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Pharmacokinetic evaluation in man of terbutaline given as separate enantiomers and as the racemate

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1 The pharmacokinetics of the two enantiomers of terbutaline, (+)T and (−)T, and the racemate (±)T, have been evaluated after single intravenous and oral dosage to six healthy volunteers.

2 The mean systemic clearance, CL, was 0.19 and 0.13 l h^{-1} kg^{-1} for (+)T and (−)T, respectively. This difference was statistically significant. The mean clearance of (±)T was 0.20 l h^{-1} kg^{-1}. Volumes of distribution were similar (1.9 l kg^{-1}) after the three intravenous administrations. The differences in CL were reflected in values of the elimination half-life and MRT.

3 The difference in CL of the isomers could be explained by a corresponding difference in their renal clearance, CL_R. Competition for stereoselective active reabsorption in the tubule might explain why (+)T seemed to enhance the CL_R of (−)T when the drug was given as the racemate.

4 Oral bioavailability, calculated from plasma data, of (+)T was 7.5% and that of (−)T was 14.8%. This difference was statistically significant and was mainly due to a difference in absorption of (+)T and (−)T, but also to a difference in their subsequent first-pass metabolism. The bioavailability of (±)T was similar to that of (−)T.

5 (−)T appears to govern the absorption properties of the racemate, while (+)T determines its elimination behaviour. Systemic metabolism of the two enantiomers was similar and, therefore, a greater first-pass metabolism of (+)T would reflect a higher capacity of the gut wall to metabolise this isomer.

Keywords pharmacokinetics terbutaline stereoisomers human

Introduction

Terbutaline (Figure 1) is a β_2-adrenoceptor stimulant, widely used for the treatment of obstructive lung diseases and for the prevention of preterm labour. The pharmacokinetics of racemic terbutaline have been described (Nyberg & Wood, 1984). However, terbutaline, like many other sympathomimetic amines, exists as two enantiomers and only the (−)enantiomer exerts the desired pharmacological effects, while the (+)enantiomer is devoid of effects in the pharmacodynamic test models used (Jeppsson *et al.*, 1984).

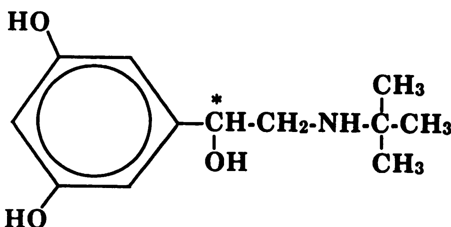

Figure 1 The structure of terbutaline. The asymmetric carbon is indicated by an asterisk. The pK_a-values are: 8.8 for the first phenolic hydroxyl group, 10.1 for the amine hydrogen and 11.2 for the second phenolic hydroxyl.

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Recently, the pharmacokinetics and pharmacodynamics of the separate enantiomers of racemic drugs have aroused a growing interest (Ariëns, 1984). Different methodological approaches have been used in the studies. In some cases (von Bahr *et al.*, 1982; Lee *et al.*, 1985), the racemic drug was given as such and the two enantiomers were separated by chiral chromatography. In other studies (Olanoff *et al.*, 1984; Vogelgesang *et al.*, 1984), a pseudo-racemate was used, one of the enantiomers being labelled with deuterium. Finally, some investigators (Godbillon *et al.*, 1981; Eichelbaum *et al.*, 1984; Wu *et al.*, 1986) administered the enantiomers separately. Interpretation of data obtained using the last two methods rests on the assumption that no chiral inversion takes place *in vivo*.

In the present study, the pharmacokinetics of terbutaline were investigated in healthy volunteers after intravenous and oral administration of the racemate and the two enantiomers.

Methods

Subjects

Six healthy Caucasian volunteers (three men and three women) aged between 23 and 44 (mean 37) years, and weighing from 53 to 81 (mean 64) kg took part in the study. The volunteers were judged to be healthy by a physician after physical examination and laboratory tests. The study was approved by the local Ethics Committee and the volunteers gave written informed consent prior to participation in the study.

Procedure

Racemic terbutaline, (±)T, and the two enantiomers, (+)T and (−)T, were administered as single doses, intravenously and orally, on six different occasions to all six volunteers.

