Pharmacokinetic modelling of a once-daily dosing regimen for intravenous tobramycin in paediatric cystic fibrosis patients

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Received 8 December 2006; returned 10 January 2007; revised 25 February 2007; accepted 5 March 2007

Objectives: This study was designed to determine an optimal dose range for the once-daily dosing (ODD) of tobramycin in the treatment of an acute pulmonary exacerbation in paediatric cystic fibrosis (CF) patients. In addition, we aimed to assess whether certain patient characteristics affect tobramycin pharmacokinetics and, therefore, dosing.

Methods: Patient characteristics and pharmacokinetic parameters of patients receiving tobramycin three times daily from 1 January 1992 to 31 October 2005 were analysed using univariate analysis and multiple linear regression to determine statistically significant relationships and to derive dosing models. The binary partitioning method was used to derive critical values to determine stratification within the chosen dosing model.

Results: Using multiple linear regression, age and sex were significantly associated with the volume of distribution divided by the body weight (\(V/kg\)). By the binary partitioning method, the critical value for age was 13.75 years.

Conclusions: Age and sex were used to derive an ODD regimen for tobramycin in paediatric CF. Using a target peak concentration range of 25–35 mg/L, the initial dose for female CF patients at least 14 years of age was calculated to be 7 mg/kg/day given intravenously as a single daily dose. All other CF patients would receive an initial dose of 9 mg/kg/day given intravenously as a single daily dose. These dosing guidelines will require prospective evaluation for safety and efficacy.

Keywords: aminoglycosides, antibiotic usage, Pseudomonas aeruginosa

Introduction

Cystic fibrosis (CF) is characterized by the depletion of the airway surface liquid, leading to a breakdown of mucociliary clearance (CL) and accumulation of mucus in the lower respiratory tract.1 The presence of inspissated secretions in the lungs creates ideal conditions for the growth of bacteria and other pathogens.1 The resultant accumulation initiates a ‘vicious cycle’ involving perpetual infections by various organisms and inflammation that leads to bronchiectasis and ultimately lung tissue destruction.1 CF patients admitted to hospital for treatment of pulmonary exacerbations frequently have sputum cultures positive for Pseudomonas aeruginosa. As a result, empirical therapy for a CF exacerbation typically involves combination antipseudomonal therapy (e.g. aminoglycoside plus an antipseudomonal \(\beta\)-lactam). At The Hospital for Sick Children, ceftazidime (200 mg/kg/day intravenously divided four times daily) and tobramycin (10 mg/kg/day intravenously divided three times daily) are routinely used as first-line antibiotic therapy.2

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The initial dose of tobramycin used in CF patients is higher than that for other indications because CF patients are believed to have higher volumes of distribution (V) and CLs of antimicrobial agents. It is thought that the higher V is due to a lower proportion of body fat or, conversely, a higher proportion of lean body mass. The mechanism for increased aminoglycoside CL in CF has not been clearly defined, but may involve extrarenal excretion.

The once-daily dosing (ODD) of aminoglycosides has potential benefits that include: (i) high peak concentrations (C\(_{\text{max}}\)); (ii) reduced risk of nephrotoxicity and ototoxicity; (iii) reduced development of adaptive resistance; and (iv) reduced labour, costs and time. These factors, among others, favour the idea of administering aminoglycosides as a single daily dose for the treatment of a CF exacerbation. The ODD of aminoglycosides has been well described in the adult population, but paediatric data are limited. Although there have been previous studies examining the ODD of aminoglycosides in paediatric CF patients, the pharmacokinetic techniques employed have not always been ideal. Specifically, serum drug concentrations were not always determined in a manner suitable for the monitoring of ODD aminoglycosides, and dose adjustments were often performed empirically without appropriate pharmacokinetic calculations.

The primary objective of the present study was to determine an optimal dose range for intravenous (iv) tobramycin given as a single daily dose for the treatment of acute pulmonary exacerbations in paediatric CF patients. The secondary objective of this study was to determine whether certain patient characteristics (i.e. age, sex, nutritional status and pancreatic status) affect the pharmacokinetics of tobramycin and hence dosing in paediatric CF patients.

