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An *in vivo* assessment of the tobramycin/ticarcillin interaction in cystic fibrosis patients

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A non-blinded, randomized, cross-over investigation of the pharmacokinetic interaction between tobramycin and ticarcillin was performed in 18 healthy cystic fibrosis (CF) patients with normal renal function. On consecutive mornings the patients were given either tobramycin intravenously (i.v.) over 3–5 min (TOB phase), or tobramycin i.v. over 3–5 min followed immediately by ticarcillin infused i.v. over 20–30 min (TOB+TIC phase). Capillary blood samples were taken 30 min and 330 min after administration of the tobramycin dose in each phase. Tobramycin was measured in serum by fluorescence polarization immunoassay (TDx). There were decreases in serum tobramycin concentrations of 11% at 30 min ($P < 0.001$) and 330 min ($P = 0.012$) when measured in the presence of ticarcillin. No difference in elimination half-life was found (TOB phase 95 ± 13 min, TOB+TIC phase 95 ± 13 min, $P = 0.86$). The volume of distribution and clearance of tobramycin increased by 14% ($P < 0.001$) and 13% ($P < 0.001$), respectively, in the presence of ticarcillin. This interaction appears to be of minor clinical importance but pharmacokinetic studies of tobramycin should exclude concurrent use of ticarcillin.

Keywords tobramycin ticarcillin cystic fibrosis interaction

Introduction

Aminoglycosides and β-lactam penicillins react to form a biologically inactive complex, the formation of which is dependent upon time, temperature, concentration and medium. The rates at which the various aminoglycosides are inactivated by different β-lactam penicillins also vary [1–6]. Tobramycin appears to be the aminoglycoside most prone to inactivation [5]. Evidence suggests that the inactivation mechanism involves nucleophilic attack by a primary amino group on the carbonyl carbon of the penicillin β-lactam ring [7]. This inactivation has been demonstrated *in vitro*, but *in vivo* has been shown to occur conclusively only in patients with renal failure, where high concentrations of both drugs are maintained for prolonged periods [8–10]. No significant interaction was detected between piperacillin and tobramycin in patients with normal renal function [11].

Cystic fibrosis (CF) patients require frequent courses of intravenous (i.v.) antibiotics to treat exacerbations of pulmonary infections owing to the chronic colonization of their lungs with *Pseudomonas aeruginosa*. The first line of treatment at the Adelaide Children's Hospital (ACH) is a combination of i.v. aminoglycoside and anti-pseudomonal penicillin (usually tobramycin and ticarcillin). The aim of this study was to investigate the extent to which tobramycin interacts with ticarcillin under routine conditions in CF patients with normal renal function.

Methods

Patients

The subjects of the study were 18 consenting CF inpatients receiving ticarcillin/tobramycin as i.v. therapy for exacerbations of pulmonary infections. The mean age was 14 years (range 4–21 years) and the mean weight was 45 kg (range 16–66 kg). Renal and hepatic function were normal in all patients. Approval for the study was obtained from the hospital Ethics Committee.

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Drug administration

Tobramycin was administered i.v. over 3–5 min, followed immediately by a 5 ml normal saline flush, then a 20–30 min ticarcillin infusion in accordance with normal hospital policy. This dosage regimen was repeated at 8 hourly intervals. After at least six doses had been administered, on consecutive mornings either tobramycin and ticarcillin were administered as described above (TOB+TIC phase) or the ticarcillin dose was omitted and tobramycin was administered alone (TOB phase). Each phase was studied in each patient on consecutive days in a randomized manner. The mean (± s.d.) doses were 2.71 ± 0.38 mg kg^{-1} for tobramycin and 84 ± 14 mg kg^{-1} for ticarcillin. The ticarcillin infusion was commenced 3.5 ± 2.4 min after completion of the tobramycin dose (range 0–9 min), and ran for 26.6 ± 4.3 min (range 21–40 min).

Sample collection

Fingerprick blood samples were collected at nominal times of 0.5 and 5.5 h after administration of the tobramycin dose in each phase. In the TOB phase, blood for the 0.5 h and 5.5 h samples was taken 31.4 ± 2.1 min (range 30–38 min) and 328.7 ± 15.7 min (range 300–362 min) after completion of the tobramycin dose, while for the TOB±TIC phase the corresponding times were 32.3 ± 2.5 min (range 30–37 min) and 339.7 ± 38.0 min (range 293–464 min). Serum was harvested and, if not assayed immediately, was stored at −70° C until analysis. After blood collection, serum samples were either assayed or frozen within 41 ± 21 min for the TOB phase (range 15–128 min) and 42 ± 18 min for the TOB+TIC phase (range 10–105 min).

Serum tobramycin analysis

Serum tobramycin concentration was measured by fluorescence polarization immunoassay using an automated analyser (TDx model no 9520, Abbott, Irving). Between-run coefficients of variation of the assay ranged from 2.9–4.3% (mean 3.4%); within-run values were 0.6–8.6% (mean 2.8%).