Terbutaline bromide (Wetterlin, 1972) (Batches DIH 1 and DLD 2-1) was used to prepare the (+)T and (−)T formulations. The optical purity of the enantiomers, determined by chiral h.p.l.c., was greater than 99%. The chromatographic separation allowed the measurement of each isomer in amounts $\geqslant$ 0.5% of the other. Terbutaline sulphate (Batches KM 351 and 448) and terbutaline hydrochloride (Batch OP 2) were used to prepare the (±)T formulations.

The subjects refrained from taking any other drug the day before and during the study days. No ingestion of alcoholic drinks was allowed during the study.

The subjects arrived at the clinic in the morning after fasting for 10 h. An indwelling catheter was inserted into an antecubital vein for blood sampling, and the bladder was emptied. Intravenous infusions (0.125 mg of (+)T or (−)T, or 0.250 mg of (±)T) were given manually over 5 min, into an antecubital vein in the arm not used for blood sampling. The syringe was weighed before and after the infusion to calculate the given dose. The oral doses (aqueous solutions; 5 mg) were administered with a total of 100 ml of water. Differences in molecular weight between the salts of terbutaline were not compensated for when determining the doses, but the molar doses actually given were used in data analysis. The doses given were at the lower end of the therapeutic range.

Two hours after the start of each experiment, a standard breakfast was served (Borgström *et al.*, 1981). Blood was sampled at 0, 3, 5, 20, 40 min, 1, 2, 3, 4, 6, 8, 10, 12, and 24 h after the start of the intravenous infusion. After oral administration, the samples at 3, 5, 20, and 40 min were omitted and instead a sample was drawn at 30 min. Over the 6 month duration of the study a total of about 700 ml of blood was withdrawn from each subject. Samples were usually taken from an indwelling catheter except for 24 h samples which were obtained by venepuncture. Urine was collected between 0–8, 8–12, 12–24, 24–28, 28–32, 32–36, 36–48, 48–54, 54–60, and 60–72 h after drug administration. In addition, for each individual and experiment, aliquots of 2% from each timed sample were pooled. Plasma was separated immediately by centrifugation and stored at −20° C until analysis. Urine samples were stored at room temperature until the collection interval was completed. The volume of urine was calculated by dividing the weight by the specific gravity (1.02) and three 10-ml portions were stored at −20° C until analysis.

Terbutaline assay

Intact terbutaline in plasma (free plus protein bound) and urine was measured by gas chromatography-mass spectrometry (GC-MS) with deuterium labelled terbutaline as the internal standard. The procedure of Jacobsson *et al.* (1980) was used to extract terbutaline from urine, whereas the drug was extracted from plasma by a new, more rapid method. The methods are outlined briefly below.

Plasma (2.00 ml) was mixed with 1.00 ml of a solution of ($^2H_6$)terbutaline (20.0 nM) in 10 mM phosphate buffer, pH 7.5. Disposable Bond Elut

C_{18} columns (200 mg) (Analytichem International, Harbor City, CA, USA) were conditioned by rinsing them twice with 3 ml of ethanol, twice with 2 ml of water, and once with 2 ml of 10 mM phosphate buffer, pH 7.5. The plasma samples were transferred to conditioned Bond Elut columns and aspirated through them by means of a vacuum manifold. The columns were rinsed twice with 2 ml of water. Terbutaline and the internal standard were eluted with 1 ml of 50% v/v ethanol in 10 mM ammonium acetate buffer, pH 7.5, into glass vials. Ethanol (1 ml) was added to the eluates and they were evaporated to dryness under nitrogen at 70° C. The recovery of terbutaline from plasma was 90–95%. To ensure that the low plasma concentrations of terbutaline between 8 h and 24 h after administration could be measured, relatively large volumes of plasma (up to 8 ml) had to be extracted. In these cases, the sample was divided into 2 ml portions and each portion was extracted on a Bond Elut column. The extracts from each portion were then combined and evaporated.

