PHARMACOKINETICS OF ATENOLOL IN PATIENTS WITH TERMINAL RENAL FAILURE AND INFLUENCE OF HAEMODIALYSIS

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- 1 The pharmacokinetics of atenolol, after 200 mg orally, were studied in 18 patients with terminal renal insufficiency (creatinine clearance < 5 ml/min), of whom twelve were being treated by chronic dialysis.
- 2 The peak plasma level, 1.59 ± 0.43 mg/l, was reached in 4.7 ± 2.1 h.
- 3 Without dialysis treatment, the apparent plasma half-life of atenolol was greatly increased (73.4 ± 28.8 h). During dialysis, it dropped to 7.5 ± 3.7 h but returned to 51.2 ± 17.3 h after dialysis. The plasma atenolol plot was a rising slope for a few hours after the end of dialysis.
- 4 Renal clearance of atenolol was very low (4.6 ± 1.5 ml/min).
- 5 Plasma clearance during dialysis was 42.6 ± 21.3 ml/min for a mean blood flow-rate of 236 ± 25 ml/min through a cuprophane membrane dialyser.
- 6 These results suggest that dosage should be modified for these patients.

Introduction

Atenolol (ICI 66 082, Tenormin®), 4-(2-hydroxy-3-isopropylaminopropoxy) phenylacetamide, is a cardioselective β -adrenoceptor antagonist (Barrett, Carter, Fitzgerald, Hull & Le Count, 1973; Brown Carruthers, Johnston, Kelly, McAinsh, McDevitt & Shanks, 1976) which is effective in the treatment of hypertension (Hansson, Aberg, Karlberg & Westerlund, 1975; Petrie, Galloway, Webster, Simpson & Lewis, 1975), and is used in hypertensive patients with renal failure; Hayduk, Hepp, Leibau, Maisch & Raff (1977) administered it to patients on chronic haemodialysis.

Since atenolol is a drug almost entirely renally excreted (Fitzgerald, Ruffin, Smedstad, Roberts & McAinsh, 1978; Flouvat, Bazin, Lucsko, Roux & Guedon, 1978), the object of the present work was to study the pharmacokinetics of atenolol in patients

undergoing regular dialysis treatment and the effects of dialysis on these pharmacokinetics.

Methods

All patients were fully informed of the nature of the study and gave formal consent to participate. Eighteen patients (11 men, 7 women) with chronic renal failure (creatinine clearance < 5 ml/min) were studied. Twelve of these were being treated by chronic dialysis two or three times weekly. None had a history of asthma or cardiac failure. No individual had been taking atenolol prior to the study. Ten patients received a diuretic treatment with frusemide (patients 1, 3, 6, 7, 9, 11, 15, 16, 17, 18); six were treated with allopurinol (patients 2, 4, 8, 12, 13, 14);

five with methyldopa or clonidine (patients 1, 6, 11, 17, 18) and seven with aluminium hydroxide (patients 3, 7, 10, 14, 16, 17, 18).

The patients fasted overnight before taking the drug. Atenolol was given orally as single dose of 200 mg (two tablets of 100 mg) with 150 ml water.

In six of the patients, not yet undergoing dialysis treatment, blood samples were taken, on dry heparin (Venoject, Terumo), just before atenolol ingestion and after 2, 4, 6, 10, 18, 24, 36, 48, 60 and 72 h.

In five of these subjects, urine was collected in 24 h fractions during 4 days following oral drug intake.

In patients undergoing regular dialysis treatment (12 subjects), atenolol was administered 6 h before dialysis. This time was chosen because it follows the peak blood level. Blood samples were taken from the arterial side of the vascular access, once at the beginning and then hourly during dialysis. Venous samples were taken exactly 2 min after arterial samples. Blood was collected on heparin.

Six of the twelve dialysis patients were also studied after dialysis. Venous blood samples were collected 2, 4, 6, 16, 24, 36 and 54 h after the end of dialysis.

