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Safety of intravenous tobramycin in combination with a variety of anti-pseudomonal antibiotics in children with cystic fibrosis

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Abstract

Objectives: Previous studies have examined renal safety of once daily intravenous tobramycin in individuals with cystic fibrosis. This has been mainly in combination with ceftazidime in an adolescent or adult population. In this report, we describe our institutional experience of once daily intravenous tobramycin in combination with a variety of second anti-pseudomonal antibiotics in children with cystic fibrosis.

Methods: We present a retrospective review including children with cystic fibrosis, who were admitted for a pulmonary exacerbation from January 2009 to December 2011, and treated using intravenous tobramycin. A literature review of once daily intravenous aminoglycoside dosing in cystic fibrosis was performed to compare our results to existing literature.

Results: A total of 35 subjects were divided into once daily dosing (n = 20) versus multiple daily dosing (n = 15) groups. Mean age was 11.3 years (± 5.7) for the once daily dosing group and 13.1 years (± 4.4) for the multiple daily dosing group (p = 0.34). All subjects had normal baseline serum creatinine at admission (once daily dosing 0.49 ± 0.14 mg/dL vs multiple daily dosing 0.62 ± 0.23 mg/dL, p = 0.07). All subjects received intravenous tobramycin, and most received piperacillin-tazobactam as their second anti-pseudomonal antibiotic (once daily dosing 45% and multiple daily dosing 40%). There was no significant change in serum creatinine in either group during antibiotic treatment (once daily dosing 0.08 ± 0.12 mg/dL vs. multiple daily dosing 0.06 ± 0.10 mg/dL, p = 0.43). All subjects had significant improvement in lung function following intravenous antibiotic therapy.

Conclusion: We show that both once daily dosing and multiple daily dosing of intravenous tobramycin in combination with a variety of second anti-pseudomonal antibiotics were safe in terms of nephrotoxicity in children with cystic fibrosis. These findings are important given existing literature mainly examines once daily tobramycin in combination with ceftazidime, a cephalosporin, and the majority of our patients were on tobramycin with piperacillin-tazobactam, an extended spectrum penicillin plus beta-lactam. This contributes new information not previously examined in a pediatric cystic fibrosis population.

Keywords

Cystic fibrosis, aminoglycoside, once daily dosing, renal function, pulmonary function, safety, efficacy, pediatrics

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Introduction

A significant contributor to morbidity and mortality in patients with cystic fibrosis (CF) is chronic lung infection with *Pseudomonas aeruginosa*. Recurrent infection with *P. aeruginosa* induces a state of chronic inflammation which in turn leads to irreversible pulmonary damage and declining lung function.[1] Antibiotics have long been used as a principal component of treatment for pulmonary exacerbations in CF. Historically, aminoglycosides were dosed in multiple daily doses. However, aminoglycosides exert

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concentration-dependent killing. The once daily dosing (ODD) interval achieves a high maximal concentration to minimum inhibitory concentration (C_{max}/MIC) ratio; thereby, enhancing killing of *P. aeruginosa*[2] compared to the traditional multiple daily dosing (MDD) regimen. Furthermore, this regimen allows trough concentrations to fall below detectable limits and provides a drug free interval which may reduce the risk of nephrotoxicity.

However, aminoglycoside therapy is still associated with adverse side effects; thereby, leading researchers to investigate the safest and most efficacious dosing regimen for these drugs.[3] Studies examining the safety of once daily IV aminoglycoside dosing report it to be safe and effective in treating CF exacerbations due to *P. aeruginosa*.[4] The Tobramycin Once-Daily Prescribing in Cystic Fibrosis (TOPIC) study, a large randomized controlled trial, specifically determined ODD of tobramycin in combination with ceftazidime was equally efficacious compared to MDD and also possibly less nephrotoxic in children with CF.[5] Cystic Fibrosis Foundation (CFF) guidelines recommend double antibiotic coverage for treatment of pulmonary exacerbations secondary to *P. aeruginosa*, with one of these antibiotics usually being an aminoglycoside.[6] Also, more recent CFF guidelines recommend ODD of IV aminoglycosides when used for treatment of a pulmonary exacerbation.[7] A survey found that 61% of CFF-Accredited Care centers have adopted ODD of IV tobramycin.[8] However, minimal data exist examining the effects once daily versus multiple daily tobramycin dosing in children with CF when combined with a variety of other anti-pseudomonal antibiotics, other than ceftazidime. In this report, we present our institutional experience with ODD of IV tobramycin in combination with a variety of second anti-pseudomonal agents.

Materials and methods

Retrospective review

Approval for this study was obtained from the Indiana University Institutional Review Board. This retrospective chart review included randomly selected participants with CF ≤ 18 years of age, with a CF-related pulmonary exacerbation, admitted to the hospital for IV antibiotic therapy with tobramycin from January 2009 to December 2011. The diagnosis of a pulmonary exacerbation was made by the attending pulmonary physician based on clinical judgment of symptoms such as cough, shortness of breath, changes in sputum, and/or weight loss. Antibiotics were chosen by the pulmonary physician and CF pharmacist. Those subjects receiving IV vancomycin were excluded due to the potential for adverse renal effects from vancomycin. Chronic inhaled aminoglycosides were not continued during the IV antibiotic course.

