

Pharmacokinetics of once and twice daily dosing of intravenous tobramycin in paediatric patients with cystic fibrosis

R. Brigg Turner¹, Fawzy Elbarbry¹, Lisa Biondo²

¹Pacific University, School of Pharmacy, Hillsboro, OR, USA, ²West Virginia University Healthcare, USA

The optimal dosing of intravenous tobramycin for treatment of pulmonary exacerbations in paediatric cystic fibrosis (CF) patients has not been completely delineated. We performed a retrospective study evaluating the pharmacokinetics and pharmacodynamics of once daily dosing (ODD) of IV tobramycin compared to twice daily dosing (TDD). Fifty-nine and 44 patients were included in the ODD and TDD groups, respectively. Once daily dosing achieved higher C_{max} as compared to TDD (29.5 ± 11.0 vs 19.0 ± 4.9 , $P < 0.001$), lower 24 hours AUC (92.8 ± 28.7 vs 128.5 ± 34.6 , $P < 0.001$), and greater time less than the MIC (13.4 ± 1.7 vs 3.9 ± 3.1 hours, $P < 0.001$). Twice daily dosing failed to achieve goal C_{max} :MIC for MICs > 1.0 mg/l. Twice daily dosing may be a viable alternative to ODD in treating organisms with MICs ≤ 1.0 mg/l; however, with MICs > 1.0 mg/l, ODD is likely necessary to achieve goal C_{max} :MIC ratios.

Keywords: Pharmacokinetics, Pharmacodynamics, Cystic fibrosis, Pulmonary exacerbation, Aminoglycoside

Introduction

In the Cystic Fibrosis Foundation (CFF) guidelines on treatment of pulmonary exacerbations, once daily dosing (ODD) of aminoglycosides is recommended over thrice daily dosing.¹ The evidence in support of this recommendation is limited but suggests ODD and thrice daily dosing to be equally efficacious with data indicating decreased side effects with ODD.¹ Since the publication of these guidelines, national surveys conducted in both adult and paediatric centres have overwhelmingly shown ODD of tobramycin to be the most common method for dosing. National surveys have identified that the most frequently prescribed interval for adults (94%) and children (78%) is ODD, although a percentage of centres use twice daily dosing (TDD).^{2,3}

Traditionally, aminoglycosides have been administered by intermittent infusions thrice daily. Although adoption of ODD of aminoglycosides in the cystic fibrosis (CF) population lagged behind the general population, several advantages to this modality led to its widespread use. Aminoglycoside ODD is designed to enhance bactericidal activity by producing a high peak concentration (C_{max}) to minimum inhibitory concentration (MIC) ratio while benefitting from the post-antibiotic effect (PAE).^{4,5} A C_{max} :

MIC ratio of 8–10 is considered optimal and correlates with better clinical outcomes in patients with CF.⁶ In addition to C_{max} , area under the concentration-time curve from 0 to 24 hours (AUC) has been associated with efficacy with an AUC:MIC ratio > 80 predicting positive outcomes.⁶ In contrast, increased time that drug concentration is below the MIC ($T < MIC$) has been associated with bacterial regrowth at the end of the dosing interval and the development of resistance in two small studies of CF patients.^{7,8} Once daily dosing has previously been shown to produce high C_{max} :MIC ratios but high $T < MIC$.⁵ Twice daily dosing may produce adequate C_{max} :MIC and AUC:MIC ratios necessary for efficacy while limiting $T < MIC$ and may be useful for prevention of resistance development. Despite consistent use, no studies have reported the pharmacokinetics of TDD of tobramycin in paediatric patients with CF. The purpose of this study is to describe the pharmacokinetics and pharmacodynamics of TDD in comparison to ODD for the treatment of acute pulmonary exacerbations in children with CF.

Materials and Methods

This single centre, retrospective study was approved by the West Virginia University (Morgantown, WV) institutional review board. In 2009, our hospital developed a protocol to guide dosing of tobramycin in paediatric CF patients, which recommends

Correspondence to: R. Brigg Turner, Pacific University, School of Pharmacy, 6 222 SE 8th Ave Suite 451, 7 Hillsboro, OR 97123, USA. Email: brigg.turner@pacificu.edu

ODD; if the initial regimen results in a calculated 16 hour tobramycin concentration <0.5 mg/l, the protocol recommends changing the regimen to TDD to limit the $T < \text{MIC}$.^{5,9,10} This protocol recommends collecting two tobramycin serum concentrations regardless of dosing interval.

