The pharmacokinetics and toxicity of once-daily tobramycin therapy in children with cystic fibrosis

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Introduction

Patients with cystic fibrosis (CF) are often treated with aminoglycoside antibiotics during an infective exacerbation due to Pseudomonas aeruginosa. In many units tobramycin is chosen because of its perceived greater anti-pseudomonal activity compared with the other agents. While the efficacy of once-daily administration of aminoglycosides has not been formally evaluated in CF, it is recognized that extending the dosing interval of tobramycin may reduce toxicity in these patients, and that the activity of tobramycin against P. aeruginosa is related to the peak antibiotic concentration. Patients with CF could benefit from the potential logistical advantages of once-daily therapy. However, the optimal dose is not known, since patients with CF have altered aminoglycoside handling, notably a high total drug clearance, compared with non-CF subjects. Aminoglycoside doses higher than the 4–7 mg/kg per day usually given in once-daily regimens may be required.

To date there have been only a few studies of once-daily aminoglycoside administration in adults with CF, but only one in children, using amikacin. This study was designed to evaluate the pharmacokinetics and toxicity of once-daily intravenous tobramycin treatment in children with CF at doses of 8 mg/kg and 15 mg/kg. The higher dose was chosen to correspond to the maximum tobramycin dose previously used in adult studies.

Materials and methods

Seven children with CF (age 10–14 years, four females and three males) requiring in-patient treatment of pulmonary infection with P. aeruginosa were recruited. Informed verbal consent from the patient and written parental consent were obtained before entry into the study, which was approved by the United Bristol Healthcare Trust Ethics Committee.

All patients received intravenous thrice-daily cefazidime 50 mg/kg and once-daily tobramycin for 10–14 days. On the first day of the study, subjects were given a tobramycin dose of 8 mg/kg by infusion over 5 min. From the second day they were given tobramycin 15 mg/kg. Blood samples were taken for tobramycin assay on the first and second day immediately pre-dose, and at 0.25, 0.5, 1, 3, 8, 12 and 24 h post-dose. Serum tobramycin concentrations were measured by polarization fluoroimmunoassay (TDx, Abbott Laboratories Ltd, Maidenhead, UK). The serum half-life (mean 2.3 h) was unchanged at the two doses, as were the total clearance and volume of distribution. All patients responded well to therapy. No nephrotoxicity occurred, but one patient showed transient ototoxicity.

The pharmacokinetics and toxicity of once-daily intravenous tobramycin were studied prospectively in seven children with cystic fibrosis. Mean 1 h post-dose concentrations of 21.9 mg/L (s.d. 3.0) and 40.2 mg/L (s.d. 8.1) were achieved following tobramycin doses of 8 mg/kg and 15 mg/kg, respectively. The half-life (mean 2.3 h) was unchanged at the two doses, as were the total clearance and volume of distribution. All patients responded well to therapy. No nephrotoxicity occurred, but one patient showed transient ototoxicity.
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The volume of distribution \( V_d \) and total clearance \( Cl \) were derived from the following formulae:

\[
V_d = \frac{\text{dose}}{C_0} \quad \text{and} \quad Cl = \frac{\text{dose}}{AUC}
\]

Nephrotoxicity was monitored using daily serum creatinine measurement and defined as a rise in creatinine of \( \geq 20\% \) of the admission value. Audiometry was performed before and at the end of the treatment period. Five patients were tested at frequencies of 500–10,000 Hz (Kamplex A C5 audiometer; PC Werth Ltd, London, U K) and two at frequencies of 500–8000 Hz (Kamplex A C4 audiometer).

Results

All seven patients received both the 8 mg/kg and the 15 mg/kg doses of tobramycin (actual doses 205–420 and 385–780 mg, respectively). The results are summarized in the Figure and Table. The mean 1 h post-dose tobramycin concentration following the 8 mg/kg dose was 21.9 mg/L (S.D. 3.0, range 16.7–25.9 mg/L) and following the 15 mg/kg dose 40.2 mg/L (S.D. 8.1, range 32.3–56.6 mg/L). In all children at both doses, the serum concentration fell to \(<2\) mg/L by 12 h post-dose, and \(<1\) mg/L by 24 h. The \( t_{1/2} \) was similar within individual patients at the two different doses, and also between patients, as were the volume of distribution and the total clearance. All 24 h trough concentrations measured during the remainder of the treatment period were \(<1\) mg/L.