Unchanged terbutaline in urine was measured at each sampling interval. In addition, unchanged terbutaline as well as the total amount of intact plus conjugated terbutaline was measured in the 2% pools after deconjugation with aryl sulphatase + β-glucuronidase from Helix pomatia (Sigma type H1) (Nyberg & Kennedy, 1984). Urine, or the mixture after deconjugation, was adjusted to pH 7.45–7.55 with solid sodium phosphate (Na_3PO_4 or NaH_2PO_4) and centrifuged. A portion (50 μl – 4.00 ml) was mixed with 1.00 ml of ($^2H_6$)terbutaline solution (100 nM) in 10 mM phosphate buffer, pH 7.5. Sample extraction was then carried out on an ion exchange column as described previously for plasma (Jacobsson *et al.*, 1980).

The evaporated plasma and urine extracts were silylated and analysed by GC-MS as described previously (Jacobsson *et al.*, 1980). A Finnigan 4500 mass spectrometer (Finnigan MAT, San José, CA, USA) interfaced to a Finnigan INCOS data system was used for the analysis. The limit of quantitation of terbutaline in plasma was 2.0 pmol, i.e. 1.0 nM in a sample volume of 2 ml. At this concentration, the within-day assay variation was 4.7% (CV). The total imprecision between days was 7.2% at a terbutaline concentration of 2.0 nM. The limit of quantitation of terbutaline in urine was 10 pmol, i.e. a concentration of 2.5 nM with a sample volume of 4 ml. The within-day assay variation was 4.2% at this level. The total imprecision between days was 5.6% at a terbutaline concentration in urine of 6.3 nM. The analytical system did not differentiate between the enantiomers. The slopes and the intercepts of the standard curves constructed for the individual enantiomers were identical.

Pharmacokinetic calculations

The actual doses administered were used in all calculations.

The area under the plasma concentration-time (C,t) curve within a specified time interval, $AUC(t_2,t_1)$, was calculated by the linear trapezoidal rule. Extrapolated areas were calculated as $C(t_{last})/k$ where $C(t_{last})$ was the plasma concentration of the last sample collected and k is the elimination rate constant determined from the terminal slope of a plot of log C *vs* t after intravenous administration.

The area under the first moment of the C,t-curve, AUMC, was calculated using the linear trapezoidal rule. The extrapolated AUMC from t_{last} was calculated as $C(t_{last})/k^2 + t_{last}{\cdot}C(t_{last})/k$.

Systemic clearance, CL, was calculated from the intravenous data as dose/AUC.

Renal clearance, CL_R, was calculated as

$$CL_R = Ae(t_2,t_1)/AUC(t_2,t_1)$$

where $Ae(t_2,t_1)$ was the amount of terbutaline excreted in the urine within the time interval t_2–t_1.

The value of CL_R between 8 and 24 h was used to convert the urinary excretion rate values obtained after the last blood sampling point to C,t-values, time-positioned in the middle of the urine collection interval. These calculated C,t-values together with the experimentally determined C,t-values were used in the pharmacokinetic calculations.

Mean residence time, MRT, was calculated from the intravenous experiments as MRT = AUMC/AUC.

The volume of distribution at steady state, V_{ss}, was calculated from the intravenous data as MRT·CL.

The elimination half-life, $t_{1/2}$, was calculated from the intravenous data as $\ln 2/k$.

Bioavailability, F, from plasma drug concentration measurements, was calculated as $AUC_{p.o.}/AUC_{i.v.}$ Calculation of F from plasma data rests upon the assumption that CL was constant between the intravenous and oral studies. For terbutaline most of CL is renal clearance, and CL_R in this study varied with time (see below). However, for each subject and enantiomer or racemate, the non-renal clearance component (CL-CL_R) was fairly constant over time, as discussed below. Thus, a value for

CL(0–24) after oral dosing could then be estimated and the value of this divided by CL after i.v. administration was used to calculate a corrected oral bioavailability.