Dialysis was performed during 5–7 h using a coil kidney with a cuprophane membrane (Gambro 13.5 μ or RP 5) area 1 m². The dialysate composition was 140 mEq/l Na⁺, 100 mEq/l Cl⁻, 1 mEq/l K⁺, 3.5 mEq/l Ca⁺⁺ and 34 mEq/l CH₃COO⁻. Dialysate flow was 0.7 l/min. The blood flow-rate into the dialyser was determined after dialysis by collecting a timed volume of physiological saline and periodically controlled by a 'Doppler effect' flow meter. The average flow-rate was 236 $\pm$ 25 ml/min. Ultrafiltration of fluid from blood during transit through the dialyser was negligible (2 ml/min maximum) and did not influence the venous atenolol concentration.

Plasma and urine atenolol concentrations were estimated using a specific high-pressure liquid chromatographic method (Decourt & Flouvat, 1979).

The elimination of atenolol was assumed to follow a single exponential model as from the tenth hour in patients of both categories outside dialysis sessions. The data were fitted using a non-linear least-squares program on a Hewlett Packard 98 25 computer to obtain an estimate of the first order elimination rate constant (k_e). Apparent plasma half-life ($T_{1/2}$) was calculated by equation

$$T_{1/2} = 0.693/k_e \quad (1)$$

The area under the plasma level vs time curve was calculated from $t=0$ to $t=\infty$:

$$AUC_{0-\infty} = AUC_{0-t} + Ct/k_e \quad (2)$$

AUC_{0-t} , the area under the plasma concentration curve with interval 0 to t (time of the last sample), was calculated on the computer using the Ralston & Wilf method (1967), Ct being the plasma level at this time.

Renal clearance, Cl , was calculated by the equation

$$Cl = U_{0-t}/AUC_{0-t} \quad (3)$$

U_{0-t} is the amount excreted in urine in the interval 0– t (24, 48, 72 h) and AUC_{0-t} is the area under the plasma concentration vs time curve during the same interval.

The clearance during dialysis, Cl_D , was calculated by

$$Cl_D = Q_p [(Ca - Cv)/Ca] \quad (4)$$

given that $Cl_D = Q_p (Ca - Cv)/(Ca - Cd)$ an equation in which the atenolol concentration in the dialysate (Cd) is negligible in comparison to Ca since the dialysate is continuously regenerated. Q_p is the plasma flow-rate into the dialyser, i.e. the measured blood flow-rate, Q_b , corrected by haematocrit, Ht ($Q_p = Q_b (1 - Ht)$). Ca is the arterial plasma level of atenolol and Cv is the venous plasma level (Gibson, Matusik, Nelson & Briggs, 1976; Wolf, Remp, Kiley & Currie, 1951).

Results

In patients not yet dialysed (following the single 200 mg oral dose), the plasma atenolol levels are shown in Figure 1. The mean peak plasma level was 1.59 ± 0.43 mg/l (range 1.04–2.03) and was reached at 4.7 ± 2.1 h. The pharmacokinetic variables (Table 1) show that the mean elimination rate constant of atenolol is 0.0104 ± 0.0035 h⁻¹, which corresponds to a mean half-life of 73.4 ± 28.8 h.

The mean value for the atenolol renal clearance is very low 4.6 ± 1.5 ml/min.

Urinary excretions of atenolol, in the first 4 days, are shown in Table 2. Only 14.9% of the administered dose is found in urine; the range is 4.7 and 21.7%.

In patients undergoing regular dialysis treatment, the effect of haemodialysis on plasma atenolol levels was studied (Figure 2). During dialysis, plasma drug levels decreased and the mean apparent plasma half-life was calculated to be 7.5 ± 3.7 h ($n=12$) (Table 3).

After haemodialysis, the plasma atenolol plot was a rising slope (Figure 2) for a few hours (6 h). From the 6–42 h after the end of dialysis, atenolol plasma concentrations decreased and showed a tendency to return to the slope of the plasma drug decay obtained before dialysis. The mean apparent plasma half-life value was 51.2 ± 17.3 h ($n=6$). This value is significantly higher than during dialysis ($P < 0.001$) (Table 3).