Nephrotoxicity was defined using the pediatric Risk, Failure, Loss, End stage renal disease (pRIFLE) criteria with an increase of ≥0.3 mg/dL or ≥1.5-fold increase in the creatinine level from baseline being considered significant.[9] In order to detect a change in serum creatinine (SCr) of 0.3 mg/dL, a sample size of 5 in each group were required with a power of 0.8. Estimated glomerular filtration rate (eGFR) was calculated using the Schwartz equation.[10] We reviewed 100 charts, 35 subjects meeting the above criteria were selected. Demographic and clinical data collected included duration of treatment, anti-pseudomonal agents used, baseline and peak SCr concentrations, tobramycin dose, and spirometry at the beginning and end of antibiotic treatment. The duration of antibiotic therapy was determined by the treating pulmonary physician.

Review of the literature

PubMed and MEDLINE databases were queried for "once daily aminoglycosides AND cystic fibrosis" from January 1994 to January 2015. Only studies in English language were included. A total of 62 articles were identified. There were 21 clinical trials and 14 review articles, with 3 of those being Cochrane reviews. Articles that addressed once daily aminoglycoside dosing and combinations with a second anti-pseudomonal agent were included in the review. These findings are presented in the discussion.

Results

Patient characteristics

A total of 35 subjects were included for analysis. They were divided into ODD and MDD groups based on the frequency of IV tobramycin administration. The ODD group received IV tobramycin every 24 h. The MDD group received IV tobramycin every 8 h or every 12 h. Table 1 illustrates their demographic and clinical characteristics. The average age was 11.3 ± 5.7 years in the ODD group and 13.1 ± 4.4 years in the MDD group (p = 0.34). In the ODD group, 45% (n = 9) were male. In the MDD group, 60% (n = 9) were male (p = 0.49). All participants were Caucasian. The mean body mass index (BMI) was 17.3 ± 2.4 in the ODD group and 17.2 ± 2.8 in the MDD group (p = 1.00). Participants receiving vancomycin were excluded; however, those receiving nonsteroidal anti-inflammatory drugs (NSAIDS) were not excluded. There were only four subjects on NSAIDS, all in the ODD group. Only one subject was on inhaled antibiotics during the course of IV therapy, and this participant was on colistin. There were similar rates of CF-related diabetes (CFRD) and CF liver disease. Indicators of renal function used were SCr and eGFR. Baseline SCr was normal in both groups and did not differ significantly between the groups (ODD 0.49 ± 0.14 mg/dL vs MDD 0.62 ± 0.23 mg/dL, p = 0.07). GFR was estimated (eGFR) using the Schwartz equation[10] and was normal in both groups (114.5 ± 24.8 mL/min/1.73 m^2 in the ODD group and 99.0 ± 44.4 mL/min/1.73 m^2 in the MDD group, p = 0.24). In order to have an estimate of hydration status, blood urea nitrogen to creatinine (BUN/Cr) ratio was used as this has been shown to be associated with increasing fluid deficit.[11] The baseline BUN/

Table 1. Demographics.

	Once daily dosing (ODD) (n = 20)	Multiple daily doses (MDD) (n = 15)	p-value
Age (years)	11.3 (5.7)	13.1 (4.4)	0.34
Weight (kg)	31.6 (13.4)	37.1 (12.8)	0.23
Height (cm)	131.4 (38.1)	147.4 (18.0)	0.07
BMI	17.3 (2.4)	17.2 (2.8)	1.00
Male	9 (45)	9 (60)	0.50
Caucasian	20 (100)	15 (100)	NA
Baseline lab measures			
Cr (mg/dL)	0.49 (0.14)	0.62 (0.23)	0.07
BUN (mg/dL)	8.7 (4.2)	10.5 (4.4)	0.22
BUN/Cr ratio	18.3 (8.6)	18.5 (10.4)	0.96
eGFR (mL/min/1.73 m^2)	114.5 (24.8)	99.0 (44.4)	0.24
Other factors			
CFRD (Y)	4 (20)	5 (33)	0.45
CF liver disease (Y)	1 (5)	1 (7)	1.00
NSAIDS (Y)	4 (20)	0 (0)	0.12

BMI: body mass index; BUN: blood urea nitrogen; eGFR: estimated glomerular filtration rate; CFRD: cystic fibrosis–related diabetes; CF: cystic fibrosis; NSAIDS: nonsteroidal anti-inflammatory drugs.

Cr ratio was 18.3 ± 8.6 in the ODD group and 18.5 ± 10.4 in the MDD dosing group (p = 0.96), both in the normal range and not significantly different.