The total urinary excretion of terbutaline is composed of intact terbutaline and conjugated terbutaline. In addition, there is a deficit, which cannot be accounted for (Hultquist *et al.*, 1984). The conjugated pool after oral administration is made up of presystemically and systemically conjugated terbutaline. The relative sizes of the three pools (intact, conjugated, and deficit), coming from systemically available drug, were assumed to be the same after intravenous and oral administration to the same subject. This assumption formed the basis for the calculation of percent systemically conjugated and deficit after oral administration. Available information indicates that first-pass metabolism of terbutaline occurs by conjugation (mainly in the gut wall). It is not known whether, in addition, some metabolite formed during first-pass might escape measurement, i.e. if there is a deficit also in first-pass. Therefore, the calculated figures for absorbed amount are minimum values and those for degree of first-pass metabolism are maximum. The systemically available (bioavailable) dose after oral administration was calculated from the urinary excretion values as the ratio between the percent of dose excreted as unchanged drug after oral and intravenous administration. Presystemic conjugation was calculated as the difference between the total urinary recoveries of conjugates after the two routes of administration. The absorbed amount was calculated as the sum of: unchanged drug, systemically and presystemically conjugated terbutaline plus deficit. The first-pass metabolism after oral dosing was calculated as the presystemically conjugated amount divided by the absorbed amount.

Expected values after oral administration of racemic terbutaline, for each of the parameters and subjects under study, were calculated from the corresponding values obtained after administration of (+)T and (−)T. For urinary recoveries of unchanged and conjugated terbutaline and deficit, the expected values after (±)T were calculated from the mean of the (+)T- and (−)T-values. For parameters such as CL_R and F, which are calculated from ratios, the expected values were calculated from $(a_1+a_2)/(b_1+b_2)$ where the enantiomer values were a_1/b_1 and a_2/b_2, and a and b represent the primary pharmacokinetic parameters used in the calculations.

The expected values of CL, V_{ss}, $t_{½}$ and MRT for the racemate were calculated by adding the observed drug concentrations of (+)T and (−)T after intravenous dosing. A pharmacokinetic analysis was then made of the sums of the enantiomer concentrations.

Differences between the kinetics of the enantiomers and between observed and predicted pharmacokinetic parameter values for the racemate were evaluated using the two-sided paired Student's *t*-test. The level of significance was set at $P = 0.05$.

Results

The mean plasma drug concentration-time curves after intravenous and oral administration are shown in Figures 2 and 3. Calculated pharmacokinetic parameters and urinary excretion values are listed in Tables 1 and 2.

Plasma drug concentration measurements

Mean systemic clearance values for (+)T and (−)T calculated from data after i.v. administration, (Table 1) were 0.186 and 0.125 l h^{-1} kg^{-1}, respectively ($P = 0.016$). The predicted CL after (±)T was 0.155 l h^{-1} kg^{-1} and the value actually observed was 0.204 l h^{-1} kg^{-1} ($P = 0.027$). The three different administrations, (+)T, (−)T and (±)T, resulted in similar mean values of the volume of distribution (1.9 l kg^{-1}). The mean terminal elimination half-life was higher for (−)T (15.3 h) than for (+)T (12.7 h) and this difference almost reached statistical significance ($P = 0.053$). The predicted (14.2 h) and measured (13.7 h) elimination half-lives after (±)T

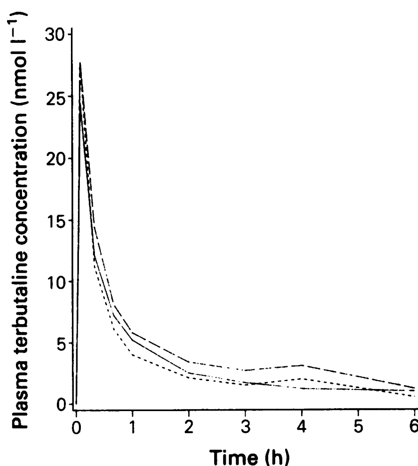

Figure 2 Mean plasma terbutaline concentrations after intravenous administration of (+), (−) or (±) terbutaline (------ (+)T, – – – (−)T and —— (±)T). Values are normalized to a given dose of 0.125 mg.