Patient selection

This study was conducted in CF patients admitted to West Virginia University Healthcare from January 2009 to October 2013. Paediatric patients (18 years or younger) with a physician diagnosis of a pulmonary exacerbation were screened for inclusion. Patients receiving ODD of IV tobramycin with at least two tobramycin serum concentrations were included in the primary analysis. Patients subsequently receiving TDD of IV tobramycin were included in the TDD group. Patients receiving renal replacement therapy or with baseline renal impairment defined as an estimated creatinine clearance (CrCl) less than 40 ml/minute/1.73 m² (modified Schwartz equation¹¹) were excluded.

Data collection

The following data were collected from the electronic medical record: gender, age, height, weight, concurrently administered antibiotics, dosing of tobramycin (dose, interval, duration, changes of regimen), tobramycin serum concentrations and serum creatinine.

Pharmacokinetic analysis of tobramycin serum concentration

Blood samples were analysed by the particle enhanced turbidimetric inhibition immunoassay (PETINIA) using the Beckman Coulter DXC auto-analyzer as a part of routine medical care (Beckman Coulter, Inc., Brea, CA, USA). Pharmacokinetic parameters were derived from individual time-concentration data sets using the Sawchuk-Zaske method.¹² The AUC was calculated as previously described by Begg and colleagues.^{4,7}

Outcomes

We defined a regimen as achieving optimal pharmacodynamics with attainment of a $C_{\text{max}}:\text{MIC} \geq 8$, 24 hour $\text{AUC}:\text{MIC} \geq 80$, and a $T < \text{MIC}$ of 10 hours or less during a 24 hour period. For broad application, standardized MIC values for *Pseudomonas aeruginosa* of 1, 2 and 4 mg/l were used in determining pharmacodynamic indices. Achievement of these pharmacodynamic goals was compared between regimens. We additionally assessed nephrotoxicity by the change in estimated creatinine clearance during the hospital admission. Nephrotoxicity was defined as meeting risk, injury, or failure as defined by the pRIFLE criteria.¹³

Statistical analysis

Data were analysed using students *T*-test for continuous variables and Chi-squared or Fishers Exact tests for categorical variables. All statistical analyses were performed in STATA (StataCorp 2013. Stata Statistical Software: Release 13. College Station, TX, USA: StataCorp LP). Data were considered significant with $P < 0.05$.

Results

Fifty-nine patients received ODD and were included in this study with a total of 188 tobramycin serum concentrations. The demographics of these patients are outlined in Table 1. After initial determination of tobramycin serum concentrations, 44 patients (74.6%) were subsequently changed to TDD and were included in the TDD group. Mean daily dose was similar between ODD and TDD regimens (11.3 ± 1.9 vs. 11.7 ± 2.4 mg/kg, $P=0.32$).

Pharmacokinetics

Calculated pharmacokinetic parameters are outlined in Table 2. Receipt of TDD was associated with a lower volume of distribution (V_d) as well as lower tobramycin clearance as compared to receipt of ODD (Table 2). Lower V_d and clearance in the TDD group resulted in 38% higher AUC as compared to the ODD group (Table 2).

Table 1 Baseline demographics

Gender, male (%)	33 (55.9)
Age, years, median (IQR)	12 (10–17)
< 1 year (%)	1 (1.7)
1–10 years (%)	18 (30.5)
> 10 years (%)	40 (67.8)
Weight, kilograms, median (IQR)	39.2 (29.6 to 48.8)
BMI	17.7 ± 2.4
BMI < 5th percentile (%)	9 (15.3)
BMI 5–85th percentile (%)	44 (74.6)
BMI 85–95th percentile (%)	4 (6.8)
BMI > 95th percentile (%)	0 (0.0)
At CFF goal ¹⁴ (%)	19 (32.2)
Creatinine clearance at admission (ml/minute/1.73 m ²)	120.4 ± 32.9

BMI = body mass index; CFF = Cystic Fibrosis Foundation; IQR = interquartile range.

