Bayesian Optimisation of Tobramycin Dosing in Paediatric Patients with Cystic Fibrosis

Michael Barras, Hana Alraman, Carl MJ Kirkpatrick, Margaret Harris, Carolyn Dakin, Katrina Jess, Melissa Pilbeam, Ross LG Norris

ABSTRACT

Background: In children with cystic fibrosis (CF), tobramycin concentrations are monitored via the area under the plasma concentration time curve (AUC) approach. Currently, a minimum of 2 plasma concentrations of tobramycin within one dosing interval are required to estimate the AUC, which is costly, painful and blood collection is often difficult to coordinate.

Aim: To evaluate the accuracy of tobramycin AUC estimated using 1 plasma concentration compared to AUC based on 2 plasma concentrations calculated using Bayesian software.

Method: Data were collected from paediatric patients with CF prescribed once daily intravenous tobramycin. Each patient had 2 blood samples taken within a dosing interval (according to usual practice at the hospital) on 2 separate occasions during their admission. Data on tobramycin dosing and concentration, and patient demographics from the first occasion were entered into the Bayesian software, TCIWorks, to establish an individual patient's pharmacokinetic model. Data from the second occasion were then also entered into TCIWorks to estimate 2 AUCs – from 1 (AUC₁) and 2 (AUC₂) plasma concentrations. The accuracy of each patient's AUCs (AUC₁ and AUC₂) were then evaluated using a Bland-Altman analysis to describe bias relative to the mean of the two values. To show the benefits of good quality data when using TCIWorks, data were obtained and analysed from 2 patient groups. For group A patients, accurate sampling and administration times of the tobramycin infusion were obtained prospectively. Group B consisted of patients from group A plus additional patients who had data collected from a retrospective medical chart review.

Results: Data were collected for 30 paediatric patients with CF – 14 in group A and 16 additional patients in group B. In group A, there was no significant bias relative to the mean of the values for AUC₁ and AUC₂ (mean bias 1; 95%CI -4.9–6.9). A similar result was seen in group B (mean bias -0.7; 95%CI -10–8.6) indicating that the 2 estimates of tobramycin AUC (using 1 and 2 blood samples) are not significantly different.

Conclusion: Once an individual paediatric patient's tobramycin pharmacokinetic model is determined with two blood samples using TCIWorks, only one blood sample is required to estimate an AUC for tobramycin.

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INTRODUCTION

Of an estimated 70 000 patients with cystic fibrosis (CF) worldwide, approximately 3000 reside in Australia.^{1,2} Cystic fibrosis is the most prevalent life-threatening genetic disorder affecting Australians and 1 in 25 people is a symptomless carrier of CF.² There has been much progress in the treatment of CF and improvement in antibiotic therapy is considered a major reason for the increased life expectancy in patients with CF. Despite this, bacterial infections of the airways continue to dictate the clinical course of CF.³

Tobramycin, an aminoglycoside antibiotic, is a mainstay in treating *Pseudomonas aeruginosa* during pulmonary exacerbations in patients with CF.^{1,3} Tobramycin is mostly administered as a daily intravenous injection in doses ranging from 7 to 15 mg/kg/day.^{1,3,4} Tobramycin's bactericidal actions are directly linked to drug exposure, however, the optimal dose is complicated by a narrow therapeutic range. Exposure to tobramycin above the therapeutic range increases the risk of nephrotoxicity and ototoxicity, which can be irreversible, and exposure below the therapeutic range leads to therapeutic failure, increased antibiotic resistance and poor patient outcomes.^{1,5-8}

As tobramycin's therapeutic range is narrow, plasma drug concentrations are used to adjust the dose. Tobramycin has a high inter- and intra-individual pharmacokinetic variability, such as clearance and volume of distribution, making the 'one dose fits all' dosing (e.g. 10 mg/kg/day for all patients) difficult to justify.^{9,10} To ensure optimal outcomes for patients, the tobramycin dose administered must achieve therapeutic concentrations as quickly as possible. Therefore, accurate dose selection and monitoring are necessary. There is consensus that therapeutic drug monitoring is essential and should be standard practice.^{1,3,11}