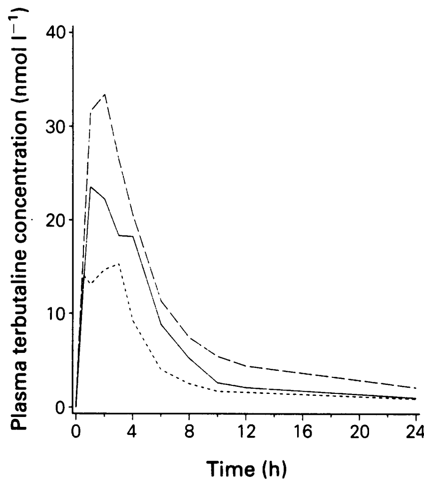

Figure 3 Mean plasma terbutaline concentrations after oral administration of 5 mg of (+), (−) or (±) terbutaline (------ (+)T, - - - (−)T and —— (±)T).

administration were similar. The mean residence times for (+)T and (−)T were 10.7 and 14.4 h, respectively (P = 0.016), and the measured mean residence time after administration of (±)T was 9.05 h while the predicted value was 12.7 h (P = 0.025). The bioavailability of terbutaline was 7.5% for (+)T and 14.8% for (−)T ($P < 0.001$). The predicted bioavailability after (±)T was 11.2% and the measured value was 14.2% (P = 0.008). The pharmacokinetic parameters calculated after administration of racemic terbutaline in this study were similar to those reported by Nyberg (1984).

Excretion in urine

Most of the urinary recovery after i.v. administration of terbutaline consisted of the unchanged drug (about 55% of the dose) (Table 2). When the enantiomers were given separately by the i.v. route, conjugates constituted about 25%

Table 1 Primary and secondary pharmacokinetic parameters calculated from plasma drug concentrations after intravenous and oral administration of (+), (−) or (±)terbutaline to six healthy volunteers

Parameter	*(+)T*		*(−)T*	*(±)T,observed*		*(±)T,predicted*
CL ($l\ h^{-1}\ kg^{-1}$)	0.186 ± 0.044	*	0.125 ± 0.029	0.204 ± 0.034	*	0.155 ± 0.024
CL_R (0–8), i.v. ($l\ h^{-1}\ kg^{-1}$)	0.159 ± 0.034	**	0.088 ± 0.020	0.134 ± 0.015	NS	0.109 ± 0.027
CL_R (0–24), p.o. ($l\ h^{-1}\ kg^{-1}$)	0.148 ± 0.024	***	0.112 ± 0.015	0.148 ± 0.024	NS	0.122 ± 0.017
V_{ss} ($l\ kg^{-1}$)	1.90 ± 0.16	NS	1.76 ± 0.42	1.79 ± 0.13	NS	1.92 ± 0.32
$t_{½}$ (h)	12.7 ± 1.5	NS	15.3 ± 2.0	13.7 ± 1.3	NS	14.2 ± 1.7
MRT (h)	10.7 ± 2.7	*	14.4 ± 2.4	9.05 ± 1.74	*	12.7 ± 2.3
F (%)	7.5 ± 2.1	***	14.8 ± 2.0	14.2 ± 1.5	**	11.2 ± 1.7

Values are mean ± s.d. for six subjects.
$^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$; NS not significant.

Table 2 Parameters calculated from urinary excretion data after intravenous and oral administration of (+), (−) or (±)terbutaline to six healthy volunteers. Values are percent of dose given, except for first-pass

Parameter	*(+)T*		*(−)T*	*(±)T,observed*		*(±)T,predicted*
Intravenous						
Intact T (%)	57.4 ± 8.6	NS	53.1 ± 8.8	56.2 ± 4.2	NS	55.5 ± 9.3
Systemic conj. T (%)	22.9 ± 16.7	NS	26.7 ± 10.3	13.3 ± 7.1	NS	25.2 ± 11.3
Deficit T (%)	19.7 ± 15.4	NS	20.0 ± 7.1	30.6 ± 5.9	*	19.4 ± 9.8
Oral						
Intact T (%)	6.0 ± 1.2	***	10.6 ± 1.7	8.7 ± 1.5	NS	8.4 ± 1.2
Systemic conj. T (%)	2.4 ± 1.5	NS	5.7 ± 3.4	2.1 ± 1.0	NS	4.1 ± 2.0
Deficit T (%)	2.0 ± 1.2	*	3.9 ± 1.5	5.1 ± 0.7	*	3.0 ± 1.0
Presystemic conj.T (%)	39.2 ± 8.3	**	54.6 ± 11.8	57.2 ± 7.1	NS	46.9 ± 9.8
Abs. T (%)	49.6 ± 8.1	***	74.8 ± 11.5	73.0 ± 8.1	NS	62.3 ± 8.8
Bioav.dose (%)	10.4 ± 1.2	**	20.3 ± 3.9	15.8 ± 2.5	NS	15.4 ± 2.0
First-pass (%)	78.4 ± 5.1	*	72.5 ± 6.4	78.3 ± 2.9	NS	75.0 ± 5.6

