Pharmacokinetics of intraperitoneal teicoplanin in patients with chronic renal failure on continuous ambulatory peritoneal dialysis

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The pharmacokinetic profile of teicoplanin, a new glycopeptide antibiotic active against Gram-positive aerobic and anaerobic bacteria, is described in five patients with end-stage renal disease on continuous ambulatory peritoneal dialysis (CAPD). A single 3 mg kg⁻¹ dose was given intraperitoneally in the dialysate during a 6 h dwell time. The drug appeared in the plasma within 15 min at 1.00–0.28 mg l⁻¹ (mean $\pm$ s.d. = 0.70 $\pm$ 0.45) in all five subjects, and peak serum concentrations ranged from 5.53 to 2.80 mg l⁻¹ (4.84 $\pm$ 1.43) at 6 h. Approximately 70% (71 $\pm$ 12) of teicoplanin was absorbed from the peritoneal dialysis fluid during a single 6 h dwell time. The rate constant for peritoneal transfer (λ_d) averaged 0.318 h⁻¹ and the half-life ($t_{1/2}\lambda_d$) was 2.18 h. Further values were serum elimination half-life 114–173 h; total body clearance 263–532 ml h⁻¹; steady-state volume of distribution 68–93 l. This drug profile closely agrees with data reported after intravenous injection in patients on CAPD and suggests that teicoplanin has bidirectional exchange characteristics through the peritoneal membrane, although transfer from the systemic circulation to peritoneal fluid is consistently low. Instillation of teicoplanin in CAPD fluid may be a useful route of administration for treatment of peritonitis and exit site infections in CAPD patients.

Keywords teicoplanin renal failure peritoneal dialysis pharmacokinetics antibiotic

Introduction

Although bacterial peritonitis and exit site infections are two common drawbacks of continuous ambulatory peritoneal dialysis (CAPD) (Rubin *et al.*, 1980; Moncrief & Popovich, 1981), this technique is now widely used for the treatment of end-stage renal disease. The most common offending organisms are Gram-positive bacteria, and penicillins, and cephalosporins, and vancomycin are usually administered.

Teicoplanin is a glycopeptide similar to the vancomycin-ristocetin group, produced by *Actinoplanes teichomyceticus* (Bardone *et al.*, 1978; Parenti *et al.*, 1978). It is a complex containing five closely related molecules. Its antibacterial activity and safety – comparable with that of vancomycin – make this new β -lactamase-resistant drug a logical therapeutic alternative for sensitive human infections.

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Its kinetic profile was previously described by our group after single intravenous doses to male volunteers (Traina & Bonati, 1984), in uraemic patients with varying degrees of renal failure (Bonati *et al.*, 1987), and in patients on CAPD (Traina *et al.*, 1986). Published data are available for volunteers and patients after multiple i.v. doses (Buniva *et al.*, 1986; Domart *et al.*, 1986) and i.m. injection (Buniva & Cavenaghi, 1985). However, the rate and extent of systemic absorption after intraperitoneal administration of teicoplanin have not been investigated. A knowledge of the pharmacokinetics of the drug given by this route in patients undergoing CAPD is important for the proper use of the compound.

Methods

Five patients of both sexes, aged 51–72 years, weighing 51–91 kg, with end-stage renal disease, maintained on CAPD for 13–74 months, agreed to participate in the study, for which approval from the Regional Health Authority Ethics Committee had been obtained. Subjects were clinically stable (four anuric, one with creatinine clearance 2 ml min^{-1}) and presented no evidence of acute or chronic peritonitis. In all patients CAPD was conducted with 1.5 l of 1.5% dextrose standard dialysis solution (Dianel®) four times daily via Tenckhoff catheters. Peritoneal dialysis fluid was instilled into the patients' peritoneal cavity by gravity over 10 min.

Protocol

The patients (admitted to hospital the day before dosing) fasted from midnight until 2 h after drug administration. On the morning of the study day, dialysate was completely drained and examined to ensure that it was clear. Teicoplanin (3 mg kg^{-1}) was added to a fresh bag of dialysate and the solution was instilled into the peritoneal cavity.

Sampling

Blood and dialysate samples were drawn aseptically after 0.25, 0.5, 1, 3, 6 h and at different dwell periods up to 7 days (at the same time of day). After separation of the serum and measurement of dialysate volumes, specimens were immediately frozen in aliquots until analyzed.