Table 2 Pharmacokinetics of ODD and TDD of IV Tobramycin

	ODD (n = 59)	TDD (n = 44)	P value
C_{max} (mg/l)	29.5 ± 11.0	19.0 ± 4.9	<0.001
C_{min} (mg/l)	0.02 ± 0.03	0.6 ± 0.4	<0.001
V_d (l/kg)	0.41 ± 0.21	0.31 ± 0.08	0.004
Clearance (L/hour/kg)	0.13 ± 0.04	0.09 ± 0.03	<0.001
AUC (mg• or •hour/l)	92.8 ± 28.7	128.5 ± 34.6	<0.001

Mean

\pm standard deviation. C_{max} : maximum concentration; C_{min} : minimum concentration; V_d : volume of distribution; AUC: area under the concentration-time curve from 0 to 24 hours; ODD: once daily dosing; TDD = twice daily dosing

Pharmacodynamics

Once daily dosing was more likely to achieve the goal C_{\max} :MIC but less likely to achieve AUC:MIC and $T < \text{MIC}$ targets as compared to TDD (Table 3). Once daily dosing achieved goal C_{\max} :MIC in almost all patients for a MIC of 1.0–2.0 mg/l but only 36% of patients at a MIC of 4.0 mg/l; TDD failed to achieve goal C_{\max} :MIC for MICs > 1.0 mg/l.

Safety

Serum creatinine values were available for all but two patients. Ten patients (17.5%) qualified as having risk per the pRIFLE criteria with none qualifying as having impairment or failure. Characteristics, including tobramycin dosing regimen (incidence of risk, ODD vs TDD; 20.0 vs 15.9%, $P=0.70$), were similar between at risk and not at risk groups. Of note, patients qualifying as at risk were not more likely to be receiving vancomycin (30.0 vs 34.0%, $P=1.0$) but were more likely to be receiving either piperacillin–tazobactam or ticarcillin–clavulante (odds ratio 3.92, 95% CI 0.95–16.2). Unfortunately, we cannot provide information regarding ototoxicity as this data were not recorded in the electronic medical record.

Discussion

In this retrospective study, we describe the pharmacokinetics of ODD and TDD of IV tobramycin in a paediatric population with CF. We demonstrated a lower V_d as well as lower tobramycin clearance with TDD as compared to ODD. The V_d for ODD found in our study was very similar to that previously reported in paediatric CF patients.^{9,15} Similar to our study, Vic and colleagues found lower V_d in those receiving thrice daily dosing as compared to ODD.¹⁶ Tobramycin clearance for ODD was very similar to that previously reported by others.^{7,9,17,18} Similar to our study, thrice daily dosing has been

associated with lower clearance as compared to ODD in several studies.^{7,16} As V_d and clearance are lower with TDD, lower daily doses may be required for TDD as compared to ODD to achieve similar AUC.

Attainment of pharmacodynamic parameters in our study (Table 3) was similar to a simulated pharmacokinetic analysis by Beringer and colleagues.⁵ In contrast to Beringer and colleagues, we identified a higher AUC in those receiving TDD of tobramycin. Similar to our results, Vic and colleagues identified higher AUC in those receiving thrice daily as compared to ODD.¹⁶ While not completely elucidated in this population, pharmacodynamics linked with efficacy are C_{\max} :MIC and AUC:MIC. Master and colleagues identified that higher C_{\max} :MIC ratios were associated with greater improvements in pulmonary function (forced expiratory volume in one second [FEV1], forced vital capacity [FVC]).⁷ Likewise, Burkhardt and colleagues reported that improvement in FEV1 correlated with AUC:MIC and C_{\max} :MIC ratios, with the most important predictor of lung improvement being the C_{\max} :MIC ratio.⁸

The impact of $T < \text{MIC}$ on clinical outcomes has not been demonstrated. Beringer and colleagues conducted a pharmacokinetic study comparing tobramycin dosed every 24, 12 or 8 hours. They concluded that every 12 hour dosing effectively balanced achievement of the desired C_{\max} :MIC while minimizing the $T < \text{MIC}$.⁵ Given the increasing survival of patients with CF, there should be increased concern regarding the potential of development of resistance with repeated antibiotic exposure. Two studies in CF patients identified increased MICs following treatment with ODD as compared to more frequent dosing.^{7,8} Burkhardt and colleagues reported the percentage of patients with a resistant gram negative bacteria (MIC > 16 mg/l) in the ODD and thrice daily dosing groups increased from 5.9 to 29.4% and 12.5 to 18.8%, respectively. The mean MIC in the ODD and thrice daily dosing increased by 6.8 mg/l ($P=0.034$) and 0.6 mg/l ($P>0.05$), respectively. Master and colleagues compared ODD of tobramycin monotherapy ($n=23$) to thrice daily dosing of tobramycin/ceftazidime ($n=23$). The monotherapy group showed a significant increase in MIC of *P. aeruginosa* from study entry to exit ($P=0.02$) while this increase was not identified in the combination group ($P=0.08$). While we demonstrated decreased $T < \text{MIC}$ in the TDD group, it is unknown if this translates into improved long term efficacy or decreased resistance.