No nephrotoxicity occurred in any of the subjects. However, one patient complained of transient dizziness, lasting 10 min, immediately after the 15 mg/kg dose. This patient showed a reduction in hearing threshold of 30 dB in the left ear and 25 dB in the right ear at 10,000 Hz at the end of his 10 day course, which was continued at the lower dose of 8 mg/kg. Hearing at other frequencies was unchanged. When reassessed 1 week later, the thresholds had returned to normal. No other side effects were observed in any of the subjects. All patients made a good clinical response to their antibiotic treatment.

Discussion

This study demonstrates that the pharmacokinetics of once-daily tobramycin at doses of 8 and 15 mg/kg in children with CF are similar to those reported in CF adults. The tobramycin \( t_{1/2} \) in children with CF appears to be similar to that of both tobramycin and netilmicin in CF adults, and the mean 1 h post-dose concentration in this study following tobramycin 8 mg/kg was similar to that in adults treated with netilmicin at the same dose. The \( C_0 \) and \( AUC_{0-24} \) increased in a linear fashion with increasing dose, and the total clearance and volume of distribution were similar in each patient at the two doses. A nontoxic accumulation was not observed.

The optimal dose for a once-daily aminoglycoside regimen has not been established for patients with CF. For non-CF adults, Begg et al. have suggested an approach in which the dose is adjusted by comparison of the \( AUC_{0-24} \) with ideal target values. The target values were derived from the \( AUC_{0-24} \) that would be expected in a multiple daily dose aminoglycoside regimen giving a peak serum concentration of 10 mg/L and a trough of \(<2\) mg/L. Patients with CF present a problem for calculating the dose in a once-daily regimen, as they are known to require high doses of aminoglycosides because of their rapid total drug clearance. The mean \( AUC_{0-24} \) values of 84.6 mg.h/L and 159.9 mg.h/L for the, respectively, 8 and 15 mg/kg tobramycin doses in this study are low compared with the ideal target values calculated by Begg et al. of 86 mg.h/L for a 6 mg/kg dose and 101 mg.h/L for a 7 mg/kg dose.
Once daily tobramycin in CF children

dose. By extrapolation from these figures, a once-daily dose of approximately 10 mg/kg would be required in a child with CF to achieve the same $\text{AUC}_{0-24}$ as a non-CF adult using a dose of 7 mg/kg.

Nephrotoxicity was not observed in our study, consistent with the experience of once-daily regimens in an adult CF patient.\textsuperscript{4,5} However, Smith et al.\textsuperscript{6} reported nephrotoxicity in one out of eight CF patients using netilmicin. Our patient who experienced transient dizziness after 15 mg/kg tobramycin had a 15 min post-dose serum concentration of 61.2 mg/L. The timing of his symptoms suggests that they were probably related to this temporarily high level. The reduction in high tone hearing threshold he experienced was not detectable clinically at the time, and his hearing reverted to normal upon stopping the antibiotic. Transient dizziness was also reported in two adult patients using tobramycin at a dose of 15 mg/kg,\textsuperscript{6} although their audiometry was normal. These transient occurrences may be related to the speed of administration as well as the high dose. In future studies we would envisage infusing high doses of aminoglycosides over a longer period. Immediate and reversible effects of high serum concentrations of tobramycin on human cochlear function have been recognized for some time.\textsuperscript{9}

The potential advantages offered by once-daily aminoglycoside administration in CF warrant further clinical studies of once daily versus multiple-daily dosing. We would suggest that a dose of 10 mg/kg per day be used.

References

7. Canis, F., Husson, M. O., Turk, D., Vic, P., Launay, V., Ategbo, S. \textit{et al.} (1997). Pharmacokinetics and bronchial diffusion of single dose. By extrapolation from these figures, a once-daily dose of approximately 10 mg/kg would be required in a child with CF to achieve the same $\text{AUC}_{0-24}$ as a non-CF adult using a dose of 7 mg/kg.

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Received 4 November 1997; returned 2 December 1997; revised 23 December 1997; accepted 23 January 1998