Pharmacokinetics of amoxycillin and clavulanic acid in haemodialysis patients following intravenous administration of Augmentin

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1 Serum concentrations of amoxycillin and clavulanic acid were measured in patients with end-stage renal disease (ESRD) following intravenous administration of 1.2 g Augmentin. Augmentin was administered on a non-dialysis day and 2 h prior to a 4 h dialysis session.

2 The mean values of total serum clearance, mean residence time, volume of distribution at steady state, and terminal half-life for amoxycillin on the non-dialysis day were 14.4 ml min⁻¹, 19.2 h, 14.9 l and 13.6 h, respectively.

3 The mean values of dialysis clearance, total serum clearance during dialysis, fractional drug removal during haemodialysis and half-life during dialysis for amoxycillin were 77.1 ml min⁻¹, 91.5 ml min⁻¹, 0.64 and 2.30 h, respectively.

4 The mean values of total serum clearance, mean residence time, volume of distribution at steady state, and terminal half-life for clavulanic acid on the non-dialysis day were 43.6 ml min⁻¹, 4.4 h, 11.0 l and 3.05 h, respectively.

5 The mean values of dialysis clearance, total serum clearance during dialysis, fractional drug removal during haemodialysis and half-life during dialysis for clavulanic acid were 92.8 ml min⁻¹, 136 ml min⁻¹, 0.65 and 1.19 h, respectively.

6 The total serum clearance on the non-dialysis day, which represents non-renal clearance, was lower than that in normal subjects for both amoxycillin and clavulanic acid. These data would suggest some degree of hepatic impairment in patients with ESRD.

7 The significant removal of both drugs from the body by haemodialysis, means of 47.2 and 34.0% of the dose for amoxycillin and clavulanic acid, respectively, suggests that a dosage supplement would be necessary at the end of the dialysis period.

Keywords amoxycillin clavulanic acid haemodialysis renal failure pharmacokinetics

Introduction

Augmentin (Beecham Pharmaceuticals), an antibiotic formulation of amoxycillin and the β -lactamase inhibitor potassium clavulanate, was introduced into clinical practice as an oral dosage form in 1981 and as an intravenous preparation

in 1985. Clinical experience has shown Augmentin to be effective in a variety of infections including those where the causative organism was bacteriologically resistant to amoxycillin alone, but sensitive in the presence of potassium clavulanate.

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Horber *et al.* (1986) studied the effects of impaired renal function on the kinetics of amoxycillin and clavulanic acid and demonstrated that total serum clearance of both compounds significantly decreased with decreasing renal function. During concomitant drug therapy, the removal of a drug by haemodialysis may be significant enough to require a dosage supplement to ensure adequate therapeutic efficacy. Knowledge of the impact of haemodialysis on the elimination of specific drugs is therefore essential to the rational design of a dosage regimen in patients undergoing haemodialysis. In the present study we have investigated the pharmacokinetics of amoxycillin and clavulanic acid in subjects with end-stage renal disease (ESRD) requiring haemodialysis.

Methods

Subjects

Four male and two female patients with chronic renal failure who required haemodialysis were studied after obtaining their written informed consent. The protocol was approved by the hospital Ethics Committee. The patients were aged between 48 and 65 years and their weight ranged from 46.0 to 79.5 kg. Patients were studied twice: first in an interdialysis period and second during a haemodialysis session. The two investigations were performed 3–8 days apart.

Experimental design

The ESRD patients received a single bolus intravenous injection of 1.2 g Augmentin (1 g amoxycillin, 0.2 g clavulanic acid) on both occasions. The second dose was administered 2 h prior to the start of haemodialysis. Haemodialysis was performed for 4 h using a Belco Unimat haemodialysis machine and a Belco BL 612-M hollow fibre filter with a surface area of 1.2 m² and cuprophane wall thickness of 11 µm.

Venous blood samples were taken from the patients before and at 0.08, 0.25, 0.5, 1, 2, 4, 6, 8, 12 and 24 h after drug administration on the first occasion and predose, 0.08, 0.5, 1 and 8 h on the second occasion. Arterial and venous blood entering and leaving the dialyser were sampled simultaneously at 2, 3, 4, 5 and 6 h after dose. Dialysate was collected at half-hourly intervals throughout the period of dialysis. Serum and dialysate samples were stored at -70°C until analysed.

