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THE EFFECT OF END-STAGE RENAL FAILURE AND HAEMODIALYSIS ON THE ELIMINATION KINETICS OF SOTALOL

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1 A single oral dose of sotalol (160 mg) was administered to control subjects with normal renal function and patients with chronic renal failure in the interdialysis period to estimate the elimination kinetics of the drug.

2 Sotalol concentrations in body fluids were measured fluorimetrically using a modified Garrett & Schnelle (1971) method.

3 Mean plasma half-life ($T_{\frac{1}{2}}$) was approximately 5 h in normals, 42 h in patients off-dialysis. During haemodialysis the mean plasma half-time was on the average 7 hours.

4 Cumulative urinary excretion of the drug was considerably lower in the patient group: 9% of the dose in 48 h as opposed to 61% in normals.

5 Comparison of sotalol concentrations in plasma versus ultrafiltrate from the coil kidney indicates that the drug *in vivo* is negligibly bound to plasma proteins in renal patients.

6 The net-lowering effect of a 6 to 7 h haemodialysis on the plasma concentration decay line was by 20%.

7 Post-dialysis plasma concentration data suggest that the rate at which sotalol returns to plasma from body tissues appears to be the rate-controlling factor in the elimination of sotalol by haemodialysis.

Introduction

The β-adrenergic receptor blocking agent sotalol, an alkylsulphonamidophenethanolamine, has been suggested to have several pharmacological features different from other β-adrenoceptor blockers. Unlike propranolol, sotalol has no quinidine-like or local anesthetic action. In addition, it lacks the intrinsic sympathomimetic activity of practolol (Lish, Weikel & Dungan, 1965; Raper & Walf, 1968; Dunlop & Shanks, 1968).

The effectiveness of sotalol in the management of cardiac arrhythmias, angina pectoris and hypertension has been documented (Berman & Gooding, 1974; Gareau, Blitte & Gilbert, 1974; Stroobandt, Emmerechts & De Geest, 1974; Tackels & Lauwers, 1974; Jadraque & Jiménez, 1974; Prichard & Boakes, 1974; Gooding & Berman, 1974; Sundquist, Anttila & Arstila, 1974).

Preliminary biotransformation studies using sotalol or its tritium-labeled hydrochloride salt in various animal species (mouse, dog and man) have shown that the drug is virtually unaffected by metabolic processes and is predominantly excreted in the urine as the unchanged drug. No metabolites have been detected or identified (Lish, Shelanski, LaBudde & Williams, 1967; Shanks, Brown, Carruthers & Kelly, 1974). There are, however, only limited pharmacokinetic data in the literature to define the disposition of sotalol in man. The plasma half-life of this drug has been reported to be close to that of practolol (Sundquist *et al.*, 1974), which has a half-life of approximately 7 to 10 h after a single oral dose (Fitzgerald & Scales, 1968; Schneck, Aoki, Kroetz & Wilson, 1972) and of 13 h after continued use (Bodem & Chidsey, 1972). As sotalol appears to be largely excreted unchanged in the urine, one would expect an accumulation of the drug in the presence of renal function impairment. Therefore, the present study was undertaken to evaluate the effect of end-stage renal insufficiency and haemodialysis on the plasma half-life and elimination of sotalol.

A preliminary account of this work was

presented at the sixth International Congress of Pharmacology, July 20th-25th, 1975, Helsinki, Finland.

Methods

Subjects and clinical protocol

Four male control subjects (mean age 22 years) with normal renal function and six patients with end-stage renal failure (Creatinine clearance <2 ml/min) participated in the study. The clinical characteristics of the patients are summarized in Table 1. Four of these patients were also followed during haemodialysis. Liver function was normal in all subjects. During the study period the subjects received no other drugs. The nature of the study was explained to all subjects participating in the study and all agreed to cooperate. None of the patients had any signs of congested heart failure, heart block, sinus bradycardia (heart rate <60 beats/min) or evidence of bronchial asthma.