As the proposed pharmacodynamic goal for C_{\max} :MIC is 8–10, TDD may be an acceptable alternative to ODD with MICs ≤ 1.0 mg/l. In addition, the benefit of decreased $T < \text{MIC}$ may lead to

Table 3 Attainment of pharmacodynamic goals in ODD and TDD groups

	ODD (n = 59)	TDD (n = 44)	P value
MIC = 1 mg/l			
C_{\max} :MIC > 8	58 (98.3)	44 (100.0)	1.0
AUC:MIC > 80	39 (66.1)	42 (95.5)	< 0.001
$T < \text{MIC} < 10$ hours	1 (1.7)	42 (95.5)	< 0.001
MIC = 2 mg/l			
C_{\max} :MIC > 8	54 (91.5)	27 (61.4)	< 0.001
AUC:MIC > 80	1 (1.7)	12 (27.3)	< 0.001
$T < \text{MIC} < 10$ hours	0 (0.0)	33 (75.0)	< 0.001
MIC = 4 mg/l			
C_{\max} :MIC > 8	21 (35.6)	0 (0.0)	< 0.001
AUC:MIC > 80	0 (0.0)	0 (0.0)	1.0
$T < \text{MIC} < 10$ hours	0 (0.0)	5 (11.4)	0.012

Data reported as incidence (percent). MIC = minimum inhibitory concentration; C_{\max} = maximum concentration; C_{\min} = minimum concentration; AUC = area under the concentration-time curve from 0 to 24 hours; ODD = once daily dosing; TDD = twice daily dosing.

slower conversion to tobramycin resistance. However, with MICs >1.0 mg/l, TDD will likely fail to achieve goal C_{\max} :MIC. Of interest, we have identified higher C_{\max} :MIC ratios yet lower AUC:MIC with ODD; the implications of this are not known, but we hypothesize that efficacy still favours achievement of goal C_{\max} :MIC.

While our analysis did not have sufficient rigour to adequately assess safety, receipt of TDD of tobramycin was not associated with increased nephrotoxicity as compared to those that received ODD. Of interest, receipt of extended spectrum penicillins (piperacillin-tazobactam and ticarcillin-clavulanate) was more likely in those at risk of nephrotoxicity. While an analysis of ticarcillin-clavulanate in CF patients demonstrated excellent tolerability,¹⁹ reports have linked piperacillin-tazobactam use to increased rates of nephrotoxicity in non-CF patients.^{20,21} Further investigation may be warranted.

There are several limitations to the current study. First, this was a retrospective study utilizing limited tobramycin serum samples. As our primary focus was the pharmacokinetics of this dosing regimen, we did not evaluate clinical markers such as FEV₁. In addition, we did not have access to changes in MICs for colonizing organisms.

In conclusion, we report the pharmacokinetics and pharmacodynamics of ODD and TDD tobramycin in paediatric CF patients. The dosing utilized in the TDD cohort of approximately 6 mg/kg every 12 hours of IV tobramycin had adequate attainment of C_{\max} :MIC, AUC:MIC, and optimized $T < \text{MIC}$ with MICs ≤ 1.0 mg/l. However, ODD may be necessary in order to ensure achievement of goal C_{\max} :MIC for MICs > 1.0 mg/l. Evaluation of TDD of IV tobramycin in a clinical or longitudinal trial is required in order to identify if a clinical benefit is present in treating paediatric patients with low MICs.

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Disclaimer statements

Contributors

LB and RBT conceived of and designed the study and obtained ethics approval. LB, FE, and RBT collected, analyzed and interpreted the data. LB, FE and RBT wrote and revised the article.

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Conflict of interest

The authors have no conflicts to disclose.

Ethics approval

This study was granted exempt status by the West Virginia University institutional board review prior to being conducted.

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