### Patients and methods

#### Patients

Patients under the age of 18 years admitted to The Hospital for Sick Children for treatment of a CF exacerbation between 1 January 1992 and 31 October 2005 were included in the study; 1 January 1992 was chosen as the earliest date of admission for which patients would be eligible for inclusion as the pharmaceutical care model of pharmacy practice was adopted at The Hospital for Sick Children at this time. The pharmaceutical care model of pharmacy practice is a comprehensive practice model wherein clinical pharmacists take responsibility for the optimization of drug therapy, in collaboration with other members of an interdisciplinary team. Other inclusion criteria included treatment with iv tobramycin and the existence of a suitable set of peak and trough levels. For the purposes of this study, a suitable peak level is defined as one drawn within 30–60 min after iv infusion of a tobramycin dose. A suitable trough level is defined as one drawn within 30 min before the next administered dose. Trough concentrations <0.6 mg/L were not used, as they were below the limit of detection of our analytical apparatus. The two levels must have been drawn with the same dose to ensure accuracy. The first set of levels from each admission episode satisfying these criteria was included for analysis. This study was approved by the Research Ethics Board (REB) at The Hospital for Sick Children (REB Approval no. 100008393).

#### Study design

This was a retrospective observational study. Charts were reviewed in reverse chronological order until the desired sample size was reached. Potential patients were identified from the Canadian Cystic Fibrosis Patient Data Registry. The most recent admission episode in which iv tobramycin was administered to a patient was used. Data were obtained from archived patient medical records, Electronic Patient Chart and KidCare, an integrated laboratory results/admissions/computerized physician order entry software application used at The Hospital for Sick Children. Subgroups based on age, nutritional status and sex were identified to examine their relationships to tobramycin pharmacokinetics, which may indirectly influence the proposed dosing scheme for once-daily tobramycin in CF patients. Pancreatic status was also explored as a possible factor affecting aminoglycoside pharmacokinetics in CF patients.

#### Sample size calculations

The Power Analysis and Sample Size Software (PASS version 2005; Number Cruncher Statistical System, Kaysville, UT, USA) program was used to estimate a sample size, based on a ‘worst-case’ standard deviation for the V/kg from values derived from the literature (Table S1, available as Supplementary data at JAC Online [http://jac.oxfordjournals.org/]). Accounting for possible interactions between the four characteristics to be analysed, the required sample size (i.e. the number of patients) was at least 100, based on a Type I error probability of 0.05, a Type II error probability of 0.20, a precision of 0.03 (i.e. the precision of the results obtained from The Hospital for Sick Children’s Therapeutic Drug Monitoring Laboratory) and an estimated standard deviation of 1.0.

#### Statistical analysis

Pharmacokinetic parameters were calculated according to standard first-order, one-compartment equations. Univariate analysis, Student’s t-test and linear regression were used as appropriate to determine the existence of significant relationships between demographic variables (i.e. sex, age, nutritional status and pancreatic status) and pharmacokinetic parameters [i.e. C\(_{\text{max}}\), elimination rate constant (k\(_{\text{el}}\)), trough concentration (C\(_{\text{min}}\)), V, CL and half-life (t\(_{1/2}\))]. Multiple linear regression, using a generalized linear models approach, was performed to determine which variables significantly affected pharmacokinetic parameters and therefore should be included in our dosing model. The PROC GLM procedure was used in SAS to perform this analysis with a class option for categorical models. Associations and correlations between explanatory variables were examined to reduce multi-collinearity. The binary partitioning method was used to determine critical values for dose stratification on the basis of significant patient variables identified by multiple linear regression. Study population-specific values for the V/kg were used to derive doses that would theoretically achieve desired pharmacokinetic targets. Statistical analyses were performed with Microsoft Excel (version 2002; Microsoft Corporation, Redmond, WA, USA), SAS (version 9.1; SAS Institute Inc., Cary, NC, USA) and R Statistical Software (version 2.0.1; The R Foundation for Statistical Computing, Vienna, Austria). A P value of 0.05 or less was considered statistically significant.

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Table 1. Patient demographics

<table>
<thead>
<tr>
<th>Parameter (n = 102)</th>
<th>n/n or mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>41/61</td>
</tr>
<tr>
<td>Age (years)</td>
<td>13.5 ± 3.5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>39.9 ± 13.6</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>148.3 ± 17.3</td>
</tr>
<tr>
<td>Pancreatic sufficient/pancreatic insufficient</td>
<td>8/94</td>
</tr>
<tr>
<td>Tobramycin dose (mg/kg)</td>
<td>9.6 ± 0.9</td>
</tr>
<tr>
<td>Serum creatinine (μmol/L) (on admission)</td>
<td>51.5 ± 11.4</td>
</tr>
<tr>
<td>(n = 90) Blood urea nitrogen (mmol/L) (on admission)</td>
<td>3.8 ± 1.2</td>
</tr>
<tr>
<td>FEV1 (% predicted) (n = 80) on admission</td>
<td>49.8 ± 15.2</td>
</tr>
<tr>
<td>on discharge</td>
<td>57.2 ± 18.3</td>
</tr>
<tr>
<td>improvement</td>
<td>7.4 ± 11.0</td>
</tr>
</tbody>
</table>

FEV1, forced expiratory volume in 1 s.