A single oral dose of sotalol (160 mg), two tablets of 80 mg each (Mead Johnson Laboratories), was administered to each patient in the fasting state. Heparinized blood samples (5 ml) were drawn prior to sotalol administration, at hourly intervals during the first 8 h, and at 10, 12, 24, 30, 36 and 48 h after dosing. In normal subjects, the blood sampling was only carried out up to 24 h after drug administration. In the four uraemic patients undergoing haemodialysis approximately 48 h after the sotalol dose, hourly blood sampling was repeated during haemodialysis and at 8, 10, 12, 24, 30 and 36 h following the start of the dialysis procedure. All blood samples were immediately centrifuged, the plasma separated and frozen at -20°C until analysis. In both the normal and uraemic subjects two 24 h urine collections were performed during the first 48 h after sotalol administration. Haemodialysis was carried out during 6-7 h using a coil kidney with cuprophane membrane.

To estimate the *in vivo* binding of sotalol to plasma proteins and its dialyzability through the dialysis membrane, ultrafiltration studies were performed at the start and at the end of the haemodialysis. This was carried out by removing the coil from the canister and putting it in a plastic bag perforated at the bottom. A period of at least 20 min was allowed each time to drain the bath water remaining in the coil before three consecutive ultrafiltrate collections, of several minutes each, were obtained. Such ultrafiltrate samples have been found to be free of proteins on electrophoretic examination. Additional blood samples were drawn in the middle of each ultrafiltration study.

Determination of sotalol concentrations

Sotalol concentration was measured fluorimetrically using the modification of Sundquist *et al.* (1974) of the method originally described by Garrett & Schnelle (1971). Standards were prepared from pooled human plasma, ultrafiltrate or urine to which known amounts of sotalol were added, resulting in the following concentrations: 0.1, 0.5, 1.0 and 2.0 μg/ml. Preparation of samples for the fluorimetric method of analysis involved the following steps: biological material (plasma, ultrafiltrate or urine, 1 ml) was first made alkaline by adding 0.1 M borate buffer pH 9 (1.5 ml). The buffered solution was then extracted with a mixture of chloroform/*n*-amylalcohol 3 : 1 (v/v). An aliquot (18 ml) of the organic phase was dried with non-aqueous sodium sulphate (about 1 g). The compound was re-extracted into 1 N sodium hydroxide solution (3 ml), an aliquot of which was

Table 1 Characteristics of patients with chronic renal failure. The aetiology of chronic renal failure in these patients is chronic glomerulonephritis

Patient	Sex	Age (years)	Weight (kg)	Blood urea nitrogen[a] (mg/100 ml)	Serum creatinine[a] (mg/100 ml)
H.W.	M	40	68.5	385	20
V.V.	F	55	53	385	17.5
S.L.	F	32	50	200	13.5
V.Y.	F	43	45	160	14.5
D.V.	F	40	38.5	370	11
M.T.	M	51	81	222	14

[a] The values of blood urea nitrogen and serum creatinine shown in this table are values obtained in the inter-dialysis period.

then measured using a Farrand spectrophotofluorimeter MK-1 at excitation and emission wavelengths of 250 and 350 nm, respectively. All samples were processed in duplicate and measured concentrations are expressed as μg sotalol-HCl/ml. Replicate determinations, using this method, on the biological material to which authentic sotalol was added did not differ by more than 2%. The lower limit of sensitivity of the method is around 0.1 μg/ml.

To check for the possible presence of conjugated derivatives of sotalol (glucuronides and sulphates) in plasma, ultrafiltrate and urine, two hydrolytic procedures were attempted in conjunction with the standard assay method for sotalol determination.

(a) *Enzymatic hydrolysis* An aliquot (1 ml) of the biological material was first adjusted to pH 4.5 with 0.2 M acetate buffer. Hydrolysis, using 5000 Fishman units of β-glucuronidase/aryl-sulphatase from *Helix pomatia* (Calbiochem) was carried out overnight at 38° C. After neutralizing the mixture with NaOH solution and readjusting it to pH 9 with 0.1 M borate buffer, the mixture was extracted according to the procedure described above.

