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Stereoselective disposition of (±)-sotalol at steady-state conditions

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The objective of this study was to assess, under steady-state conditions, the stereoselective disposition of (±)-sotalol in man. In all patients studied ($n = 7$) values of oral clearance (137 ± 51 ml min^{-1}), renal clearance (96 ± 42 ml min^{-1}) and nonrenal clearance (41 ± 25 ml min^{-1}) of (−)-sotalol were greater than those for (+)-sotalol (123 ± 45 ml min^{-1}, 89 ± 39 ml min^{-1} and 34 ± 23 ml min^{-1}, respectively; $P < 0.05$, Student's paired t-test). Binding to plasma proteins was greater for (+)-sotalol (38 ± 9% *vs* 35 ± 9% for the (−)-enantiomer; $P < 0.05$) such that unbound oral clearance (+)/(−) ratio (0.95 ± 0.06) and unbound renal clearance (+)/(−) ratio (0.97 ± 0.06) were not stereoselective. In contrast, estimated unbound nonrenal clearance, which represents ≈25% of the total unbound clearance of the drug, was greater for the (−)-enantiomer (64 ± 42 ml min^{-1}) compared with (+)-sotalol (57 ± 42 ml min^{-1}; $P < 0.05$). The difference in the pharmacokinetics of sotalol enantiomers is mainly related to stereoselectivity in plasma protein binding.

Keywords sotalol stereoselectivity pharmacokinetics steady-state

Introduction

(±)-Sotalol is a non-cardioselective β-adrenoceptor antagonist which prolongs cardiac action potential (class III) [1, 2]. As for most other β-adrenoceptor blockers, β-adrenergic antagonism resides mainly in the (−)-enantiomer [3]. On the other hand, the enantiomers of sotalol are equipotent class III antiarrhythmic agents [4, 5]. Currently, the drug is used clinically as the racemic mixture but (+)-sotalol is undergoing investigation as a pure class III antiarrhythmic agent.

(±)-Sotalol, a highly hydrophilic drug, is well absorbed after oral administration and its bioavailability is close to 100% [6]. The drug is eliminated largely by glomerular filtration in man with 75% of a dose being excreted unchanged in urine [6,8]. Complete data on the stereoselective disposition of sotalol after administration of the racemate are lacking. One study has reported that the pharmacokinetics of (+)-sotalol and (±)-sotalol were similar in healthy volunteers after a single oral dose of either (+)-sotalol or the racemate [9]. In contrast, others have presented data suggesting stereoselective disposition of sotalol in man [10, 11].

In this study the disposition of sotalol enantiomers was assessed under steady-state conditions in patients treated with the racemate. Simultaneous assessment of the disposition of both enantiomers was possible using a stereoselective h.p.l.c. assay [12].

Methods

Study design

The seven patients enrolled in this study (five males and two females) had been treated for supraventricular arrhythmias with either 80 mg ($n = 3$) or 160 mg ($n = 4$) racemic sotalol · HCl (Sotacor®, Bristol-Myers Squibb, Montreal) given orally every 12 h for at least 3 days. Their mean (± s.d.) age was 60 ± 11 years (range, 43–74) and their mean body weight was 75 ± 14 kg (range, 49–89). At 08.00 h (trough of the dosing interval), on the morning of study day and after an overnight fast, patients emptied their bladder and received their respective oral dose of sotalol · HCl. Blood samples (5 ml) were obtained at 0, 15, 30, 45 min and 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 12 h after drug administration. Blood was collected in Vacutainers® tubes containing EDTA and plasma was separated by centrifugation and frozen at −20°C until assay. An aliquot of urine collected over a dosing interval was stored at −20°C until assay.