Results

Demographics

A total of 179 charts were reviewed. Seventy-seven patients were excluded: 7 because their trough tobramycin concentrations were ≤0.6 mg/L; 2 because they were not admitted to hospital during the study period; 10 because they did not have a complete set of tobramycin serum concentrations and 58 because they were not prescribed tobramycin during the study period.

Among the 102 included children, there were 41 males and 61 females. Twenty-five patients (25%) were malnourished defined by an actual body weight (ABW) that was <90% of ideal body weight (IBW). All patients were within age-appropriate limits for blood urea nitrogen and serum creatinine. The characteristics of the study population are summarized in Table 1. P. aeruginosa was the most common organism isolated, accounting for 48 of 99 (48%) respiratory cultures. Fifty-six percent of these isolates were susceptible to tobramycin. Approximately half (52%) of P. aeruginosa isolates were mucoid in morphology. Other common organisms isolated included Staphylococcus aureus (30%), Stenotrophomonas maltophilia (10%) and Burkholderia cepacia (7%). Respiratory culture specimens most often yielded a single pathogen [38 of 99 patients (38%)] or two pathogens [28 of 99 patients (28%)].

Table 2. Univariate analysis: sex, age, nutritional status and pharmacokinetic parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sex</th>
<th>Nutritional status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>male</td>
<td>female</td>
</tr>
<tr>
<td>Cmax (mg/L)</td>
<td>11.87 ± 2.97</td>
<td>13.53 ± 3.81</td>
</tr>
<tr>
<td>CL (L/min/kg)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>V (L)</td>
<td>10.38 ± 3.70</td>
<td>8.89 ± 3.06</td>
</tr>
<tr>
<td>V/kg (L/kg)</td>
<td>0.27 ± 0.09</td>
<td>0.23 ± 0.06</td>
</tr>
</tbody>
</table>

Values are presented as means ± SD.

Cmax, peak concentration; CL, clearance; V, volume of distribution; R, Pearson’s correlation coefficient.

Overall, patients appeared to respond to antibiotic therapy as reflected by a mean improvement in forced expiratory volume in 1 s (FEV1) of 7.4 ± 11.0%.

Pharmacokinetic parameters

By univariate analysis, sex, age and nutritional status were found to be significantly associated with the Cmax. CL (except for sex), the V and the V/kg (Table 2). Pancreatic status was not significantly associated with any pharmacokinetic parameter. Using multiple linear regression, age and sex were found to be associated with both the V and the V/kg [Table S2, available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/)]. Nutritional status and sex were significantly associated with the V/kg. After adjusting for nutritional status, the association between age and V/kg was no longer significant. This did not change regardless of the order of analysis (P = 0.0816). Nevertheless, age was preferentially retained in the construction of a dosing model because of its practicality and general evidence in the literature of age-related effects on aminoglycoside pharmacokinetics. Using the binary partitioning method, the critical value for age was 13.75 years. The statistically derived dosage stratification was as follows: patients younger than 13.75 years of age; males at least 13.75 years of age; and females at least 13.75 years of age. If nutritional status and sex were chosen to create the dosing regimen, the stratification would be as follows: males with ABW <96% IBW; females with ABW <96% IBW; males and females with ABW ≥96% and <110% IBW; and males and females with ABW ≥110% IBW.

Table 3 is a summary of the mathematical simulation of doses required to achieve a desired Cmax of 30 mg/L, with an acceptable range of 25–35 mg/L. The desired Cmax is based on a tobramycin MIC of ≤4 mg/L for susceptible P. aeruginosa as defined by the CLSI guidelines. About 49% to 67% of the P. aeruginosa isolates from these patients had an MIC of ≤4 mg/L, with the majority (~80%) having an MIC of ≤2 mg/L. Ideally, the target Cmax range should equal 8–10 times the MIC for an organism to produce an adequate clinical response, but concerns about potential toxicity (i.e. nephro- and ototoxicity) led to the adoption of a more conservative target range for the purposes of this study. From the simulation, male and female patients younger than 14 years of age (rounded up for practical reasons) and males 14 years of age and older would receive an initial dose of 9 mg/kg/day intravenously given as a single daily dose. Female CF patients 14 years and older would receive an initial dose of 7 mg/kg/day intravenously as a single daily dose.
Using these initial doses, 50% of the patients in the study population would theoretically achieve a \( C_{\text{max}} \) (based on each patient's individual pharmacokinetic parameters) within our proposed target range (Figure 1a). This is comparable with the proportion of patients (48%) achieving the target concentrations (8–13 mg/L) with the current thrice-daily regimen (Figure 1b).