(b) *Hot acid hydrolysis* To an aliquot (1 ml) of either plasma, ultrafiltrate or urine, 6 N HCl (2 ml) was added. The acidified sample was then heated at 100° C in a stoppered glass tube for 30 minutes. After adjusting this mixture to pH 7 with 6 N NaOH, borate buffer was added and extraction was performed as described for unchanged sotalol.

Both groups of subjects were also monitored for possible blood pressure and heart rate lowering effects induced by sotalol. Heart rate and blood pressure, using the standard cuffed sphygmomanometer, were recorded in either the sitting position (normal subjects) or in the supine position (uraemic patients) whenever a blood sample was collected in the first 48 h following sotalol administration.

Data analysis

The apparent biologic half-life ($T_{\frac{1}{2}}$) of sotalol in plasma was estimated using the equation $T_{\frac{1}{2}} = \ln 2/k$ where ln 2 is the natural logarithm of 2. The overall plasma elimination constant k can be calculated from the slope of the linear decline of the semilogarithmic plot of plasma concentrations by the following equation:

$$a = -\frac{k}{2.303},$$

where a represents the calculated slope of the regression line (Goldstein, Aronow & Kalman, 1974). Each regression line was based on at least five points of plasma concentrations. The $T_{\frac{1}{2}}$ values obtained in normal subjects were compared to those found in uraemic patients in the interdialysis period and during haemodialysis. Results are presented as mean ± s.e. mean in the text, figures and tables. The range of values within each pharmacokinetic parameter is listed in Table 2.

Table 2 Pharmacokinetic parameters of sotalol obtained following oral administration of sotalol (160 mg) in normal subjects and patients with end-stage renal insufficiency in the interdialysis period

Group	*Subject*	*Peak plasma concentration (μg/ml)*	*t_{max} (h after administration)*	$T_{\frac{1}{2}}$	*Elimination rate constant (k) (h^{-1})*
Normal	P.J.	1.3	3	4.5	0.154
	B.J.	2.0	2	5.3	0.132
	C.R.	1.2	2	6.0	0.116
	D.G.	1.8	2	5.0	0.139
	Mean ± s.e. mean	1.6 ± 0.2	2.3 ± 0.3	5.2 ± 0.3	0.135 ± 0.008
Renal insufficiency off-dialysis	H.W.	1.8	2	37	0.019
	V.V.	1.9	4	64	0.011
	S.L.	2.0	4	48	0.014
	V.Y.	1.8	2	22	0.032
	D.V.	2.8	2	42	0.017
	M.T.	1.2	4	35	0.020
	Mean ± s.e. mean	1.9 ± 0.2	3 ± 0.5	41.3 ± 4.7	0.019 ± 0.003

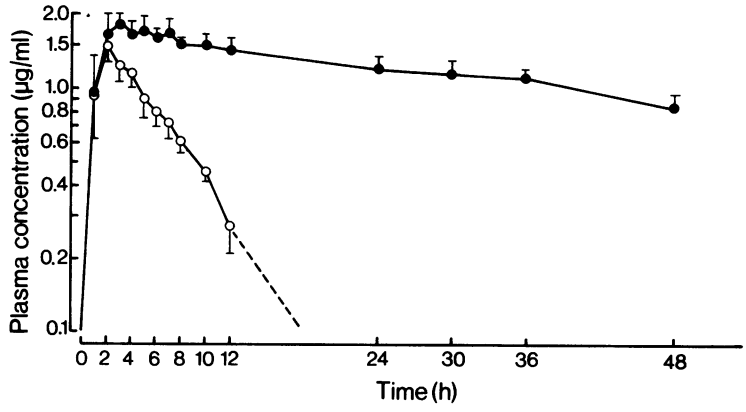

Figure 1 Semilogarithmic plot of mean ± s.e. mean plasma concentration of sotalol in the first two days after the oral administration of 160 mg. The apparent half-life in the control group (○, $n = 4$) was 5.2 ± 0.3 h and 41.3 ± 4.7in the uraemic patients (●, $n = 6$).