Teicoplanin assay

Teicoplanin in serum and dialysate was measured by microbiological assay using a multiresistant

isolate *Bacillus subtilis* ATCC6633 as the test organism (Cavenaghi *et al.*, 1986). Basal measurements were made before the start of the study to exclude any antibacterial activity of previous treatments. The limit of sensitivity for the assay was fixed at 0.05 mg l^{-1} . All assays were performed at the Lepetit Research Centre.

Although microbiological assay does not distinguish individual components of the teicoplanin complex, this is the technique still currently employed. However, unpublished data by our group showed a good correlation between teicoplanin concentrations obtained by microbiological, radiolabelled, and chromatographic assays.

Data analysis

The method of residuals was employed, indicating that dialysate and serum concentrations over time were described by a monoexponential function curve in all five patients. Experimental data were fitted by a nonlinear regression iterative program (Sacchi-Landriani *et al.*, 1983) on a HP-85 desk computer (Hewlett-Packard).

Dialysate and serum kinetic parameters were obtained from standard formulae (Gibaldi & Perrier, 1982): the area under the curve ($\text{AUC} = \text{AUC}(0,t) + C_t/\lambda$) by the trapezoidal rule and extrapolated to time infinity adding the quotient between the last measured concentration and the terminal slope of the log-linear curve, the final elimination rate constant (λ_z) by log-linear least-squares fitting of the last four serum samples (2–7 days), or by fitting of dialysate concentrations over the dwell time (λ_d); the elimination half-life ($t_{1/2,z}$, $t_{1/2,d}$) from $\ln 2$ divided by the terminal slope (λ_z , λ_d) the volume of distribution (V or V_d for the volume of distribution of dialysate) from $V = \text{available dose}/\text{AUC}\lambda_z$ and $V_d = \text{dose}/(\text{AUC}\lambda_d)$; the clearance (CL) from $V\lambda_z$, or $V_d\lambda_d$.

The total amount of teicoplanin absorbed from the peritoneal cavity (A_a) was calculated by subtracting the amount of drug remaining in the peritoneal dialysate drained at the end of the first dwell from the instilled dose.

Statistical analyses used were linear regression, t -test or ANOVA (Rocchetti & Recchia, 1982). Probabilities (P) less than 0.05 were considered statistically significant.

Results

Semilogarithmic plots of the time courses of mean serum and dialysate concentrations are shown in Figure 1, and estimated pharmaco-

Figure 1 Teicoplanin concentration-time curves in dialysate (a) and serum (b) over a 6 h dwell time in five patients. Insert (b) shows log-linear least-squares fit of the four last serum samples for estimation of the final serum elimination rate constant (λ_z). Data points represent means and vertical bars s.d.

kinetic parameters are reported in Table 1. The rate of disappearance of teicoplanin from the dialysate was monoexponential (Figure 1a) and the mean kinetic parameters were: $AUC = 345 \text{ mg l}^{-1} \text{ h}$; $\lambda_d = 0.318 \text{ h}^{-1}$; $t_{1/2d} = 2.18 \text{ h}$; $CL = 454 \text{ ml h}^{-1}$; and $V = 1.6 \text{ l}$, close to the added dialysate volume. Teicoplanin appeared rapidly in serum of all five subjects (Figure 1b), beginning 15 min after intraperitoneal instillation

(average concentration 0.70 mg l^{-1} , s.d. ± 0.45) and achieving a mean peak of $4.84 \pm 1.43 \text{ mg l}^{-1}$ at the end of dwell (6 h). At this time serum concentrations were still rising and, according to the monoexponential profile of drug disappearance from dialysate and appearance in serum, extrapolation of time curve profiles suggested that complete equilibration would take about 10 h, by which time serum and dialysate concentrations would be around 7.34 mg l^{-1} . The calculated transfer of teicoplanin from the peritoneal space was $71 \pm 12\%$. The average half-life for elimination of teicoplanin from the serum after the first dwell period ($t_{1/2\lambda_z}$) was 135 h, ranging from 114 to 173 h in the five patients studied (insert Figure 1b).

The very low teicoplanin levels in dialysate when it was replaced by a fresh solution at the 6 h exchange confirmed the finding after i.v. injection that the drug is poorly removed by CAPD.

