Bayesian Estimation of Tobramycin Exposure in Patients with Cystic Fibrosis

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Fixed tobramycin (mg/kg) dosing is often inappropriate in patients with cystic fibrosis (CF), as pharmacokinetics are highly variable. The area under the concentration-time curve (AUC) is an exposure metric suited to monitoring in this population. Bayesian strategies to estimate AUC have been available for over 20 years but are not standard practice in the clinical setting. To assess their suitability for use in clinical practice, three AUC estimation methods using limited sampling were compared to measured true exposure by using intensive sampling tobramycin data. Adults prescribed once daily intravenous tobramycin had eight concentrations taken over 24 h. An estimate of true exposure within one dosing interval was calculated using the trapezoidal method and compared to three alternate estimates determined using (i) a two-sample log-linear regression (LLR) method (local hospital practice); (ii) a Bayesian estimate using one concentration (AUC1); and (iii) a Bayesian estimate using two concentrations (AUC2). Each method was evaluated against the true measured exposure by a Bland-Altman analysis. Twelve patients with a median (range) age and weight of 25 (18 to 36) years and 66.3 (51 to 76) kg, respectively, were recruited. There was good agreement between the true exposure and the three alternate estimates of AUC, with a mean AUC bias of <10 mg/liter·h in each case, i.e., −8.2 (LLR), 3.8 (AUC1), and 1.0 (AUC2). Bayesian analysis-based and LLR estimation methods of tobramycin AUC are equivalent to true exposure estimation. All three methods may be suitable for use in the clinical setting; however, a one-sample Bayesian method may be most useful in ambulatory patients for which coordinating blood samples is difficult. Suitably powered, randomized clinical trials are required to assess patient outcomes.

Approximately 70,000 patients worldwide have cystic fibrosis (CF) (1), and it is the most common life-threatening genetic disorder. The mortality and morbidity in CF patients are often attributed to Pseudomonas aeruginosainduced pulmonary exacerbations for which intravenous (i.v.) and inhaled antibiotics are used to prevent and treat recurrence (2, 3).

Intravenous tobramycin, an aminoglycoside antibiotic, is a mainstay in the treatment of Pseudomonas infection in patients with CF (1, 4). Tobramycin is most commonly administered as a daily i.v. injection in doses ranging from 7 to 15 mg/kg of body weight per day (1, 4, 5). The bactericidal actions of tobramycin are directly linked to drug exposure; however, dosing is complicated, as exposure must be maintained within a narrow therapeutic range (TR) (4–6). Exposures above the TR increase the risk of nephrotoxicity (1) and ototoxicity, of which the latter can be irreversible (1, 7). Exposures below the TR can lead to therapeutic failure, increased antibiotic resistance, and poor patient outcomes (2, 3). To help ensure optimal therapy, a therapeutic exposure must be achieved as quickly as possible (8, 9), preferably after the first dose of a treatment course, which can last up to 14 days (10).

Unfortunately, in CF patients, tobramycin has high between-subject variability in its pharmacokinetic (PK) parameters, such as clearance (CL) and volume of distribution (V) (11, 12). Serum tobramycin concentrations are used to estimate exposure after a given dose, often by the area under the concentration-time curve (AUC). There is consensus that therapeutic drug monitoring (TDM) should be conducted as part of standard practice (1, 4). A target used to assess efficacy for aminoglycosides is the AUC/MIC ratio (13) with an acceptable target range of 70 to 100 mg/liter·h (14, 15), assuming an MIC of 1.

Locally, clinical pharmacists perform tobramycin monitoring and estimate an AUC for dose adjustment by using two blood concentrations and the log-linear regression (LLR) method. However, from a practical point of view, the collection of two blood samples is difficult and time-consuming to coordinate, especially in an outpatient setting, where patients are administered the antibiotic in hospital and are able to leave between blood tests. However, they often fail to present for their second blood sample at the correct time. Bayesian analysis-based software can be used to estimate AUC (16) and has the potential to be more accurate than conventional methods and to allow the collection of samples at unrestricted, patient-preferred times (17).