Where appropriate, statistical analysis was performed using Student's *t*-test. A P value of 0.05 or less was considered to be statistically significant.

Results

Plasma concentrations

The time course of the mean plasma concentrations after administration of single oral doses of sotalol (160 mg) to control subjects and to the patient group is shown in Figure 1. On a weight basis the mean dose of sotalol administered to the patients with chronic renal failure was 3.04 ± 0.32 mg/kg (range : 1.98 to 4.16 mg/kg) and to the control group 2.56 ± 0.29 mg/kg (range 1.84 to 3.27 mg/kg). There was a rapid increase in the plasma concentration during the first 2 h following the dose to reach maximum concentrations in the control group after 2.3 ± 0.3 h (range 2 to 3 h) and in the patient group after 3 ± 0.5 h (range 2 to 4 h). This was followed by a linear decline in the semilogarithmic plot between 2 h and the end of the sampling period at 24 h in normals, while in patients the decline lasted from 3 to 48 hours. The correlation coefficients of individual regression lines in the linear parts of the slopes were between 0.91 and 0.98 for the control group with a mean value of 0.96 ± 0.015 and between 0.91 and 0.99 for the patient group (0.95 ± 0.016). The mean peak plasma concentration attained in the four control subjects was 1.6 ± 0.2 µg/ml (range : 1.2 to 2.0 µg/ml), while the corresponding value achieved in the patient group was 1.9 ± 0.2 µg/ml (range : 1.2 to 2.8 µg/ml).

Although the average value was approximately 0.3 µg/ml higher in the patient group, the difference in the peak plasma concentrations reached in both groups was statistically not significant. The linear portion of the plasma concentration curve had an apparent mean half-life in normal subjects of 5.2 ± 0.3 h (range : 4.5 to 6 h) as opposed to 41.3 ± 4.7 h (range : 22 to 64 h) in patients with chronic renal failure ($P < 0.01$). The mean value of the overall plasma elimination rate constant k, calculated by multiplying the slopes of the regression lines by 2.303 was 0.135 ± 0.008 h^{-1} for normals and 0.019 ± 0.003 h^{-1} for patients with chronic renal failure.

Plasma sotalol concentrations before, during and after the 6-7 h haemodialysis periods are shown in Figure 2. The mean plasma half-time during haemodialysis, i.e. the time required for the plasma concentration to decrease to half the value at the onset of the dialysis, for the four patients studied was 6.9 ± 1.2 h (range : 3.5 to 9.5 h). This plasma half-time is significantly ($P < 0.05$) shorter than the interdialysis half-life values but is not significantly different from the apparent half-life in normal subjects.

The decrease in the plasma concentrations of sotalol during haemodialysis, in relation to the drug concentrations found in the collected ultrafiltrate samples at the start and at the end of the dialysis was such that the mean plasma concentrations in these two instances, 0.83 ± 0.13 µg/ml and 0.4 ± 0.1 µg/ml respectively, were almost identical to the average values found in the