Pharmacokinetic analysis

Pharmacokinetic parameters were calculated using the measured serum drug concentrations and assuming monoexponential disposition [12].

Statistical analysis

A two-sided paired Student's *t*-test was used for comparison of sample means at the 5% level.

In vitro *analysis*

Plasma spiked with 27 mg l^{-1} of tobramycin and 250 mg l^{-1} of ticarcillin was maintained at 37° C and samples were assayed in duplicate for tobramycin at 0, 10, and 30 min after mixing. The concentration of tobramycin used was similar to a mean concentration of 19 mg l^{-1} measured in three patients at 5–6.5 min after an i.v. dose of 2.5 mg kg^{-1} given over 3 min. A control plasma containing tobramycin only was incubated in the same way.

Results

Mean serum tobramycin concentrations in the TOB phase and the TOB+TIC phase and the corresponding pharmacokinetic parameters are shown in Table 1. Administration of ticarcillin was associated with decreases in tobramycin concentrations at 30 min ($P < 0.001$) and 330 min ($P = 0.012$). There was no difference in tobramycin half-life between the TOB phase and the TOB+TIC phase ($P = 0.86$). In the TOB+TIC phase, there were increases in the volume of distribution (V) and clearance (CL) of 14% ($P < 0.001$) and 13% ($P < 0.001$), respectively.

Assay of *in vitro* incubates indicated mean tobramycin concentrations of 27.1, 26.1 and 26.7 mg l^{-1} (tobramycin alone) and 27.1, 26.7 and 26.4 mg l^{-1} (tobramycin/ticarcillin) at 0, 10 and 30 min, respectively.

Discussion

Enzyme multiplied immunoassay (EMIT) has been shown to generate falsely high aminoglycoside concentrations in the presence of β-lactam penicillins because of an inability to distinguish between the aminoglycoside/penicillin complex and free aminoglycoside [6, 13–16]. In contrast, radioimmunoassay and TDx assays have been shown to be reliable measures of tobramycin in the presence of β-lactam penicillins [13].

Aminoglycoside inactivation can still occur *in vitro* after blood has been taken. Only storage at −70° C will prevent this [3, 4], hence care was taken either to assay the samples immediately, or store them at −70°C and assay immediately upon thawing. There was no correlation between the percent decrease in tobramycin concentration in the TOB+TIC phase relative to that in the TOB phase and the time taken to assay the sample ($r^2 = 0.029$).

The values of parameters describing the kinetics of tobramycin were consistent with those reported by others using more time points [17–20]. Both V and CL were increased in the presence of ticarcillin and it is clear that pharmacokinetic studies of tobramycin should avoid concurrent use of penicillins.

The data suggest that the antibacterial effect of tobramycin will be compromised only marginally if the β-lactam is administered with an aminoglycoside as described in this study.

An average ticarcillin dose of 85 mg kg^{-1} would be anticipated to be associated with peak drug concentrations of 250–400 mg l^{-1} [21], although the *in vitro* study indicated that such concentrations of ticarcillin together with high transient concentrations of tobramycin during the brief period of the distribution

Table 1 Mean parameters describing the disposition of tobramycin in the presence (TOB) and absence (TOB+TIC) of ticarcillin (n = 18)

Parameter	*TOB phase (mean ± s.d.)*	*TOB+TIC phase (mean ± s.d.)*	*95% CI (difference between phases)*	P
$C(30)$ (mg l^{-1})	10.2 ± 1.2	9.0 ± 1.0	0.75–1.68	<0.001
$C(330)$ (mg l^{-1})	1.2 ± 0.4	1.0 ± 0.4	0.03–0.23	0.012
$t_{1/2}$ (min)	95 ± 13	95 ± 13	−4.1–2.3	0.86
V (l kg^{-1})	0.22 ± 0.03	0.25 ± 0.05	0.015–0.047	<0.001
CL (ml^{-1} min^{-1} kg^{-1})	1.64 ± 0.38	1.86 ± 0.41	0.133–0.303	<0.001

$C(30)$, serum tobramycin concentration at 30 min.
$C(330)$, serum tobramycin concentration at 330 min.

phase of tobramycin would not explain the decrease in serum tobramycin concentration seen *in vivo*.

In contrast to our findings, Lau *et al.* [11] found no significant change in serum tobramycin concentrations in the presence of piperacillin in patients with normal renal function. However, they used lower doses of tobramycin (< 1.5 mg kg^{-1}) and β-lactam penicillin (59 mg kg^{-1}), a smaller study population (n = 10), and piperacillin is known to be less reactive with tobramycin than ticarcillin [22].

In conclusion the results of the present study indicate that serum tobramycin concentrations are decreased by about 11% when given as a 3–5 min i.v. infusion immediately preceding a 20–30 min ticarcillin infusion. Although this is unlikely to be of clinical significance, pharmacokinetic studies of tobramycin should exclude the concurrent use of penicillins.

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