Assay

Concentrations of amoxycillin and clavulanic acid were estimated using microbiological large

cup-plate assay methods. That for amoxycillin employed *Staphylococcus saprophyticus* NCTC 8340 as assay organism. Clavulanic acid was estimated by its β-lactamase inhibition properties using *Klebsiella pneumoniae* NCTC 11228 in the presence of benzyl penicillin. Neither compound interfered in the assay of the other at the concentrations encountered during this study. The limit of detection was 0.02 µg ml⁻¹ for amoxycillin and 0.08 µg ml⁻¹ for clavulanic acid (Jackson *et al.*, 1980) in both serum and urine. The precision of the assay (CV%) for clavulanic acid in serum and urine was 7.61 and 6.48%, respectively, whereas, the corresponding values for amoxycillin were 6.35 and 5.32%, respectively.

Pharmacokinetics

The area under the serum concentration-time (AUC) and serum concentration × time/time curves (AUMC) were calculated by the logarithmic trapezoidal and a combination of logarithmic and linear trapezoidal methods, respectively. The total serum clearance (CL) was calculated from the ratio of dose to AUC and mean residence time from the ratio of AUMC to AUC. The steady state volume of distribution was calculated using the formula $V_{ss} = D \cdot AUMC / AUC^2$, where D = dose. Dialysis clearance (CL_D) was calculated from the ratio of the amount of drug recovered in the dialysate to the AUC during the same time interval. Fractional drug removal was calculated using the formula proposed by Takki *et al.* (1978):

$$f = CL_D / CL + CL_D \cdot [1 - \exp(-(CL + CL_D)t/V)]$$

where CL is the total serum clearance during dialysis, t is the duration of dialysis and V is the apparent volume of distribution. V is calculated using the formula CL/λ_z where CL and λ_z are the total serum clearance and terminal rate constant, respectively, determined on the non-dialysis day.

In normal subjects $CL = CL_{NR} + CL_R$ therefore, in ESRD patients $CL = CL_{NR}$.

Results

The mean serum concentrations of amoxycillin on the non-dialysis and the dialysis days are presented in Figure 1. The mean serum concentrations of clavulanic acid on the non-dialysis and the dialysis days are presented in Figure 2.

Non-compartmental pharmacokinetic parameters for both amoxycillin and clavulanic acid are presented in Table 1.

Figure 1 Mean serum concentrations of amoxycillin following intravenous administration of Augmentin during an interdialysis period (●) and during haemodialysis (■, □). The open squares represent venous concentrations taken from dialyser outlet. Arrows signify beginning and end of haemodialysis.

Figure 2 Mean serum concentrations of clavulanic acid following intravenous administration of Augmentin during an interdialysis period (●) and during haemodialysis (■, □). The open squares represent venous concentrations taken from dialyser outlet. Arrows signify beginning and end of haemodialysis.

Table 1 Model-independent pharmacokinetic parameters of amoxycillin and clavulanic acid in patients with chronic renal insufficiency following intravenous administration of 1.2 g of Augmentin

Subject	AUC ($\mu\text{g ml}^{-1} \text{ h}$)		MRT (h)		V_{ss} (l)		CL^* (ml min^{-1})		V (l)	
	AM	CA	AM	CA	AM	CA	AM	CA	AM	CA
1	1263	169	20.1	6.99	15.9	8.3	13.2	19.7	17.4	8.1
2	1164	67.5	14.5	3.97	12.5	11.8	14.3	49.4	12.3	11.5
3	1110	65.9	20.0	4.31	18.0	13.1	15.0	50.7	18.8	12.5
4	2774	90.1	33.1	3.53	12.0	7.9	6.0	37.0	11.7	8.1
5	903	59.8	14.6	4.97	16.2	16.6	18.5	55.7	16.4	17.2
6	853	67.7	12.7	2.84	14.9	8.4	19.5	49.2	15.9	8.1
Mean	1345	86.7	19.2	4.44	14.9	11.0	14.4	43.6	15.4	10.9
CV%	53	48	39	32	15	32	33	30	18	33

AM, amoxycillin.