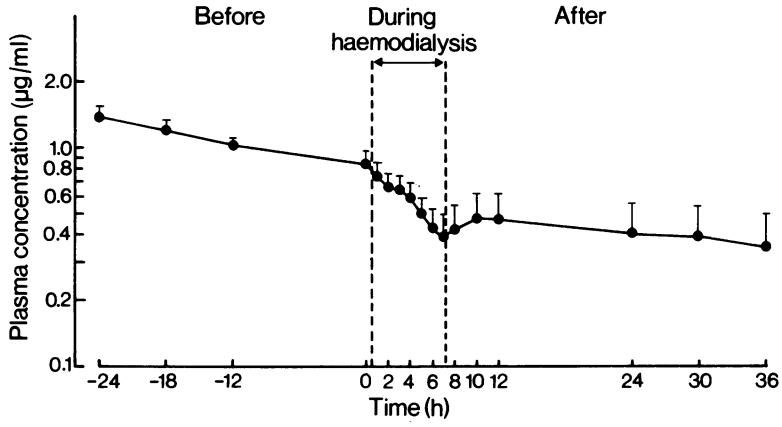

Figure 2 Time course of the mean ± s.e. mean plasma sotalol concentrations in four patients with end-stage renal insufficiency undergoing haemodialysis approximately 48 h after the oral administration of sotalol (160 mg). Note the increase in plasma concentration within 2 h after discontinuing haemodialysis. The plasma half-time during dialysis was 6.9 ± 1.2 hours.

corresponding ultrafiltrate samples, i.e. 0.86 ± 0.2 μg/ml at the start and 0.58 ± 0.16 μg/ml at the end of the haemodialysis.

Urinary excretion

The cumulative urinary excretion of sotalol in both the normal and patient group after the 160 mg oral dose of the drug is shown in Figure 3. The amount of unchanged drug excreted by normals during the first 24 h was on the average 54.3 ± 1.3% of the ingested dose, while the corresponding value in patients with chronic renal failure

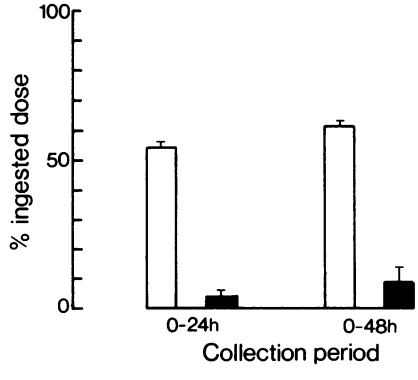

Figure 3 Mean ± s.e. mean cumulative urinary excretion of sotalol in normal subjects (□, $n = 4$) and patients with advanced chronic renal failure (■, $n = 5$) in the first 2 days after the oral administration of 160 mg.

(4.1 ± 2.1%) was markedly lower ($P < 0.05$). The additional amount excreted in the urine after 24 h (up to 48 h) in these two groups was 7.2 ± 0.5% and 4.9 ± 2.6% respectively.

Side effects

No side effects attributable to drug intake were observed in the present study. The mean arterial blood pressure was lowered in both groups by 20 mmHg 2 h following the oral dose of sotalol associated with a maximal lowering effect in the heart rate of 10 beats/min in normals, reached within 2 h, and of about 20 beats/min in patients, achieved 6 h after dosing. These effects subsided gradually and the values regained near normal levels approximately 36 h after the dose.

Discussion

Our results show that after oral administration of sotalol (160 mg), both normal subjects and patients with end-stage renal insufficiency absorb sotalol rapidly to attain peak plasma concentrations within 2-3 h (Figure 1). The slightly higher average peak plasma concentration achieved in the uraemic group (1.9 μg/ml) as compared to normals (1.6 μg/ml) can be explained in the first place by the, on a weight basis, larger dose of sotalol received by the patients, and secondly by impairment of its renal excretion in the presence of renal insufficiency.

After achieving peak plasma concentrations, the

concentrations of sotalol declined rapidly in normal subjects with an apparent mean $T_{\frac{1}{2}}$ of 5 h to reach very low levels 24 h following administration. In patients with chronic renal failure, however, the decline of the plasma concentrations was much slower with a greatly prolonged average $T_{\frac{1}{2}}$ of 41 hours. Concentrations of as high as 1.2 μg/ml and 0.8 μg/ml could still be detected in the plasma 24 and 48 h after ingestion of the drug. This markedly prolonged plasma $T_{\frac{1}{2}}$ value associated with advanced chronic renal failure is a reflection of the severity of the existing impairment in the urinary excretion of sotalol. Moreover, only 9.0 ± 4.7% of the administrated dose was recovered in the 48 h urine of uraemic patients, in contrast to 61.5 ± 1.4% in the same period in normals.

