Atenolol pharmacokinetics in patients on continuous ambulatory peritoneal dialysis

A. K. SALAHUDEEN¹, R. WILKINSON¹, J. McAINSH² & D. N. BATEMAN³

¹Department of Renal Medicine, Freeman Hospital, Newcastle upon Tyne, ²Safety of Medicines Department, Pharmaceutical Division, Imperial Chemical Industries PLC, Alderley Park, Macclesfield, Cheshire and

³Department of Clinical Pharmacology, Freeman Hospital, Newcastle upon Tyne

The elimination of atenolol (20 mg i.v.) has been studied in seven patients with renal failure on continuous ambulatory peritoneal dialysis (CAPD). Although atenolol was eliminated in the peritoneal fluid, the amount recovered in 24 h was relatively low (1.2 ± 0.15 mg). The calculated urinary ($n = 4$) and peritoneal ($n = 7$) clearance was 0.289 ± 0.058 l/h and 0.152 ± 0.018 l/h respectively. This was considerably less than calculated total body clearance (1.21 ± 0.086 l/h). The kinetics of atenolol in CAPD are worthy of further study.

Keywords atenolol pharmacokinetics continuous ambulatory peritoneal dialysis

Introduction

Continuous ambulatory peritoneal dialysis (CAPD) is an increasingly important therapy for patients with chronic renal failure. The technique involves the continuous presence of a dialysate fluid within the peritoneal cavity throughout the 24 h period apart from short periods during which the fluid is drained and fresh solution re-instilled.

Previous work has shown that significant amounts of water soluble drugs may be eliminated by the peritoneal route during CAPD (Paton *et al.*, 1982a, b). This study was undertaken to investigate the peritoneal clearance of atenolol, at widely used cardioselective β -adrenoceptor blocking agent. In normal volunteers and patients it has been shown that the principal route of excretion of atenolol is by elimination unchanged in the urine (Reeves *et al.*, 1978). Handling of drug in patients on CAPD is therefore of practical as well as theoretical interest.

Methods

Seven patients with end-stage renal failure who had been maintained on CAPD for a mean $\pm$

s.e. mean of 16.1 ± 5.7 months (range 5–48 months) agreed to participate in the study, for which approval from the Newcastle Health Authority Ethics Committee had been obtained. Their mean age was 34.6 ± 6.1 years and two were male. These patients performed four exchanges of dialysate per day using commercially produced (Travenol) dialysis fluid. No patient had had peritonitis in the 4 month period before the study. None of the patients had received therapy with β -adrenoceptor blocking drugs for 1 month prior to the study. The patients were studied in hospital for a 24 h period and all routinely underwent four dialysis exchanges within every 24 h at 09.00 h, 14.00 h, 19.00 h and 00.00 h. In each patient the same strength dialysis fluid was used, 1.36% dextrose.

On the morning of the study day, patients attended hospital and the peritoneal contents were drained. At the same time as the fresh peritoneal dialysate was introduced 20 mg of atenolol was infused by a forearm vein over a period of 30 min. Blood for measurement of plasma atenolol was obtained from a separate indwelling cannula before the dose was administered, at the end of the infusion and at intervals over the 24 h study period in four

patients and 48 h in three patients. In addition the peritoneal dialysate was collected after each of the four 'dwell' periods in the first 24 h after atenolol administration. When there was residual renal function (in five patients) urine was collected for the 24 h period of the study. Blood samples were separated by centrifugation and plasma deep frozen prior to analysis (Scales & Copsey, 1975). The total volume of urine and peritoneal dialysate was measured and aliquots deep frozen. Blood pressure and pulse rate measurements were performed throughout the 24 h period of the study using ECG monitoring and a random zero sphygmomanometer.

Pharmacokinetic analysis was performed using an exponential stripping programme and the plasma concentration was fitted to a bi-exponential equation (Bateman *et al.*, 1981). Clearance was derived by measuring the area under the plasma concentration time curve by the trapezoidal rule and calculating the unknown area using the last concentration time point measured and the derived slope of the elimination curve. Peritoneal and urinary clearances were calculated by measuring the recovery of atenolol in peritoneal dialysate and urine over 24 h and by measuring the area under the plasma concentration time curve (AUC) during this period using the trapezoidal rule.

$$\text{Thus clearance} = \frac{\text{Recovery}}{\text{AUC}}$$

Results

All seven patients completed the study. Two patients did not pass urine during the study period and in one the collection of urine was incomplete. All other samples were obtained as required in the protocol. The total volume of peritoneal dialysate instilled in each patient in

the 24 h period was 8.32 l and the mean recovery was $106.6 \pm 3\%$ of this volume, as is to be expected with a mildly hypertonic dialysate. In these patients the mean elimination half-life of atenolol was $27.6 \pm 2.18 \text{ h}$ (see Table 1, Figure 1). The mean volume of distribution was $46.6 \pm 1.04 \text{ l}$ and total body clearance was $1.21 \pm 0.086 \text{ l/h}$. The renal clearance of creatinine in the five patients who were passing urine was $2.6 \pm 0.4 \text{ ml/min}$ (0.156 l/h). Recovery of unchanged atenolol in the urine in the four patients from whom collections were obtained revealed that approximately 12% of the dose was recovered in the first 24 h ($2.4 \pm 0.66 \text{ mg}$). Recovery of atenolol in the dialysate fluid accounted for just over 6% of the dose in this time period being $1.2 \pm 0.15 \text{ mg}$. The calculated urinary clearance in the four patients was thus $0.289 \pm 0.058 \text{ l/h}$ and the calculated peritoneal clearance was $0.152 \pm$

Figure 1 Plasma atenolol concentration ($\pm$ s.e. mean) in seven patients on CAPD following i.v. administration of atenolol 20 mg. The 48 h concentration curve was measured in only three of the seven patients (see text).