The clearance of atenolol during dialysis, calculated by equation 4, is shown in Table 4. The mean clearance during dialysis for atenolol was 42.6 ± 21.3 ml/min for a mean blood flow-rate into the dialyser of 236 ± 25 ml/min.

Figure 1 Time course of plasma atenolol levels (mean $\pm$ s.d.) following oral administration of atenolol (200 mg) in six patients not yet undergoing dialysis treatment.

Table 1 Pharmacokinetic parameters in patients before the first dialysis treatment

Subjects	Sex	Age (years)	Weight (kg)	C_{max} (mg/l)	k_e (h^{-1})	$T_{1/2}$ (h)	$AUC_{0-\infty}$ ($mg\ l^{-1}\ h$)	Cl_r ($ml\ min^{-1}$)
1	M	45	60	1.04	0.0131	52.9	67.0	5.3
2	M	65	68	1.87	0.0067	103.4	115.9	5.8
3	M	72	49	2.03	0.0090	77.0	218.9	3.0
4	M	57	57	1.33	0.0106	65.4	104.7	3.0
5	M	21	61	2.04	0.0157	44.1	101.5	6.1
6	M	69	50	1.27	0.0071	97.6	167.3	—
Mean		55	57	1.59	0.0104	73.4	129.2	4.6
s.d.		19	7	0.43	0.0035	28.8	54.6	1.5

Table 2 Urinary excretion of atenolol, in patients before the first dialysis (amount excreted mg and percent of dose)

Subjects	0–24 h		0–48 h		0–72 h		0–96 h	
	Amount (mg)	%	Amount (mg)	%	Amount (mg)	%	Amount (mg)	%
1	5.97	2.99	8.97	4.49	13.23	6.62	15.64	7.82
2	12.08	6.04	24.77	12.38	34.98	17.48	43.51	21.75
3	2.14	1.07	12.24	5.62	19.81	9.90	25.92	12.96
4	3.90	1.95	7.29	3.64	9.40	4.70	—	—
5	7.97	3.98	21.53	10.76	30.38	15.19	34.35	17.13
Mean		3.21		7.38		10.78		14.92
s.d.		1.92		3.93		5.46		5.94
n		5		5		5		4

Figure 2 Time course of plasma atenolol levels (mean $\pm$ s.d.) in twelve patients following oral administration of atenolol (200 mg) during dialysis (upper line) and in six patients before and after dialysis (lower line). The arrows indicate the start and end of dialysis.

Table 3 Apparent elimination rate constant and half-life during and after dialysis

Subjects	Sex	Weight (kg)	Age (years)	During dialysis		After dialysis	
				k_e (h^{-1})	$T_{1/2}$ (h)	k_e (h^{-1})	$T_{1/2}$ (h)
7	F	52	29	0.0645	10.7	0.0181	38.3
8	F	44	72	0.1338	5.2	—	—
9	F	48.5	36	0.1817	3.8	0.0145	47.8
10	F	62	50	0.0957	7.2	0.0126	55.0
11	F	47.4	44	0.1120	6.2	0.0083	83.5
12	M	56.3	64	0.0812	8.5	0.0150	46.2
13	F	68.6	62	0.1440	4.8	—	—
14	M	51	54	0.1090	6.4	0.0192	36.1
15	M	57	47	0.1411	4.9	—	—
16	F	48.5	36	0.0997	7.0	—	—
17	M	68	65	0.0389	17.8	—	—
18	M	59	27	0.1151	7.0	—	—
Mean		55.2	49	0.1097	7.5	0.0146	51.2
s.d.		8.0	15	0.0383	3.7	0.0039	17.3
n		12	12	12	12	6	6

Discussion

After atenolol is administered orally to patients with a severely impaired renal function, peak plasma levels are reached in about 4.7 h. These values are observed later than in hypertensive patients or volunteers with a normal renal function: about 3 h (Fitzgerald *et al.*, 1978; Flouvat *et al.*, 1978). This delay in the appearance of plasma peak was observed by Kaye, Kumana, Franklin & Baker (1975) for practolol, by Thompson, Joeles & Foulkes (1972) for propranolol. This delay was not observed for propranolol by either Bianchetti, Graziani, Brancaccio, Morganti, Leonetti, Manfrin, Sega,

Gomeni, Ponticelli & Morselli (1976), or Lowenthal, Briggs, Gibson, Nelson & Cirksena (1974).