The fate of the remaining fraction (approximately 40% of the ingested dose in normals) has not been determined in the present study. This fraction may be unabsorbed or may theoretically be metabolized. However, as preliminary studies in animals and man showed that the greater part of a dose sotalol was excreted unchanged by the kidney and that no sotalol metabolites could be identified or detected (Lish, *et al.*, 1967; Shanks *et al.*, 1974), it is less likely that this part should represent a metabolized fraction. In support of this interpretation is our finding that hydrolysis of several samples of the biologic material both enzymatically (β-glucuronidase/aryl-sulfatase) and with strong acid treatment (6 N HCl) did not reveal the presence of any conjugated metabolites of sotalol in either plasma, ultrafiltrate or urine.

In four patients in whom the plasma concentrations were further followed hourly during a 6-7 h haemodialysis, there was a considerable reduction in sotalol plasma concentration (Figure 2). The mean plasma half-time during haemodialysis of approximately 7 h is comparable to the mean plasma $T_{\frac{1}{2}}$ found in normals (approximately 5 h) and is significantly lower ($P < 0.05$) than the average value from the patients in the interdialysis period (41 h).

The rapid removal of sotalol from the plasma by haemodialysis is demonstrated by the clearly accelerated fall in the plasma concentration of the drug shown in Figure 2. A mean plasma concentration of 0.8 μg/ml at the start of the haemodialysis declined with 6-7 h to an average value of 0.4 μg/ml by the end of the procedure. Interestingly, the average values for sotalol concentrations in the ultrafiltrate samples in the two instances were nearly identical to the corresponding values found in plasma. Aside from demonstrating dialyzability of the drug, the present finding of similar concentrations of sotalol in both the plasma and ultrafiltrate samples indicates a lack of protein binding of sotalol circulating in the plasma *in vivo*.

The present results further indicate that, although haemodialysis significantly decreased plasma concentrations of sotalol, it may be misleading to judge effectiveness of haemodialysis to remove the drug from the body on the basis of the plasma half-time shortening alone. Plasma concentration data of sotalol in the period after haemodialysis, shown in Figure 2, demonstrate that the plasma concentrations of the drug return to a slightly higher level within 2 h following cessation of the dialysis. This may imply that after haemodialysis, a redistribution of the drug takes place from body tissues back into the plasma, a compartment, which previously has more rapidly been cleared of the drug by haemodialysis. A similar phenomenon has earlier been observed with the β-adrenoceptor blocking agent practolol (Harvengt, Desager, Muschart, Tjandramaga, Verbeeck & Verberckmoes, 1975), and even more clearly for serum digoxin. This latter drug was shown to return to almost pre-dialysis values within 2 h after haemodialysis (Iisalo & Forsström, 1974), indicating that removal of the drug from the body is much less that what might be anticipated by the rate of decline of plasma concentrations during haemodialysis. In the case of sotalol, however, extension of the pre-dialysis decay line of plasma concentrations to the post-dialysis period shows that dialysis has lowered plasma sotalol concentrations by approximately 20%.

In conclusion, orally administered sotalol (160 mg) is absorbed both in normal subjects and in patients with end-stage renal insufficiency to reach peak plasma concentrations within approximately 2 hours. Associated with a significnatly reduced renal excretion of the unchanged drug, the apparent plasma $T_{\frac{1}{2}}$ of sotalol is markedly prolonged in the presence of advanced renal function impairment ($C_{Cr} < 2$ ml/min). During haemodialysis the plasma half-time was comparable to half-life values in normals. In the uraemic patients, unchanged plasma sotalol appears to exist essentially in the free form, unbound to plasma proteins. Equilibrium concentrations between plasma and other distribution compartments do not seem to be readily maintained during haemodialysis. The therapeutic implications of this study are that, in patients with advanced renal insufficiency less than customary doses of sotalol should be administered during maintenance treatment and that a 6-7 h haemodialysis can result in a net reduction of the average sotalol plasma decay line by around 20%.

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