Data analysis

Creatinine clearance was estimated from serum creatinine using the equation of Cockcroft and Gault [13]. Plasma concentrations of (−)- and (+)-sotalol were measured by a stereoselective h.p.l.c. assay [12]. The limit of

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determination of each enantiomer was 12.5 ng ml^{-1} using 1 ml of plasma or urine. Intra-day and inter-day coefficients of variation were less than 10% for each enantiomer in the range of 0.125–2.5 μg ml^{-1} in plasma and 0.25–2.5 μg ml^{-1} in urine [12]. Plasma concentration data for each enantiomer were subject to non-compartmental pharmacokinetic analysis [14]. The extent of binding of sotalol enantiomers to plasma proteins was determined in triplicate by ultrafiltration using the Centrifree® micropartition system (Amicon Canada Limited, Ontario, Canada).

Statistical analysis

Difference in the pharmacokinetic parameters between (+)- and (−)-sotalol were compared using the two-tailed Student's paired *t*-test. A *P* value less than 5% was considered to be statistically significant.

Results

The measured ratio of (+)- to (−)-sotalol in the tablets was not different from unity ((+)/(−) 1.0 ± 0.03; $n = 4$ P = NS).

Mean plasma concentrations of both enantiomers in two representative patients are shown in Figure 1. In every patient and throughout the dosing interval, plasma concentations of (+)-sotalol were higher than those of (−)-sotalol. Thus, the oral clearance of (−)-sotalol was 10 ± 5% ($P < 0.05$) higher than that of (+)-sotalol (Table 1).

Urinary recoveries of unchanged (+)- and (−)-sotalol (41 ± 19 mg and 40 ± 19 mg, respectively) were similar (Table 1). In contrast, the renal clearance of (−)-sotalol was 1.09 ± 0.06 times higher than that of (+)-sotalol ($P < 0.05$). The nonrenal clearance of (−)-sotalol was 17 ± 8% greater than that of (+)-sotalol ($P < 0.05$).

The free fraction of (−)-sotalol in plasma was 1.05 ± 0.03 times greater than that of (+)-sotalol (Table 1) ($P < 0.05$). Unbound oral and unbound renal clearances were similar for the two isomers (Table 1). However, in all patients the unbound renal clearance was greater than that of creatinine clearance (81 ± 38 ml min^{-1}). The unbound nonrenal clearance was 1.18 ± 0.13 times greater for (−)-sotalol compared with the (+)-enantiomer.

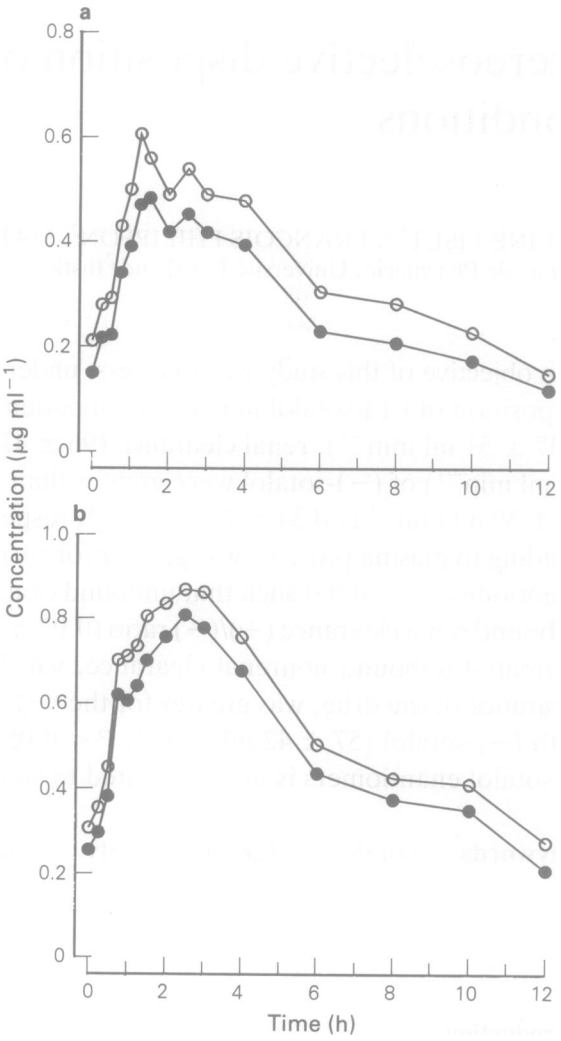

Figure 1 Plasma concentrations of (+)-sotalol (○) and (−)-sotalol (●) in two patients receiving either a 80 mg (a) or a 160 mg (b) 12-hourly oral dose of racemic sotalol·HCl (Sotacor®).