Bayesian analysis-based programs use embedded population PK models (16–18). The user can input known patient demographics (age, sex, weight, renal function) to allow the estimation of a concentration-time curve based on the population model. As tobramycin concentration data are obtained, these, along with dosing details, can be input to estimate patient-specific PK parameters, which can be used to estimate an exposure metric such as AUC, maximum concentration (Cmax), or minimum concentration (Cmin). Given these individualized values, dosing and moni-
Toring strategies can be personalized in a dynamic way. As subsequent patient data and tobramycin concentrations are collected, further individualization can occur, potentially with the use of only one concentration (17, 19, 20).

The aim of this study was to evaluate three AUC estimation methods by comparison to true measured exposure, calculated using intensive sampling data, in adult CF patients to assess their suitability for use in clinical practice.

**MATERIALS AND METHODS**

Figure 1 shows the flow chart for recruitment and data analysis. Data were collected from adult CF patients admitted as inpatients to the Mater Health Service (MHS) Respiratory Unit, Brisbane, Australia, over a 3-month period. On admission, tobramycin was administered as a once daily infusion over 30 min, per hospital protocol. This dose was either 10 mg/kg, based on total body weight, or a dose equivalent to the last dose that was prescribed during the previous admission.

Patients were treated using local dosing and monitoring methods until a suitable day was organized for the patient to participate in a rich sampling protocol. This occurred only after the patient had attained a therapeutic AUC as required by the treating physician, commonly between 70 and 100 mg/liter · h. At the MHS, patients do not have to remain in hospital while on their 10- to 14-day course of i.v. tobramycin and return only for daily dose administration or blood sampling. Local hospital practice is to collect two serum tobramycin concentrations from each patient within one dosing interval: the first is collected 1 to 1.5 h after the commencement of the infusion, and the second is collected at 8 to 12 h after commencement of the infusion. An AUC from 0 to 24 h (AUC0–24) is estimated using an LLR method (21) embedded in a Microsoft Excel-based program, and the dose is adjusted to the TR if necessary.

For this study, a rich sampling strategy was implemented following a morning dose, with eight serum drug concentrations taken over the 24-h dosing interval, i.e., a predose sample and an additional seven samples at 50, 70, 100, 160, 280, 520, and 640 min after the start of infusion (30-min duration) to enable calculation of true tobramycin exposure (AUC0–24) after this dose.

**Comparison of AUC estimation methods.** AUCs were estimated using four methods (Fig. 1): calculation of a true exposure by use of the traditional trapezoidal method (linear-up log-down) (22), a Bayesian method with either one serum drug concentration (AUC1) or two serum drug concentrations (AUC2), and the local hospital method utilizing the LLR method (21). It has been postulated that Bayesian software does not require a minimum number of concentrations to calculate an AUC (20); therefore, an AUC was calculated using one concentration, taken at 520 min postdose. In addition, a two-sample AUC was calculated using concentrations taken at 100 and 520 min postdose. The times were chosen as they match those used at the hospital to estimate an LLR AUC (local method). Previous reports have demonstrated that no additional reliability in the estimation of concentrations is gained by sampling beyond 6 h postdose (11, 19); however, the concentration at 520 min would not compromise the estimation of the AUC and matches local practice. All AUC calculations used the sampling data from the same dosing interval, and no Bayesian optimization using previous patient data occurred before the study day for this study.

Demographic data were summarized using standard statistics. Bland-Altman difference plots were used to compare the AUC of each method to the true AUC (trapezoidal). The mean difference (bias) and upper and lower limits of agreement (95% confidence interval [CI]) were calculated and plotted. The percentage change in bias was reported. Statistical difference was considered at a P value of <0.05 (Tukey’s test).

Ethics approval was obtained from the MHS Human Research Ethics Committee. The software TDMx (23) was used for the Bayesian analyses, embedded with the population PK model described by Hennig et al. (6). All statistical and graphical analyses were performed using the software Prism (version 7).

**RESULTS**

Data were collected from 12 patients with CF. Table 1 shows the demographics of the population. The medians (ranges) for age, weight, and tobramycin dose of the population were 25 (18 to 36) years, 66.5 (51 to 76) kg, and 400 (320 to 640) mg, respectively.
The estimated AUC values using the four methods for each of the 12 patients are shown in Table 2.