**Discussion**

The once-daily doses derived in the present study are based on patient-specific pharmacokinetic parameters, which is in contrast to previous studies (including the TOPIC Study by Smyth et al.) in which once-daily doses of aminoglycosides in CF treatment were simply based on the sum of the thrice-daily doses.\(^{15,16}\) Because our doses were derived directly from the pharmacokinetic parameters of our CF patients, we feel that our dosing regimen is a more accurate representation of the appropriate empirical once-daily dose of tobramycin in treatment of an acute pulmonary exacerbation at our institution. In addition, by examining correlations between patient characteristics and pharmacokinetic parameters, we were able to stratify dosing based on age and sex, allowing therapy to be individualized.

In the present study, age was significantly associated with the \( V, V/kg, \) CL and \( C_{\text{max}}. \) As paediatric patients grow older, their size increases, hence increasing the volume of body water (i.e. the \( V \)) available for distribution of tobramycin. Owing to the close relationship between CL and \( V, \) CL will increase with age. Although there was a direct relationship between age and \( V, \) there was an inverse relationship between age and \( V/kg. \) This is expected because as patients grow older, less of their total body composition is made of body water.\(^ {10} \) Because tobramycin is preferentially distributed into the body water, having a lesser proportion of body water would imply a lower \( V \) for the drug. The lower \( V/kg \) associated with increasing age also results in a higher \( C_{\text{max}} \) with increasing age.

Sex was significantly associated with \( V, V/kg \) and \( C_{\text{max}}. \) Our data indicate that males and females were given similar tobramycin doses on a per kilogram basis. Females generally have a greater proportion of body fat when compared with males, which may explain the lower \( V \) and \( V/kg \) in females.\(^ {17} \) This may also account for the greater \( C_{\text{max}} \) seen in female patients. Sex differences in dose could not be explained by differences in renal function based on the data collected in the present study, as average baseline serum creatinine values were similar in both groups.

Nutritional status was also found to be significantly associated with the \( V, V/kg, \) CL and \( C_{\text{max}}. \) Well-nourished patients are generally larger than those who are malnourished, implying a greater \( V. \) It follows from this that the CL would also be larger. However, being well nourished also implies a greater proportion of body fat, decreasing the \( V \) for tobramycin and explaining the inverse relationship between nutritional status and \( V/kg. \) The lower \( V/kg \) also results in a higher \( C_{\text{max}} \) of tobramycin in better nourished patients.

Multiple linear regression showed significant associations of age and sex with \( V \) and \( V/kg. \) Nutritional status and sex were significantly associated with the \( V/kg. \) However, when age, nutritional status and sex were included in the same regression model, the association of age with \( V/kg \) was no longer significant. Despite this observation, age, rather than nutritional status,
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was retained for further analysis because it is a more practical parameter to use in the prescribing of antibiotics. Our model, therefore, does not adjust dosing based on nutritional status.

From the simulation, half of the patients in the study population would achieve our proposed $C_{\text{max}}$ target of 25–35 mg/L (Table 3). This is similar to the proportion of patients (48%) achieving the target $C_{\text{max}}$ range of 8–13 mg/L on the current thrice-daily regimen and supports the importance of therapeutic drug monitoring (TDM) in the optimization of aminoglycoside therapy. Although ~50% of patients would theoretically attain $C_{\text{max}}$ values outside the target range, one of the goals of TDM is to individualize therapy to bring these patients within the target concentration range. Attainment of therapeutic goals would be confirmed with additional serum drug concentrations.