The effectiveness and toxicity of aminoglycosides are monitored by the area under the plasma concentration time curve (AUC).¹²⁻¹⁴ The therapeutic range for tobramycin used at the Mater Children's Hospital, Brisbane is 70 to 100 mg/L/h and its use is monitored by clinical pharmacists. Currently, a minimum of two plasma concentrations of tobramycin within one dosing interval are required to estimate the AUC, which is costly, painful and blood collection is often difficult to coordinate. Additionally, the software used to estimate tobramycin's AUC incorporates a one-compartment pharmacokinetic model. According to recent evidence, tobramycin follows a two-compartment pharmacokinetic model and an AUC estimated under the assumption of a one-compartment model would produce an erroneous result of tobramycin exposure.^{9,15-17}

A public domain model-based Bayesian predictive software, TCIWorks, theoretically estimates AUC using one plasma drug concentration, however, it needs to be evaluated in the clinical setting.¹⁸ TCIWorks requires individual patient data to 'customise' a population pharmacokinetic model from which it generates patient-specific concentration–time curves. An AUC, based on a proposed dosing regimen can be estimated, allowing dose selection suited to the therapeutic needs of the patient.

METHOD

Ethics approval for the study was obtained from the Mater Health Services Human Research Ethics Committee. The flow chart of data collection and analysis is displayed in Figure 1. Data were collected from paediatric patients with CF admitted to the respiratory unit of the Mater Children's Hospital, Brisbane, from January to March 2010. TCIWorks (version 1.0-RC1) was used to analyse all the data with the population pharmacokinetic model described by Hennig⁹ as the prior model. The prior model is a two-compartment model developed from 318 tobramycin concentrations, taken from 35 paediatric patients with CF. The final covariate model included total body weight scaled allometrically with a 0.75 exponent for clearance and central volume of

distribution. Readers are referred to the original publication for values of all parameter estimates, including between subject variability and inter-occasion variability.⁹ Renal function was not included in the covariate model because none of the patients studied had impaired renal function. The model was evaluated using methods, such as non-parametric boot-strapping, visual predictive checks and goodness-of-fit plots.

On admission, as per hospital protocol, tobramycin was administered as a once daily infusion over 30 minutes. The initial tobramycin dose administered was either 10 mg/kg (based on total body weight) or the dose used during the last admission. After the first tobramycin dose, each patient had two tobramycin plasma concentrations measured according to usual practice at the hospital. The first blood sampling occurred 1 to 1.5 hours after the start of the infusion and the second blood sampling 8 to 12 hours after the start of the infusion. To determine an individual patient's pharmacokinetic model, data on tobramycin dosing and concentration, and patient demographic data (e.g. total body weight, age) were entered into TCIWorks. A second set of blood samples was organised during the patient's admission at the discretion of the respiratory unit's clinical team (usual practice at the hospital, if a dose adjustment is necessary).

Using the individual patient's pharmacokinetic model, tobramycin dosing and concentration, and demographic data from the second sampling occasion were then also entered into TCIWorks to estimate two AUCs (both an AUC 0–24) – from one (AUC_1) and two (AUC_2) plasma concentrations. The accuracy of each patient's AUCs (AUC_1 and AUC_2) were then evaluated using a Bland-Altman analysis to describe bias relative to the mean of the two values.

To show the benefits of good quality data when using TCIWorks, data were obtained and analysed from two patient groups. For group A patients, accurate sampling and administration times of the tobramycin infusion were obtained prospectively. Group B consisted of patients from group A plus additional patients who had data on tobramycin infusion collected from a retrospective medical chart review. Although these were retrospective data and could not be accurately confirmed, it allowed analysis of a large cohort of patients.

All graphical and statistical analyses were performed using PRISM (GraphPad Prism version 5 for Windows). Usual clinical practice at the hospital was not altered.

RESULTS

Data were collected for 30 paediatric patients with CF – 14 in group A and 16 additional patients in group B. Patient demographics are presented in Table 1, as well as the mean and standard deviation dose of tobramycin, mean AUC_1 and mean AUC_2 of each group. In both groups, the mean age and total body weight were approximately 10 years and 35 kg, respectively, which align closely to those

Figure 1. Flow chart of data collection and analysis (AUC_1 = area under the plasma concentration time curve estimated using 1 plasma concentration, AUC_2 = area under the plasma concentration time curve estimated using 2 plasma concentrations).