CA, clavulanic acid.

*, these values represent non-renal clearance (CL_{NR}).

Pharmacokinetic parameters calculated from the dialysis data are presented in Table 2. Elimination by haemodialysis is high with CL_D values of 77 ± 9.7 and 92.8 ± 14.2 ml min^{-1} for amoxycillin and clavulanic acid, respectively. A greater proportion of the administered dose of amoxycillin was recovered in the dialysate compared with clavulanic acid, means of 47.2 ± 5.5 and $34.1 \pm 8.1\%$ of the dose, respectively.

Discussion

The pharmacokinetics of amoxycillin and clavulanic acid were significantly altered by ESRD. A comparison of the values obtained in this study with those obtained in normal subjects (Staniforth *et al.*, 1984; Davies *et al.*, 1985; Bolton *et al.*, 1986) is presented in Table 3. The terminal half-lives of amoxycillin and clavulanic acid in patients with chronic renal failure, 13.6 and 3.05 h, respectively, were considerably longer than those reported for normal subjects.

Francke *et al.* (1979) reported a mean terminal half-life for amoxycillin of 13.8 h and Horber *et al.* (1986) reported mean terminal half-lives of 12.6 and 3.81 h for amoxycillin and clavulanic acid, respectively, in ESRD patients. Mean total serum clearance values of amoxycillin and clavulanic acid were considerably lower than values in normal subjects.

In ESRD patients total serum clearance represents non-renal clearance. The values reported here are lower than non-renal clearance values in normal subjects suggesting some degree of hepatic impairment. Horber *et al.* (1986) reported that in patients with impaired renal function, despite the absence of clinical and anamnestic evidence of liver disease, galactose elimination capacity was either decreased or in the low normal range, indicating impaired liver function. The reduction in drug clearance in chronic renal failure was more marked with amoxycillin than with clavulanic acid. This is not unexpected since renal clearance of amoxycillin

Table 2 Pharmacokinetic parameters calculated following administration of Augmentin to patients with chronic renal insufficiency undergoing a four hour haemodialysis session

Subject	Dialysis clearance (ml min^{-1})		Total clearance* during dialysis (ml min^{-1})		Half-life during dialysis (h)		Amount recovered in dialysate (mg)		Fractional drug removal	
	AM	CA	AM	CA	AM	CA	AM	CA	AM	CA
1	72.9	89.6	86.1	109	2.64	1.48	490	92.7	0.59	0.79
2	91.3	89.3	106	139	1.88	0.99	550	69.0	0.75	0.61
3	78.5	78.5	93.5	129	2.48	1.23	431	51.3	0.59	0.56
4	74.4	92.6	80.4	130	1.88	1.01	473	65.6	0.75	0.70
5	82.9	120	101	176	2.88	1.37	496	79.2	0.63	0.62
6	62.7	86.6	82.2	136	2.05	1.08	391	50.6	0.54	0.63
Mean	77.1	92.8	91.5	136	2.30	1.19	472	68.1	0.64	0.65
CV%	13	15	11	16	18	17	12	24	14	13

AM, amoxycillin.

CA, clavulanic acid.

*, $CL_{NR} + CL_D$.

Table 3 Comparison of mean pharmacokinetic parameters of amoxycillin and clavulanic acid in haemodialysis patients with those observed in normal subjects

	$t_{1/2}$ (h)		CL (ml min^{-1})		CL_{NR} (ml min^{-1})		MRT (h)		V_{ss} (l)	
	AM	CA	AM	CA	AM	CA	AM	CA	AM	CA
Normal subjects	1.03	0.91	237	215	53	110	1.53	1.00	21.8	15.7
ESRD	13.6	3.05	14.4*	43.6*	14.4	43.6	19.2	4.44	14.9	11.0
Haemodialysis	2.30	1.19	91.5**	136**	14.4	43.6	NC	NC	NC	NC

*, These values represent CL_{NR} .