Values are mean ± s.d. for six subjects.
$^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$; NS not significant.

of the dose. Thus, the deficit was about 20%. These figures are similar to those reported previously for children and adults (Hultquist *et al.*, 1984; Tegnér *et al.*, 1984). However, the proportion of the dose conjugated after intravenous administration of the racemate was smaller than previously found. The deficit was consequently higher with the racemate.

After oral dosing, only 6.0% (Table 2) of the given (+)T dose could be recovered intact in the urine, while after (−)T 10.6% was recovered intact (P = 0.001). Systemically conjugated terbutaline accounted for 2.4 and 5.7% of the given dose after (+)T and (−)T dosing, respectively. Presystemic conjugates represented 39.2 and 54.6% of the dose of (+)T and (−)T (P = 0.002) and the absorbed amounts were 49.6 and 74.8% of the dose after (+)T and (−)T, respectively ($P < 0.001$). A lower fraction of absorbed (+)T, 22%, than of (−)T, 27%, escaped first-pass metabolism, and this difference was statistically significant (P = 0.016). The bioavailable dose calculated from urinary data therefore was twice as high, 20.3%, for (−)T as for (+)T, 10.4% (P = 0.003). The predicted percentages for intact and conjugated terbutaline after oral administration of (±)T were similar to those observed. The difference between the found and expected values for the deficit was due to the high deficit value for (±)T after intravenous dosing (see above), a value which formed the basis for the calculation of deficit after oral administration. The percentage of the dose absorbed, 73.0%, after (±)T dosing in the present study, was substantially higher than previously reported values of 30–60% (Davies, 1984; Hultquist *et al.*, 1984; Tegnér *et al.*, 1984).

Renal clearance, CL_R, was calculated both after intravenous and oral dosing (Table 1), and the general finding was that renal clearance after (−)T was lower than after (+)T administration. Renal clearance of (±)T after intravenous dosing was 0.134 l h^{-1} kg^{-1}, a value similar to that reported by Nyberg (1984).

Discussion

Volume of distribution

Enantiomers have the same physical properties (e.g. lipophilicity) in a non-chiral environment. Thus, if the distribution of terbutaline in the body is a passive process and if no stereoselective tissue binding exists, the volumes of distribution for (+)T and (−)T should be similar. V_{ss} was 1.90 l kg^{-1} for (+)T and 1.76 l kg^{-1} for (−)T. Therefore, the influence of the different molecular configuration of the two enantiomers seems to be of minor importance with respect to distribution.

Systemic clearance

Systemic clearance values calculated after intravenous dosing indicated that (+)T was cleared at a faster rate than (−)T. The difference in clearance between the two enantiomers (0.061 l h^{-1} kg^{-1}) was largely a reflection of the difference in their renal clearance (0.071 l h^{-1} kg^{-1}). This implies that non-renal clearance, by metabolism, was similar for the two enantiomers. The main metabolite of terbutaline is the sulphate conjugate (Tegnér *et al.*, 1984), which is formed in the liver and, after oral administration, predominantly in the gut wall (Nyberg, 1984). The recovery of drug conjugates in the urine after intravenous administration was similar for both enantiomers, 22.9% for (+)T and 26.7% for (−)T. Thus, after intravenous administration both enantiomers seem to be metabolized to the same extent.

The predicted CL after (±)T was calculated on the assumption that (+)T and (−)T do not affect the clearance of one another when given together as the racemate. There was however a significant difference between the observed (0.204 l h^{-1} kg^{-1}) and predicted (0.155 l h^{-1} kg^{-1}) systemic clearance after (±)T. This suggests an interaction between (+)T and (−)T with respect to the process of elimination of terbutaline when the enantiomers are given together. As the CL of (±)T was similar to that of (+)T this finding is consistent with an influence of (+)T on the clearance of (−)T.