Table 1. Patient demographics and key results

Population	Mean weight (kg)	Gender	Mean age (years)	Mean AUC_1 (mg/L/h)	Mean AUC_2 (mg/L/h)	Mean dose (mg)	Mean bias* (mg/L)
Group A (n = 14)	35 (±16.7)	7 male, 7 female	10 (±3.8)	86 (±13)	84 (±12)	323 (±114)	1.0 (95%CI -4.9-6.9)
Group B (n = 30)	36 (±17.1)	14 male, 16 female	10 (±4.1)	85 (±12)	85 (±12)	326 (±130)	-0.7 (95%CI -10-8.6)

*Bland-Altman analysis.

AUC_1 = area under the plasma concentration time curve estimated using 1 plasma concentration. AUC_2 = area under the plasma concentration time curve estimated using 2 plasma concentrations. CI = confidence interval.

Table 2. AUC results for all patients

Patient	AUC ₁ (mg/L/h)	AUC ₂ (mg/L/h)	Mean AUC (mg/L/h)
1	82	85	84
2	92	93	93
3	77	86	82
4	69	68	69
5	98	93	96
6	89	86	88
7	78	74	76
8	110	109	110
9	82	80	81
10	86	74	80
11	64	68	66
12	85	76	81
13	111	100	106
14	87	88	88
15	81	76	79
16	87	88	88
17	73	75	74
18	85	85	85
19	80	85	83
20	99	100	100
21	89	95	92
22	88	91	90
23	91	95	93
24	81	78	80
25	86	89	88
26	71	69	70
27	79	78	79
28	64	60	62
29	103	102	103
30	90	90	90
Mean	85.2 (SD 11.5)	84.5 (SD 11.5)	-

AUC₁ = area under the plasma concentration time curve estimated using 1 plasma concentration. AUC₂ = area under the plasma concentration time curve estimated using 2 plasma concentrations.

reported by Hennig et al.⁹ who had a mean age of 9.5 years and total body weight of 34 kg. The mean tobramycin dose administered to group A was 323 mg and for group B it was 325 mg, which also approximates the data presented by Hennig⁹ where patients were administered a mean tobramycin dose of 312 mg. Individual patient's results are presented in Table 2.

The results for the Bland-Altman analyses are presented in Table 1 and the plots for group A and B are displayed in Figures 2a and 2b, respectively. In group A, the estimated values for AUC₁ and AUC₂ were unbiased (mean bias 1; 95%CI -4.9–6.9), as were the AUC₁ and AUC₂ values in group B (mean bias -0.7; 95%CI -10–8.6). The tight confidence intervals are suggestive of good clinical applicability. The wider confidence intervals seen in group B most likely reflect the inaccuracy of the data on tobramycin use that were collected retrospectively for these patients. For example, in daily clinical practice

Figure 2a. Bland-Altman plot of AUC₂ vs AUC₁ for group A (mean bias 1; 95%CI -4.9–6.9) (AUC₁ = area under the plasma concentration time curve estimated using 1 plasma concentration, AUC₂ = area under the plasma concentration time curve estimated using 2 plasma concentrations).

Figure 2b. Bland-Altman plot of AUC₂ vs AUC₁ for group B (mean bias -0.7; 95%CI -10–8.6) (AUC₁ = area under the plasma concentration time curve estimated using 1 plasma concentration, AUC₂ = area under the plasma concentration time curve estimated using 2 plasma concentrations).

nursing staff often do not record the exact administration time of the tobramycin infusion. The scrutiny of the research environment ensured more accurate recording of data for Group A.

DISCUSSION

Pseudomonas aeruginosa commonly infects the lungs of individuals with CF.¹ Although once daily intravenous tobramycin is a conventional treatment strategy, patients with CF require large doses of tobramycin and often for extended periods of time (10 to 21 days), which makes them susceptible to acute and long-term toxicities of the drug.^{1,3,4,6–8,18} It is now standard practice in many Australian hospitals to use the AUC approach to monitor tobramycin used to treat pulmonary exacerbations in paediatric patients with CF.¹² The *Therapeutic Guidelines: Antibiotic* recommend computerised methods to estimate a 24-hour AUC as the preferred way of monitoring and dose-adjusting aminoglycosides administered daily.¹¹ According to the *Therapeutic Guidelines: Antibiotic*, computerised methods are preferred as they 'adjust for significant variation in volume of distribution and elimination rate'.¹¹ The

Therapeutic Guidelines: Antibiotic have also provided links to TCIWorks <www.tciworks.info/> and Aladdin software <www.asainc.net.au>.¹¹

Aladdin, like other pharmacokinetic software such as SeBA-GEN is useful in the therapeutic monitoring of aminoglycosides especially when using the AUC approach.^{19,20} These software use the input of two plasma drug concentrations that are fitted to a one-compartment pharmacokinetic model to estimate exposures of interest (e.g. AUC). They have proven superiority over nomograms in adult populations.²⁰ However, usefulness in the CF population is debatable as the pharmacokinetic profile of tobramycin best fits a two-compartment pharmacokinetic model.^{9,10,15-17} The study by Hennig et al.⁹ is of relevance to the paediatric CF population, as they found that a two-compartment model best described the data collected from 35 paediatric patients with CF. Their model was validated and proven to be stable and suitable for inclusion into Bayesian-based software.