Moore et al.\textsuperscript{14} specify that the serum concentration of an aminoglycoside should be targeted to 8–10 times the MIC for an organism to achieve a 90% clinical response rate. Using the tobramycin MIC of $\leq 4$ mg/L for susceptible *P. aeruginosa*, this would imply an ideal target range of 32–40 mg/L. However, concerns about potential toxicity (i.e. nephro- and ototoxicity) at such high concentrations led to the adoption of the more conservative target range of 25–35 mg/L. Several other groups, including the TOPIC Study Group, targeted $C_{\text{max}}$ values of 20–30 mg/L.\textsuperscript{16} Despite the more conservative numbers, our simulation demonstrates that patients in the study population would achieve areas under the tobramycin concentration–time curve near the upper end of the therapeutic range (i.e. 70–100 mg·h/L). However, the mean drug-free interval for all groups is ~15 h (Table 3). A study recently published by Burkhardt et al.\textsuperscript{18} described increased *P. aeruginosa* resistance to tobramycin with ODD in adult CF patients when compared with thrice-daily dosing, implying that it may be linked to a long dosing interval. The potential for development of antibiotic resistance with ODD and the clinical implications of this will require ongoing study.

The dosing regimen derived in the present study in CF patients shows some similarities to that derived in a previous study of bone marrow transplant recipients.\textsuperscript{9,19} There is some evidence for higher doses being needed in younger CF patients, although the differences are not as clear as they are in the bone marrow transplant population.\textsuperscript{9} The bone marrow transplant study was performed in two phases with the first phase (on which the present study is modelled) retrospectively deriving once-daily doses for tobramycin using data from a pre-existing patient database.\textsuperscript{9} The retrospectively derived doses were then used as the basis for the second phase of the study, which found that ODD tobramycin was not associated with an increase in the incidence of nephrotoxicity when compared with thrice-daily tobramycin. Once-daily tobramycin was also significantly more efficacious when compared with thrice-daily tobramycin.

There are several limitations to our study, which are inherent to its retrospective nature. Some patients were excluded from the study as their trough tobramycin levels were below the limit of detection of the analytical apparatus. The exclusion of these patients did not significantly change the demographic profile of the study population. However, age was less significantly associated with $V$/kg when data from these patients were included ($P = 0.0491$). A full assessment of renal function pre- and post-tobramycin therapy could not be completed, as only baseline renal function tests (i.e. serum creatinine and blood urea nitrogen) were performed. Urine output was not routinely recorded. However, this is not expected to significantly impact our results, as renal function in CF patients at The Hospital for Sick Children tends to remain relatively stable. Renal function was not directly incorporated into our pharmacokinetic model; rather, the model mathematically accounts for differences in renal function based on concomitant differences in $k_{\text{el}}$. The regression model used does not include renal function parameters. Renal function data pre- and post-treatment are currently being collected in a prospective study validating the dosing regimen described in the present report. Audiograms were not routinely performed, so the incidence of ototoxicity could not be fully assessed. Again, this does not significantly impact our results, as toxicity parameters were not directly included in the pharmacokinetic model. However, the existence of complete toxicity markers would be useful to compare the incidence and degree of toxicities experienced in both the thrice-daily and the once-daily settings in our patient population. Ototoxicity data are also being collected in the above-mentioned prospective study validating the present dosing regimen. The relationship (if one exists) between cumulative tobramycin dose and tobramycin pharmacokinetics was not examined. It would be useful to determine whether cumulative dose affects tobramycin pharmacokinetics, which may possibly lead to suboptimal therapeutic outcomes. Cumulative dose information would also be beneficial in determining whether differences exist between males and females; differences in cumulative dose between sexes may partially explain differences in the initial dose required. Finally, the pharmacokinetic model was only applied to the first set of drug levels for each patient. Whether the model remains stable over time will be examined in a future study.

Conclusions

In conclusion, based on population pharmacokinetic parameters, we recommend that the following initial dosing regimen be followed for the treatment of an acute pulmonary exacerbation: females 14 years of age and older should receive an initial iv tobramycin dose of 7 mg/kg/day as a single daily dose, whereas all other children should be given a starting dose of 9 mg/kg/day intravenously as a single daily dose. Dosage adjustments, if necessary, should be calculated on the basis of the standard equations and targeted to the proposed therapeutic range.

Acknowledgements

We thank the following from The Hospital for Sick Children: Annie Dupuis, Research Institute; L. Lee Dupuis, Department of Pharmacy; and Daina Kalnins, Department of Clinical Dietetics. The present work was previously presented in poster form at the Twentieth Annual North American Cystic Fibrosis Conference held 2–5 November 2006. An abstract was published in the proceedings of the conference as a supplement to Pediatric Pulmonology. The work described in the present report was supported by a grant for CF research by the Irwin family and by the Department of Pharmacy, The Hospital for Sick Children.

Transparency declarations

None to declare.
Supplementary data

Tables S1 and S2 are available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

References