Table 1 Pharmacokinetic parameters of sotalol enantiomers

Pharmacokinetic parameters	*(+)-Sotalol*[b]	*(−)-Sotalol*[b]	*Mean % difference between enantiomers*
AUC(τ) (μg ml^{-1} h) (80 mg)	4.1 ± 0.2	3.6 ± 0.3*	11.2 (5.0, 17.4)
AUC(τ) (μg ml^{-1} h) (160 mg)	14.0 ± 7.6	12.8 ± 6.8*	8.8 (6.3, 11.4)
CL (ml min^{-1})	123 ± 45	137 ± 51*	11.3 (5.1, 17.5)
Ae (mg)	41 ± 19	40 ± 19*	2.3 (0.2, 4.4)
fe (%)	70 ± 15	69 ± 15*	2.3 (0.2, 4.4)
CL_R (ml min^{-1})	89 ± 39	96 ± 42*	8.7 (3.3, 14.1)
CL_{NR} (ml min^{-1})	35 ± 23	41 ± 25*	24.1 (12.9, 35.3)
fu (%)	62 ± 9	65 ± 9*	4.8 (2.0, 7.6)
CLu (ml min^{-1})	202 ± 77	212 ± 74	6.3 (−0.4, 12.9)
CLu_R (ml min^{-1})	145 ± 65	148 ± 60	3.8 (−2.2, 9.8)
CLu_{NR} (ml min^{-1})	57 ± 42	64 ± 42*	18.4 (7.4, 29.4)

[b] Values are reported as mean ± s.d.
[c] Values in parenthesis represent 95% confident intervals.
*$P < 0.05$ *vs* (+)-sotalol.

Discussion

At steady-state the disposition of (±)-sotalol exhibits modest stereoselectivity. Throughout the dosing interval plasma concentrations of (−)-sotalol were about 10% lower than those of (+)-sotalol as a result of slightly greater oral, renal and nonrenal clearances of the (−)-enantiomer. This is in agreement with previously observed differences in the plasma concentrations of sotalol enantiomers [10, 11].

Our results also confirm the previous finding that sotalol is eliminated mainly unchanged by the kidneys [6–8]. The data sugest that sotalol is not excreted solely by glomerular filtration. Thus, in all patients the unbound renal clearances of the sotalol enantiomers exceeded creatinine clearance.

Sotalol is moderately bound (22–40%) to plasma proteins [15]. In all but one of the patients the free fraction of (−)-sotalol was greater than that of (+)-sotalol. Since the degree of difference observed in binding affinities between (+) and (−)-sotalol was of the same order of magnitude as the difference observed in the (+)/(−) plasma concentration ratio, unbound oral and renal clearances were not stereoselective. In contrast, the unbound nonrenal clearance was greater for (−)-sotalol.

In summary, our results indicate that the enantiomers of sotalol exhibit modest stereoselectivity in their plasma protein binding which accounts for a small but significant difference in oral, renal and nonrenal clearance. Since the relative potency of the enantiomers with respect to β-adrenoceptor antagonism (+:−) is 1:50 and there is no material difference in their cardiac potassium channel blocking properties or in their pharmacokinetics, it can be concluded that, following oral administration of racemic sotalol, about ≈45% of the total plasma concentration of racemic sotalol is associated with β-adrenoceptor adrenergic antagonism.

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