibration curves for (+)- and (−)-sulpiride were obtained at the serum and urine concentration range of 0·05–1·0 μg ml^{-1} with correlation coefficients of >0·998 and were generated in each set of the study.

Pharmacokinetic analysis

The serum concentration profiles were fitted to a two-compartment open model using a non-linear regression analysis technique. The area under the serum concentration–time curve from 0 to 8 h (AUC_{0-8}) was obtained by a trapezoidal rule. The area to time infinity (AUC) was calculated by adding the AUC_{0-8} to the area obtained by dividing the concentration at 8 h after administration by the terminal elimination rate constant calculated by least-squares regression analysis of the terminal concentration–time curve. Renal clearance (CL_{renal}) of sulpiride was calculated from the following equation:

$$CL_{renal} = U_{t1-t2}/AUC_{t1-t2}$$

where U_{t1-t2} is the amount of sulpiride excreted in urine over the period from time $t1$ to $t2$ after administration and AUC_{t1-t2} is the corresponding area under the serum sulpiride concentration–time curve over the same interval.

The Student's t-test was used for statistical analysis, taking p of 0·05 as the level of significance.

RESULTS AND DISCUSSION

The binding study of ^{3}H-labelled sulpiride in the rat striatal membrane indicated that (−)-sulpiride is 40 times more active than (+)-sulpiride.[7] It has been reported that sulpiride increases milk secretion in puerperium. Polatti[8] reported that *d*-sulpiride and *dl*-sulpiride exhibited a similar activity both in insufficient lactation and in the absence of milk, while *l*-sulpiride induced the greatest milk production and the quickest increase in secretion. Caldara *et al.*[9] showed that racemic sulpiride and its enantiomer exerted different effects on gastric acid secretion and gastrin release. Whereas racemic sulpiride and *l*-sulpiride inhibited gastrin release after meal, but not gastric acid secretion, *d*-sulpiride reduced both a gastric acid output and the volume of gastric juice without reducing gastrin release. It was also reported that *d*-sulpiride can act as a mixed agonist–antagonist, at least at peripheral receptors.[10–12]

Enantiomeric ratios in serum and urine after oral administration of racemic sulpiride were almost unity in humans (Table 1). Serum concentration–time profiles of sulpiride enantiomers after intravenous administration of 25 mg kg^{-1} of racemic sulpiride in rats are shown in Figure 2 and cumulative amounts of sulpiride enantiomers excreted in urine are shown in Figure 3. Recently, Yamada *et al.*[13] reported the pharmacokinetic profile of racemic sulpiride after intravenous administration of racemic solution at a dose of 20 mg kg^{-1} to rats, which was in good agreement with our results expressed as a racemate. Concentration–time profiles and urinary excretion patterns were observed to be similar between both enantiomers. No pharmacokinetic parameters were significantly different (Table 2, $p > 0{\cdot}05$).

Similar results were obtained after intravenous administration of 25 mg kg^{-1} of each enantiomer in rats (Figures 4 and 5, Table 3). No antipode was observed after intravenous administration of either isomer of sulpiride. Racemic sulpiride is excreted almost entirely unchanged in urine in man, while percentage of sulpiride excreted in urine has been reported to be approximately 40%, and the rest is metabolized mostly by glucuronidation in rats.[14,15]

Table 1. Enantiomeric ratios of sulpiride in serum and urine in humans. Mean ± SEM, $n = 32$

	Serum	Urine
[(−)/(+)] ratio	0·994 ± 0·0271	0·904 ± 0·0371

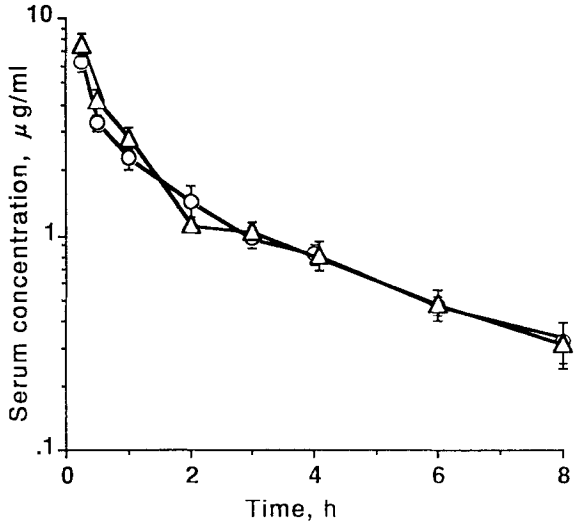

Figure 2. Serum concentration–time curves of (+)- (○) and (−)- (△) sulpiride after intravenous administration of 25 mg kg^{-1} of (±)-sulpiride in rats. Mean ± SEM, $n = 4$

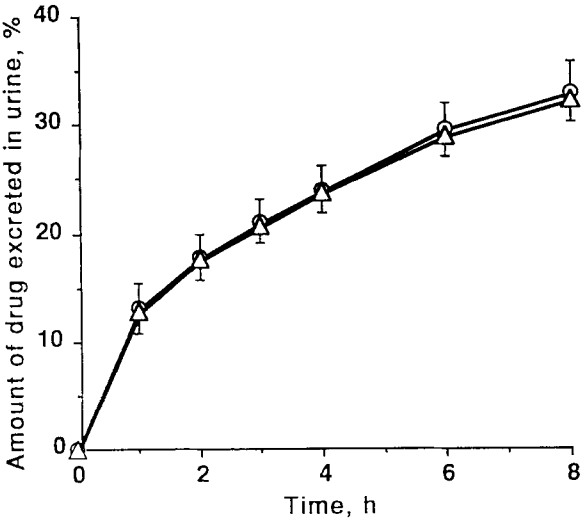

Figure 3. Cumulative amounts of unchanged (+)- (○) and (−)- (△) sulpiride excreted in urine after intravenous administration of 25 mg kg^{-1} of (±)-sulpiride in rats. Mean ± SEM, $n = 4$

It is known that R-enantiomers are inverted to the respective S-antipodes in arylpropionic acid derivatives such as ibuprofen,[16] ketoprofen,[17] and loxoprofen.[18,19] Enantiomeric inversion of sulpiride enantiomers was not observed in rats.