Table 1 Pharmacokinetic parameters for atenolol (20 mg i.v.) in seven patients on CAPD

Patient	$t_{1/2,\lambda_1}$ (h)	$t_{1/2,z}$ (h)	V (l)	CL (l/h)	Urinary creatinine clearance (l/h)	24 h urine recovery (mg)	24 h P.D. recovery (mg)	Peritoneal clearance (l/h)
1	0.45	33.2	49.5	1.03	anuric	—	0.58	0.079
2	0.58	34	45.4	0.93	anuric	—	1.17	0.136
3	0.25	23.9	49.4	1.43	0.12	1.24	1.71	0.221
4	0.43	32.7	47.2	1.00	0.24	4.32	1.50	0.156
5	0.29	23.4	45.21	1.34	0.18	1.92	0.86	0.115
6	1.02	26.7	48.0	1.25	0.12	2.02	1.31	0.179
7	0.08	19.2	41.8	1.50	0.12	incomplete	1.38	0.181
Mean	0.44	27.6	46.6	1.21	0.15	2.4*	1.22	0.152
s.e. mean	0.114	2.18	1.04	0.086	0.032	0.657	0.146	0.018

* $n = 4$

0.018 l/h. Calculated urinary and peritoneal clearances were therefore considerably less than the total body clearance calculated from the plasma concentration data.

Atenolol at the dose given produced significant decrease in supine pulse rate which was maximum at 30 min after the end of the infusion (pulse rate pre-infusion 83.7 ± 2.5 beats/min; 30 min after infusion 62.7 ± 2.0 beats/min; 24 h after infusion 75.1 ± 3.9 beats/min). This data was uncontrolled but the reduction in pulse rate observed is compatible with a biologically significant β -adrenoceptor antagonist effect of atenolol.

Discussion

Atenolol is a water soluble β -adrenoceptor blocking drug which is excreted in normal volunteers with a half-life of approximately 6 h (Mason *et al.*, 1979). The half-life of atenolol has been shown to be prolonged in patients with renal impairment and to correlate inversely with creatinine clearance (McAinsh *et al.*, 1980). Previous studies have shown that patients having creatinine clearance less than 10 ml/min would be expected to have atenolol half-lives of between 35 and 100 h. In contrast in patients with chronic renal failure who undergo haemodialysis the elimination of atenolol during the period of dialysis is more rapid and the measured half-lives approximate to those observed in normal volunteers with normal renal function, suggesting that atenolol is cleared across the dialysis membrane (Flouvat *et al.*, 1980). CAPD is increasingly used in the U.K. as therapy for chronic renal failure but the clearance of atenolol into the peritoneum has not been previously studied. The current data demonstrates that atenolol is eliminated via the peritoneal route, but the quantity of drug excreted in this way is considerably less than that that would be eliminated by haemodialysis.

One criticism of the present study is that plasma urine and peritoneal concentrations of atenolol may not have been followed for a sufficiently long period to obtain accurate measurements of atenolol elimination. In only three patients were plasma concentrations obtained for a period greater than one half-life. The total body clearance estimates for atenolol may therefore be somewhat inaccurate. These data do, however, suggest that in patients on peritoneal dialysis, atenolol elimination rate is greater than would be expected from previous studies in patients with chronic renal failure, although the elimination half-lives were approximately four times greater than those observed in normal volunteers. It is noticeable that the total body plasma clearance and calculated renal and peritoneal clearance do not equate and there are various possible reasons for this. As mentioned previously, the clearance calculations may be inaccurate. Atenolol is, however, eliminated in the bile (Exquis *et al.*, 1982) and excretion by this route could be enhanced. A less likely possibility is an increase in the degree of metabolism. Studies using radio-labelled atenolol in normals and unlabelled atenolol in anephrics suggest, however, that significant metabolism of atenolol does not occur in humans (McAinsh *et al.*, 1980; Reeves *et al.*, 1978).

In conclusion, our studies suggest that in patients on CAPD atenolol is excreted across the peritoneum and that the half-life of the drug is approximately four times that of normal volunteers. The dose of atenolol should therefore be reduced in patients on CAPD and this is to be the subject of a further study. More studies are indicated to assess whether metabolism of atenolol occurs in patients on CAPD, a technique which removes uraemic toxins in the middle molecule range more efficiently than haemodialysis (Bergstrom, 1982).

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