**, $CL_{NR} + CL_D$.

NC, not calculated.

AM, amoxycillin.

CA, clavulanic acid.

constitutes a greater proportion of total serum clearance than is the case for clavulanic acid, means of 78 and 49%, respectively (Staniforth *et al.*, 1984; Sjøvall *et al.*, 1985). These reductions in total serum clearance are consistent with the data reported by Horber *et al.* (1986).

The mean residence time values for both amoxycillin and clavulanic acid, 19.2 and 4.44 h, respectively, were increased in the ESRD patients compared with normal subjects, with a much greater effect on amoxycillin compared with clavulanic acid. The mean residence time of clavulanic acid calculated from the data of Jungbluth *et al.* (1986) also showed an increase with decreasing renal function. The V_{ss} of both amoxycillin and clavulanic acid was reduced in ESRD patients compared with normal controls. It has been reported that the volume of distribution of a number of drugs is reduced in renal failure (Fabre & Balant, 1976; Gibaldi, 1977). Using recirculatory moment analysis, Yamaoka *et al.* (1985) modelled the changes in MRT and V_{ss} with decreasing renal function. They demonstrated that with a decrease in the kidney extraction ratio towards zero, V_{ss} tended to decrease, whereas MRT was dramatically increased. This is in agreement with the changes observed in the present study.

The reduction in total serum clearance is much greater than the reduction in the volume of distribution for both amoxycillin and clavulanic acid leading to decreases in their respective elimination rate constants and, hence increases in half-lives. Overall the pharmacokinetic parameters were similar to those quoted previously (Francke *et al.*, 1979; Jackson *et al.*, 1984).

Dialysis led to a significant increase in the elimination rate of amoxycillin and clavulanic acid with dialysis half-lives of 2.30 and 1.19 h, respectively, and mean dialysis clearance values of 77.1 and 92.8 ml min⁻¹, respectively. Francke *et al.* (1979) found a dialysis half-life of 2.84 h for amoxycillin. The equation used for calculation of fractional drug removal is based on clearance and volume of distribution and as such is dose-independent. However, the equation is only applicable to a multicompartment system in which drug dialysis takes place in the log-linear phase. If dialysis is begun immediately or shortly after intravenous drug administration, the percentage

of total-body drug burden removed may actually be increased compared with what would have been removed had dialysis been begun after drug distribution was complete. In the present study, haemodialysis was started during the post-distribution elimination phase of both amoxycillin and clavulanic acid. The fraction of the amount of drug in the body at the start of dialysis removed during the haemodialysis procedure was 0.64 for amoxycillin and 0.65 for clavulanic acid, corresponding to a loss into the dialysate of 47.2 and 34.0% of the dose of amoxycillin and clavulanic acid, respectively. The non-renal clearance of clavulanic acid in the ESRD patients is considerably larger than that of amoxycillin and, therefore, the fraction of the dose remaining in the body at the start of dialysis will be lower for clavulanic acid than for amoxycillin. Hence, there is less of the dose available for removal leading to differences in the percentage of the dose removed by haemodialysis. As the protein binding and volume of distribution, the two major determinants of dialysability, of amoxycillin and clavulanic acid are of the same order, the two drugs would be expected to dialyse to a similar extent. This is confirmed by the close similarity of their fractional drug removal values.

For most drugs administered to ESRD patients, it is considered appropriate to give a loading dose similar to that given in patients without renal disease. This provides a clinically desirable blood concentration which can then be sustained by a dosage regimen adjusted to the degree of renal failure and the extent of a drug's renal excretion. Dosage regimens for Augmentin in ESRD patients have been adequately addressed by Horber *et al.* (1986). At the end of a haemodialysis session, a supplemented maintenance dose should be given to compensate for the drug loss during the dialysis interval. The significant loss of the administered Augmentin during the dialysis session suggests that a dosage supplement may be necessary following the period of dialysis. The size of the supplement would depend on the timing of haemodialysis relative to administration of Augmentin and the duration of haemodialysis. Administering a dose of Augmentin equivalent to the normal maintenance dose in ESRD patients adjusted for the percent of body store lost would be suitable adjustment therapy.

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