The Bland-Altman plots are shown in Fig. 2a to c, and a summary of the bias, percent change in bias, and limits of agreement (95% CIs) between the true exposure and the results of the three estimation methods is shown in Table 3. There was no significant difference in bias relative to the mean of the true measured exposure for any of the three AUC methods, with the mean AUC bias less than 10 mg/liter · h in each case. The AUC2 method was the least biased. There was a wide range between the lower and upper limits of agreement for all methods; however, the AUC2 method, with a range of 24.9 mg/liter · h, was the most preferred (change in bias, 1.03%).

When the two Bayesian methods are compared, Fig. 2 shows that the AUC2 method performs better than AUC1 method when patient results are farther away from the population average. This is expected, as the Bayesian software will use the prior model rather than the actual data to optimize model parameters. Generally, these results indicate that when estimating a tobramycin AUC, it would be reasonable to use all three methods.

DISCUSSION

_Pseudomonas aeruginosa_ is the most common bacterium to infect the lungs of individuals with CF (1), and tobramycin, given i.v. once daily, is a first-line antibiotic to treat and prevent infection (1, 4, 5, 24). However, the TR for tobramycin is often difficult to achieve with standard dosing and monitoring methods (11, 17, 25), which is hazardous, as toxicity is linked to severe adverse effects such as irreversible nephrotoxicity and ototoxicity (7, 26, 27). CF patients generally require large doses of tobramycin, often for extended periods of time (10 to 14 days), which can increase the risk of toxicities (7, 26, 27). In addition, patients may attend

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**TABLE 1 Patient demographics**

<table>
<thead>
<tr>
<th>Demographic</th>
<th>No. or median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>25 (18–36)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>66.3 (51–76)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>170 (154–185)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7</td>
</tr>
<tr>
<td>Female</td>
<td>5</td>
</tr>
<tr>
<td>Serum creatinine, μmol/liter</td>
<td>73 (55–92)</td>
</tr>
<tr>
<td>Dose at study day, mg</td>
<td>400 (320–640)</td>
</tr>
<tr>
<td>Dose, mg/kg</td>
<td>6.3 (5.2–8.4)</td>
</tr>
<tr>
<td>Day of therapy for sampling</td>
<td>6 (4–7)</td>
</tr>
</tbody>
</table>

**TABLE 2 Tobramycin AUC by method**

<table>
<thead>
<tr>
<th>Patient</th>
<th>AUC (mg/liter · h) by:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trapezoidal method</td>
</tr>
<tr>
<td>1</td>
<td>88.9</td>
</tr>
<tr>
<td>2</td>
<td>94.9</td>
</tr>
<tr>
<td>3</td>
<td>71.9</td>
</tr>
<tr>
<td>4</td>
<td>79.3</td>
</tr>
<tr>
<td>5</td>
<td>79.8</td>
</tr>
<tr>
<td>6</td>
<td>81.5</td>
</tr>
<tr>
<td>7</td>
<td>71.9</td>
</tr>
<tr>
<td>8</td>
<td>102.4</td>
</tr>
<tr>
<td>9</td>
<td>102.8</td>
</tr>
<tr>
<td>10</td>
<td>62.7</td>
</tr>
<tr>
<td>11</td>
<td>77.6</td>
</tr>
<tr>
<td>12</td>
<td>51.1</td>
</tr>
</tbody>
</table>

aAUC, area under the concentration-time curve; AUC1, sampling at 520 min postdose; AUC2, sampling at 100 and 520 min; LLR, log-linear regression; trapezoidal method, true exposure calculated using the linear-up log-down trapezoidal method.
exposure is growing (4,14), a number of dose prediction software
packages (16,28, 29). This may be attributed to a lack of one or more
features of the clinical setting, in particular in Australia and the United King-
dom (16, 28, 29). There is ongoing concern about toxicity due to the repetitive
nature of tobramycin exposure (4).