It seems likely that a severely impaired renal function has no influence on drug absorption (200 mg), as indicated by the relatively high peak plasma concentrations reached in patients 1.59 ± 0.43 mg/l. These values are in close agreement with those obtained by Fitzgerald *et al.* (1978) in volunteers (1.75 ± 0.85 mg/l) and with our previous studies in hypertensive patients (Flouvat *et al.*, 1978) (1.04 ± 0.19 mg/l).

Nevertheless, the calculated AUC (plasma concentration against time) gave a value of 129.2 ± 54.6 mg h^{-1} , which is higher than that

Table 4 Plasma clearance during dialysis (Cl_D) of atenolol

Subject	Time (h)	Qb (ml/min)	Haematocrit (%)	Ca (mg/l)	Cv (mg/l)	Cl_D (ml/min)
7	1	230	16.9	0.48	0.42	22.4
	2			0.44	0.35	34.2
	3			0.42	0.33	36.7
	4			0.39	0.32	33.7
8	1	240	17	3.17	1.70	92.7
	2			2.64	1.55	81.8
	3			1.83	1.32	55.4
	4			1.82	1.17	71.1
9	1	240	17.5	2.43	1.67	62.3
	2			2.12	1.42	64.9
	3			1.75	1.37	42.0
	4			1.47	1.15	42.9
10	1	250	36	1.37	1.21	17.9
	2			1.21	1.04	22.3
	3			1.08	0.96	17.4
	4			1.11	0.91	28.4
11	1	250	24	1.15	0.68	77.7
	2			1.06	0.63	76.8
	3			0.87	0.55	70.4
	4			0.79	0.54	59.7
12	2	250	28.4	1.08	0.73	57.5
	3			0.94	0.70	45.6
	4			0.85	0.55	63.2
13	1	240	28.6	1.07	0.78	45.8
	2			0.92	0.67	47.7
	3			0.80	0.59	44.6
	4			0.72	0.53	44.9
14	1	240	24	0.73	0.63	24.5
	2	240		0.67	0.62	13.3
	3	170		0.59	0.53	15.0
	4	170		0.56	0.47	19.2
15	1	280	24	4.89	3.87	44.4
	2			4.42	3.80	29.6
	3			4.04	3.15	59.5
16	1	240	17.5	0.71	0.57	36.3
	2			0.62	0.53	29.2
	3			0.60	0.43	76.2
	4			0.56	0.43	45.6
17	1	220	21.1	0.59	0.51	24.5
	2			0.57	0.43	42.0
	3			0.58	0.42	49.4
	4			0.51	0.48	11.0
18	1	220	23	0.98	0.85	22.3
	2			0.84	0.71	26.1
	3			0.73	0.65	19.0
	4			0.71	0.65	13.2
Mean		236				42.6
s.d.		25				21.3
n		15				46

Ca arterial plasma level.

Cv venous plasma level.

Qb measured blood flow rate.