Table 2. Pharmacokinetic parameters of (+)- and (−)-sulpiride after intravenous administration of 25 mg kg^{-1} of (±)-sulpiride in rats. Mean ± SEM, $n = 4$

Parameters	(+)-Sulpiride	(−)-Sulpiride
k_{12} (h^{-1})	2·9 ± 0·67	2·1 ± 0·85
k_{21} (h^{-1})	0·93 ± 0·14	0·80 ± 0·11
$t_{1/2}$ (h)	2·6 ± 0·22	2·4 ± 0·17
V_c* (l kg^{-1})	0·90 ± 0·34	0·92 ± 0·31
AUC_{0-8} ($\mu g\ ml^{-1} \cdot h$)	9·8 ± 0·94	11·0 ± 0·90
AUC ($\mu g\ ml^{-1} \cdot h$)	11·0 ± 0·89	12·0 ± 1·1
CL_{total} (ml min^{-1})	5·7 ± 1·1	5·1 ± 1·0
CL_{renal} (ml min^{-1})	2·4 ± 0·40	1·9 ± 0·26

*V_c: the apparent volume of the central compartment.

Table 3. Pharmacokinetic parameters of (+)- and (−)-sulpiride after intravenous administration of 25 mg kg^{-1} of each enantiomer in rats. Mean ± SEM, $n = 5$

Parameters	(+)-Sulpiride	(−)-Sulpiride
k_{12} (h^{-1})	2·3 ± 0·44	2·5 ± 0·33
k_{21} (h^{-1})	0·77 ± 0·091	0·68 ± 0·11
$t_{1/2}$ (h)	2·2 ± 0·11	2·5 ± 0·33
V_c* (l kg^{-1})	0·60 ± 0·076	0·91 ± 0·029
AUC_{0-8} ($\mu g\ ml^{-1} \cdot h$)	22·0 ± 2·1	19·0 ± 1·0
AUC ($\mu g\ ml^{-1} \cdot h$)	24·0 ± 2·1	21·0 ± 1·0
CL_{total} (ml min^{-1})	5·0 ± 0·43	5·8 ± 0·30
CL_{renal} (ml min^{-1})	1·6 ± 0·23	2·0 ± 0·22

*V_c: the apparent volume of the central compartment.

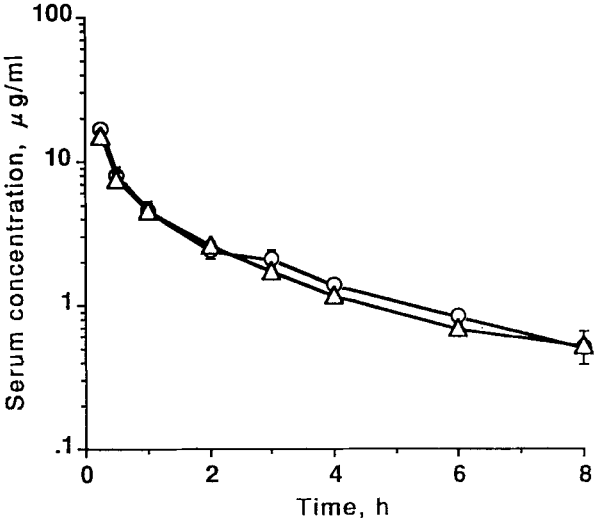

Figure 4. Serum concentration–time curves of (+)- (○) and (−)- (△) sulpiride after intravenous administration of 25 mg kg^{-1} of each enantiomer in rats. Mean ± SEM, $n = 5$

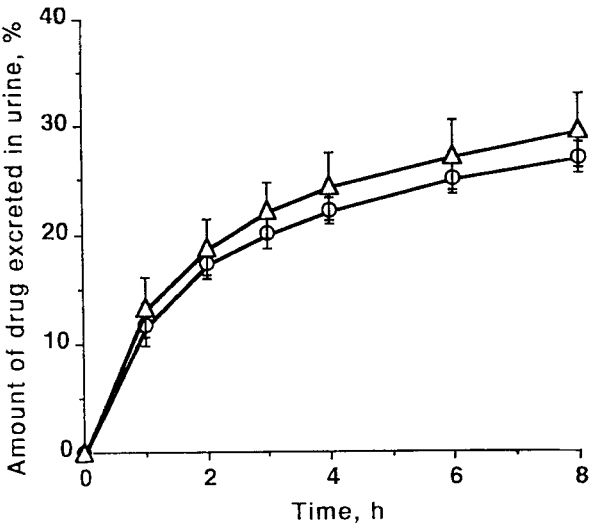

Figure 5. Cumulative amounts of unchanged (+)- (○) and (−)- (△) sulpiride excreted in urine after intravenous administration of 25 mg kg^{-1} of each enantiomer in rats. Mean ± SEM, $n = 5$

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