Bayesian methods have been used in the TDM of drugs for over
20 years; however, they are still not a commonly used strategy in
the clinical setting, in particular in Australia and the United King-
dom. Bayesian methods have gained importance in the CF population
due to the narrow TR and the sufficient unexplained interpatient vari-
ability of the drug (17). In addition, tobramycin distribution may be better
described using two-compartmental PK models (30). As such, fixed-dos-
ing, traditional nomograms (31) and PK software that use non-
compartmental models should be used with caution if only one or
two serum concentrations are available (17).

As the use of the AUC method for monitoring tobramycin exposure is growing (4, 14), a number of dose prediction software
packages are available (16–18, 31). However, they can be unpal-
able, as they often lack networking capabilities, use databases
that are not compatible with hospitals’ information technology
(ITT) systems, or have little readily accessible IT support. The new
Bayesian method-based software used in this analysis can be accessed
from the Internet (http://www.tdmx.eu/Resources/) free of charge.

Our study has shown that the Bayesian estimation of AUC is
similar to the local method using LTR with two concentrations. Other studies have shown the superiority of Bayesian dosing and monitoring methods over traditional methods for aminoglyco-
side exposure estimation (17, 18, 25). Recently, Henning et al. (17)
compared Bayesian estimation to LTR and nomogram methods
for the dosage adjustment of tobramycin in children with CF. The
LTR method and Bayesian forecasting methods showed negligible
bias but imprecision of 20% in predicting subsequent observed
concentrations. The Bayesian methods were recommended as the
first line for dose adjustment. However, this study had no measure
of total exposure for comparison. Our study is the first in which
true tobramycin exposure was used as a comparator and allows a
robust evaluation of Bayesian methods.

Learning about the patient is the strength of a Bayesian ap-
proach. The clinician gains a better knowledge of each patient’s
true PK response; i.e., the clinician “learns” about the patient, the
true benefit of a Bayesian system. This is in contrast to the local
LLR method, which assumes a one-compartment PK model for
tobramycin. As no prior PK parameters are included, two blood
concentrations are required at every monitoring occasion.

The practical difficulties when using LLR for tobramycin TDM
is that patients and phlebotomy staff have to present on two occa-
sions for blood collection, which is often difficult to coordinate. As
a consequence, pathology results are seldom available during
work hours, which is problematic for medical and pharmacy staff.
Dose individualization may be compromised, which delays the
time to TR and thus increases the risk of unwanted patient out-
comes. In addition, regular dose adjustments result in further
blood sampling, which is costly to the hospital and cumbersome
for staff and patients. A one-concentration AUC means that pa-
ients are not required to remain as inpatients and adds to the
argument of the cost-effectiveness of a coordinated TDM ap-
proach (32).

Finally, as intrapatient variability is low in CF patients (33),
an accurate estimation of a patient’s PK parameters after one hospital
stay aids dose selection in the future. Currently, a 10-mg/kg fixed
dose is often administered to patients on admission. Our results
suggest that an ideal method for monitoring would be to use a
two-sample method for the first dosing interval, which allows opti-
mization of the patient’s PK parameters, and then a one-sample
method thereafter. A prospective evaluation of this hypothesis is
required.

There are limitations to our study, notably with the generaliz-
ability of results. We had a small sample size (n = 12), limited by
funding and time; however, this prospective study provides im-
portant data to design adequately powered investigations. A large
comparative study may allow the investigation of relevant patient
outcomes, such as disease progression, lung function, time to ex-
acerbation, and drug toxicity (nephrotoxicity or ototoxicity). Un-
fortunately, few data exist demonstrating the benefits of a Bayesian
dosing and monitoring approach using tobramycin for clinical
outcomes, and we cannot make clinical assumptions using a small
sample. Finally, the population PK model embedded in the soft-
ware was developed from patients with CF and therefore should
be used only in this population.

Conclusion. An AUC approach for the dosing and monitoring
of tobramycin is advocated practice in CF populations. Both
Bayesian and LLR estimation methods of tobramycin AUC are
equivalent to a true exposure estimate. However, Bayesian estima-
tion using a single serum concentration may be a more practical
method. Suitably powered, randomized clinical trials are required
to assess patient outcomes.

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This paper is in memory of coauthor David Serisier, who tragically
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