On comparing the data reported here with the findings in patients on CAPD given the same dose i.v. (Table 1), except for the available amount of drug (71% vs 100%), and consequently the AUC, no differences were found in pharmacokinetic values. It is worth noting the similarity of the three clearance values (dialysis clearance and total serum clearance after i.p. and i.v. administration).

The percentage of the instilled teicoplanin dose that was bioavailable was also estimated from AUC values multiplied by the elimination rate constants, as suggested by Wagner (1967), to reduce the individual variability of AUC alone. Thus, $(AUC_{i.p.} \lambda_z / AUC_{i.v.} \lambda_z) 100 = (1.87/2.71) 100 = 70\%$.

No adverse effects were reported during or after the study.

Table 1 Pharmacokinetic parameters of teicoplanin in patients with end-stage renal disease undergoing CAPD after 3 mg kg^{-1} dose^a

Parameter ^b		Intraperitoneal instillation		Intravenous injection ^c
		Peritoneal fluid	Serum	Serum
Aa	(% of dose)	—	71 ± 12	100
AUC	($\text{mg l}^{-1} \text{ h}$)	345 ± 77	356 ± 107	609 ± 130
CL	(ml h^{-1})	454 ± 62	421 ± 107	359 ± 97
V	(l)	—	85 ± 33	79 ± 11
V_d	(l)	1.6 ± 0.4	—	—
λ_z	(h^{-1})	—	0.0051 ± 0.0008	0.0047 ± 0.0016
$t_{1/2,z}$	(h)	—	135 ^d	149 ^d
λ_d	(h^{-1})	0.318 ± 0.095	—	—
$t_{1/2,d}$	(h)	2.18 ^d	—	—

^a Data are mean $\pm$ s.d. of five subjects.

^b Symbols for parameters are defined in the Data analysis section.

^c (Traina *et al.*, 1986)

^d Harmonic mean

Discussion

Our results show that teicoplanin given intraperitoneally, was rapidly and effectively absorbed into the blood, and that reverse exchange was negligible. Independent of the route of administration (i.p. or i.v.), in patients on CAPD, teicoplanin is poorly excreted across the peritoneum, its elimination half-life being approximately three times that in normal volunteers (135 and 149 vs 45 h). The dose of teicoplanin must, therefore, be reduced or the interval between doses lengthened in patients on CAPD.

Although particular caution must always be used in extrapolating *in vitro* or *in vivo* experimental findings to clinical indications, it is worth noting that the peritoneal and serum drug concentrations needed to exceed the teicoplanin MIC against all sensitive microorganisms tested, particularly *Staphylococcus aureus* (0.125–1.0 mg l⁻¹) and *Staphylococcus epidermidis* (0.03–2.0 mg l⁻¹) (Dixon *et al.*, 1984), can be achieved by intraperitoneal instillation of the drug. This is of interest for the potential clinical use of this route of administration, since peritonitis and infections of the catheter tunnel are the most frequent complications of CAPD (Rubin *et al.*, 1980; Moncrief & Popovich, 1981). However, further investigation is necessary to determine the exact drug doses to be added during dialysate exchanges and whether acute peritonitis influences the disposition profile of the drug. For other drugs such as gentamicin (Somani *et al.*,

1982) no kinetic change has been found in CAPD patients with and without acute peritonitis.

The reliability of the pharmacokinetic analysis performed is supported by the close estimate of the available fraction of the administered dose (calculated by measuring the recovered dialysate and from AUC ratios), by the similarity of the estimated peritoneal volume of distribution and added dialysate volume, and comparing present findings with those previously reported after the same i.v. dose. It is worth underlining the similarity of the values for dialysis and total serum clearance ($V\lambda_z = V_d\lambda_d$ or $V/V_d = \lambda_d/\lambda_z$) suggesting that since V greatly exceeds V_d , it follows that λ_d greatly exceeds λ_z ; this is consistent with a predominantly one-way transfer of the drug from the peritoneal space into the intravascular compartment. Like other compounds such as gentamicin (Somani *et al.*, 1982), tobramycin (Bunke *et al.*, 1983a), vancomycin (Bunke *et al.*, 1983b), atenolol (Salahundeen *et al.*, 1984), ornidazole (Merdjan *et al.*, 1985) and cefotaxime (Albin *et al.*, 1985), teicoplanin is poorly transferred from the systemic circulation to peritoneal fluid. Intraperitoneal drug instillation in patients on CAPD may be an effective route of administration during peritoneal or exit site infections due to sensitive microorganisms.

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