Renal clearance

Terbutaline is bound to plasma proteins to the extent of about 20% (Ryrfeldt & Ramsay, 1984). Pilot studies from our laboratory did not show any differences in protein binding between the two enantiomers. The degree of protein binding indicates that the expected glomerular filtration rate of terbutaline should be around 0.085 l h^{-1} kg^{-1}. However, much higher values for CL_R were obtained after (+)T and (±)T administration (Table 1). This implies that, in addition to being filtered, terbutaline must also be actively secreted in the renal tubule. The observed difference in CL_R between (+)T and (−)T could then be due to stereoselective secretion or stereoselective reabsorption. Stereoselective mechanisms in renal clearance have been reported, e.g. for pindolol, (Hsyu & Giacomini, 1985), quinidine/quinine (Notterman

et al., 1986), and for amino acids (Pitts, 1974; Ross & Holohan, 1983).

In addition, it has been shown (Quebbeman & Rennick, 1969) that catecholamines are actively transported in the renal tubule. The presence of a phenyl ring and phenolic hydroxyl groups enhance the efficiency of transport, when compared with amines without these substituents. Terbutaline is a resorcinol derivative with a secondary amino group and, at physiological pH, the drug bears a net positive charge (on the nitrogen atom). Nothing has been reported that singles it out from catechols with respect to the described active renal transport. Rennick (1981) has suggested that the only structural requirement for charged organic cations to be actively transported in the renal tubule is the presence of a charged nitrogen.

Whether or not tubular secretion of terbutaline is stereoselective cannot be elucidated from the present data. The difference between the observed and predicted values for CL_R after administration of racemic terbutaline indicates that (+)T increases the renal elimination of (−)T. A possible explanation for this is that although both enantiomers are actively secreted, they are also actively reabsorbed (*c.f.* Balant *et al.*, 1981), and that (+)T competitively blocks the transport of (−)T.

The higher bioavailability values, when calculated from urinary data, could be due to an intraindividual difference in CL_R after intravenous and oral dosing. For two of the subjects CL_R was followed during the first 8 h in 2 h intervals. In these subjects there was a tendency towards higher CL_R-values after oral dosing when the observed plasma concentrations were maintained at a higher level for a longer period of time.

Elimination half-life and mean residence time

Since V_{ss} values were similar for the two enantiomers, the observed difference in the CL of (+)T and (−)T was reflected in the corresponding elimination half-lives and mean residence times. The predicted and observed MRT-values after (±)T dosing were significantly different, the observed value (9.05 h) being similar to that for (+)T (10.7 h). As described above, this correspondence is due to the similarity in total and renal clearance of (±)T and (+)T.

Bioavailability and absorption

There was a large difference in absorption between (+)T and (−)T, (49.6 *vs* 74.8%) when given separately. When given as the racemate, terbutaline was absorbed to the same extent, 73.0%, as (−)T and to a larger extent than predicted from the (+)T and (−)T values. This observation might be explained by an influence of terbutaline itself on the absorption process in the gut wall. Nakamura *et al.* (1979) have shown that pretreatment of the rat small intestine with isoprenaline enhances the absorption of some poorly absorbable dyes due to an increased membrane permeability. Terbutaline has a chemical structure very similar to isoprenaline and, if the pharmacologically active (−)isomer selectively enhances the membrane permeability of the intestine, this would also affect the absorption of the (+)isomer when they are given together.

There was a small, but significant, difference in first-pass metabolism between the enantiomers (78.4% for (+)T and 72.5% for (−)T). As systemic metabolism of the two enantiomers was similar, the greater first-pass metabolism of (+)T would indicate a higher capacity of the gut wall to metabolize this enantiomer. Since the first-pass metabolism of the racemate equalled that of (+)T, it appears that (+)T governs the elimination behaviour, both first-pass metabolism and renal clearance, of the racemate whereas (−)T determines its absorption.

The combination of a higher absorption and a lower first-pass metabolism of (−)T, as compared with (+)T resulted in a bioavailability of (−)T which was twice as high as that of (+)T. The racemate had about the same bioavailability as (−)T when calculated from plasma data.

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