reported in subjects with a normal renal function: 16.02 (Flouvat *et al.*, 1978) and 13.45 mg h⁻¹ (Fitzgerald *et al.*, 1978) for the same dose (200 mg). The mean plasma levels 1.12 ± 0.37 mg/l, observed 24 h after dose administration, account for the increase in AUC (∞). In normal subjects this value is only about 0.2 mg/l (Fitzgerald *et al.*, 1978; Flouvat *et al.*, (1978). Sassard, Pozet, McAinsh, Legheand & Zech (1977) in patients with severe renal insufficiency (inulin clearance 16 ± 4 ml min⁻¹ 1.73 m⁻²) 24 h after a 100 mg oral dose, found plasma levels of about 0.4 mg/l. Their patients maintained a relative whole body clearance of atenolol (38 ± 10 ml min⁻¹ 1.73 m⁻²); in our patients, atenolol renal clearance is very low (4.6 ± 1.5 ml/min) and in good agreement with creatinine clearance. These values can be compared because atenolol is almost entirely renally excreted (Fitzgerald *et al.*, 1978; Flouvat *et al.*, 1978), and predominantly in the unchanged form (Reeves, McAinsh, McIntosh & Winrow, 1978). This is not the case for propranolol, acebutolol and metoprolol which undergo extensive biotransformation.

In this study the percentage of the dose excreted unchanged in 96 h urine was $14.9 \pm 5.9\%$; in our earlier work (Flouvat *et al.*, 1978), we found $54 \pm 14\%$ in hypertensive patients with normal renal functions. Furthermore, this study shows that, in terminal renal insufficiency, the apparent plasma half-life increases and reaches an average value of 73.4 h. This value is similar to those obtained with practolol, a drug which is renally excreted entirely: 58 h (Harvengt, Desager, Muschart, Tjandramaga, Verbeeck & Verberckmoes, 1975) and 78.2 h (Eastwood, Curtis & Smith, 1973).

During haemodialysis, the mean apparent plasma half-life of atenolol (7.5 h) is significantly lower ($P < 0.001$) than the average value after dialysis (51.2 h) and in patients not yet dialysed (73.4 h). The rapid removal of atenolol from plasma by haemodialysis is demonstrated by a clearly accelerated decrease of the plasma concentration of the drug (Figure 2). This is consistent with a satisfactory dialysis of atenolol through the membrane; we found a clearance of atenolol during dialysis of 42.6 ± 21.3 ml/min for a mean blood flow-rate of 236 ± 25

ml/min, which is similar to the clearance of acebutolol during dialysis (42.6 ± 12.7 ml/min) and that of its *N*-acetyl metabolite (40.4 ± 16.3 ml/min) for a blood flow-rate of 238 ± 35 ml/min (Flouvat, Roux, Aubert & Guedon, 1979). This value is a plasma clearance during dialysis, calculated from plasma concentrations (arterial and venous) and plasma flow-rate. The very low plasma protein binding of atenolol (3%) (Barber, Hawksworth, Kitteringham, Petersen, Petrie & Swann, 1978) accounts for the good clearance of this drug during dialysis.

The plasma half lives of practolol (Eastwood *et al.*, 1978; Harvengt *et al.*, 1975), acebutolol and its acetylmethylmetabolite (Flouvat *et al.*, 1979), and sotalol (Tjandramaga, Thomas, Verbeeck, Verbesselt, Verberckmoes & De Schepper, 1976), drugs which all bind poorly to plasma proteins, are similar in both patients undergoing haemodialysis and normal subjects. Except for acebutolol, these half-lives increase greatly between dialyses. The plasma half-life of propranolol, a β -adrenoceptor blocking drug tightly bound to plasma proteins, is similar in patients during and between haemodialyses and in normal subjects (Bianchetti *et al.*, 1976; Flouvat, Decourt & Potaux, 1979; Lowenthal *et al.*, 1974; Thompson *et al.*, 1972). When haemodialysis was discontinued, the plasma atenolol levels rose from 0.69 mg/l to 0.80 mg/l at 6 h after the end of dialysis, then declined with a half-life of 51.2 h. If haemodialysis was effective in decreasing circulating atenolol, the increased plasma levels observed in the post-dialysis period indicate that distribution of atenolol took place from the tissue to the plasma. Harvengt *et al.* (1975) have made the same observation for practolol.

In terminal renal failure, atenolol plasma elimination is greatly decreased. This compound is quite well dialysed, which accounts for considerable drop of plasma half-life during dialysis. It seems necessary to adjust the dose and the frequency of dosing when atenolol is prescribed to renal patients undergoing repeated haemodialysis.

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