TCIWorks is capable of predicting tobramycin exposure from one plasma concentration. Like other Bayesian predictive programs, TCIWorks uses population pharmacokinetic models that contain population values for pharmacokinetic parameters, such as clearance and volume of distribution. Initially, the user can input patient-specific demographics, such as age, gender, weight and renal function to estimate the individual's pharmacokinetic parameters, which can be used to develop a pharmacokinetic curve (tobramycin concentration vs time post-dose). This can provide an estimated first dose of tobramycin for a new patient. As tobramycin concentration data are obtained, these, along with dosing details can be input to further 'individualise' the pharmacokinetic model. TCIWorks can then predict a new concentration–time curve that can be used to estimate an AUC or other measures of exposure. Any number of dose regimens can then be collated and collaboratively discussed with the prescriber on optimal future dosing. As subsequent tobramycin plasma concentrations are collected and entered with dosing details, TCIWorks further individualises the model, using Bayesian algorithms, resulting in greater predictive accuracy.

The TCIWorks method of monitoring is based on the target concentration intervention, which is an extension of the therapeutic drug monitoring principles. The difference is that the target concentration intervention uses population pharmacokinetic models to optimise therapy to a target concentration rather than a target range. If a target concentration that maximises an individual's response (or minimises an adverse response) is known, a tailored dose and dosing interval can be determined using the individual's pharmacokinetic parameters.²¹

The target concentration intervention is important in patients with CF for numerous reasons. Firstly, tobramycin pharmacokinetics is vastly different in patients with CF compared to normal paediatric populations.^{1,22} As CF patients tend to have a large volume of distribution and clearance, the dosage, therapeutic range and monitoring strategies typically seen in normal populations are not suitable. Secondly, like the normal population, there is sufficient unexplained inter- and intra-patient pharmacokinetic variability to warrant dose adjustment beyond the familiar covariate-based dosing (mg/kg),

which only achieves therapeutic concentrations in 60% of subjects.^{9,10} If a target concentration is required, then a target concentration intervention is essential. Thirdly, traditional nomograms and software are not suitable for tobramycin's two-compartment pharmacokinetics.^{20,23,24}

Our study demonstrated an unbiased association between the two AUCs (AUC₁ and AUC₂) tested and supports the potential use of TCIWorks in hospitals that use one plasma drug concentration. However, we advocate that newly diagnosed patients with CF or newly admitted patients with CF have two plasma drug concentrations estimated in the first instance to ensure individualised pharmacokinetic parameters and a more accurate dose prediction.

The study has some limitations. The two AUCs that were compared were generated from the same pharmacokinetic model and were not compared to a gold standard AUC. A gold standard AUC could be achieved with the use of rich sampling over one dosing interval – at least six samples to ensure accurate estimation of a two-compartment pharmacokinetic profile. However, the ethics of taking multiple samples from paediatric patients, makes such as study difficult. We also decided not to compare AUCs generated from other pharmacokinetic software as these programs use one-compartment models. As a consequence, the AUCs would rarely match and little would be gained by comparing them without a gold standard.

In conclusion, once an individual paediatric patient's tobramycin pharmacokinetic model is determined with two blood samples using TCIWorks, only one blood sample is required to estimate an AUC for tobramycin.

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Competing interests: None declared

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Erratum. Figure 1 on p. 133 of the article by Seleem M, et al. (Managing patients on antiplatelet drugs requiring emergency non-cardiac surgery. *J Pharm Pract Res* 2011; 41: 132-4.) did not indicate whether or not to proceed to surgery in high-risk situations. The corrected version of Figure 1 is provided below.

Figure 1. Proposed algorithm to manage non-stented patients on antiplatelet drugs requiring emergency non-cardiac surgery (CVA = cerebrovascular accident, MI = myocardial infarction, PCI = percutaneous coronary intervention).