Antibiotics and outcomes

All subjects were administered IV tobramycin. Most subjects were on piperacillin-tazobactam as their second anti-pseudomonal antibiotic (45%, n = 9 in the ODD group and 40%, n = 6 in the MDD group, p = 1.00). The breakdown of anti-pseudomonal agents is displayed in Table 2. Note, a few subjects in the ODD group received more than one antibiotic agent duringtheir treatment course in addition to tobramycin, and one subject in the MDD group was missing data. Table 3 shows study outcomes including days of inpatient and outpatient IV aminoglycosides, area under the curve (AUC), and change in SCr. AUC was calculated to measure aminoglycoside exposure between the two groups. There was no significant difference in AUC between the ODD and MDD groups (1035 ± 609 vs 1045 ± 517, respectively, p = 0.96). The duration of IV aminoglycoside therapy did not significantly differ between the two groups (ODD inpatient 10.7 ± 5.5 days vs MDD inpatient 9.4 ± 4.8 days, p = 0.49). The duration of therapy outpatient for the ODD group was 10.9 ± 3.4 days versus that for the MDD group which was 8.7 ± 4.8 days (p = 0.26). A dosing adjustment was made in 40% (n = 8) of participants in the ODD group and 53% (n = 8) in the MDD group based on measured AUC during their antibiotic course. Mean baseline creatinine was 0.49 ± 0.14 mg/dL in the ODD group and 0.62 ± 0.23 mg/dL in the MDD group without significant difference between the groups (p = 0.07). The mean change in creatinine was 0.08 ± 0.12 mg/dL in the ODD group and 0.06 ± 0.10 mg/dL in the MDD group (p = 0.43), which was not statistically significant between groups and not clinically significant based on pRIFLE criteria as noted in the methods. Lung function was measured at the start and end of IV antibiotic therapy including forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and forced expiratory flow between 25% and 75% of vital capacity ($FEF_{25–75}$). These values are displayed in Table 4 using

Table 2. Second anti-pseudomonal antibiotic.

Antibiotic agent	Once daily dosing (ODD) (n = 20)	Multiple daily doses (MDD) (n = 15)	p-value
Piperacillin-tazobactam	9 (45)	6 (40)	1.00
Cefepime	5 (25)	2 (13)	0.67
Ticarcillin-clavulanate	3 (15)	2 (13)	1.00
Meropenem	4 (20)	2 (13)	0.68
Ceftazidime	0 (0)	1 (7)	0.43
Imipenem	0 (0)	1 (7)	0.43
Cefoxitin	1 (5)	0 (0)	1.00
Ceftriaxone	1 (5)	0 (0)	1.00

Table 3. Study outcomes.

	Once daily dosing (ODD) (n = 20)	Multiple daily doses (MDD) (n = 15)	p-value
Inpatient IV aminoglycoside (days)	10.7 (5.5)	9.4 (4.8)	0.49
Outpatient IV aminoglycoside (days)	10.9 (3.4)	8.7 (4.8)	0.26
AUC (inpatient)	1035 (609)	1045 (517)	0.96
Baseline SCr (mg/dL)	0.49 (0.14)	0.62 (0.23)	0.07
Change in SCr (mg/dL)	0.08 (0.12)	0.06 (0.10)	0.43

IV: intravenous; AUC: area under the curve; SCr: serum creatinine.

Table 4. Lung function.

	Once daily dosing (ODD) (n = 17)	Multiple daily doses (MDD) (n = 15)	p-value
FVC z-score (start)	−2.59 (1.62)	−2.99 (2.32)	0.57
FVC z-score (end)	−1.22 (1.34)	−1.84 (2.66)	0.43
FVC z-score (difference)	1.39 (1.31)	1.14 (1.01)	0.61
FEV_1 z-score (start)	−3.59 (1.52)	−4.68 (−2.35)	0.78
FEV_1 z-score (end)	−2.38 (1.55)	−2.55 (2.21)	0.83
FEV_1 z-score (difference)	1.24 (1.53)	1.27 (1.15)	0.96
$FEF_{25–75}$ z-score (start)	−3.40 (1.58)	−3.89 (2.24)	0.49
$FEF_{25–75}$ z-score (end)	−2.63 (2.10)	−2.93 (2.39)	0.74
$FEF_{25–75}$ z-score (difference)	0.91 (1.46)	1.16 (1.13)	0.63

FVC: forced vital capacity; FEV1: forced expiratory volume in 1 sec; $FEF_{25–75}$: forced expiratory flow between 25% and 75% of vital capacity.

z-scores. It shows abnormal lung function (z-score less than –1.96) at the start of therapy in both groups and in all lung function parameters measured. These all improved with IV antibiotic therapy.

Discussion

In our retrospective review, we show a clinically significant improvement in lung function without nephrotoxicity in pediatric CF subjects on ODD and MDD of IV tobramycin in combination with a variety of second anti-pseudomonal agents. Although we only included a small number of subjects, this is an important finding. Based on CFF recommendations for double antibiotic coverage of pulmonary exacerbations suspected to be due to *P. aeruginosa*,[6] IV aminoglycosides are frequently used in combination with a variety of second anti-pseudomonal antibiotics. It is therefore pertinent to consider the safety and efficacy of these drug combinations. Most importantly, we show the safety and efficacy of once daily IV aminoglycosides combined with a second anti-pseudomonal agent as this regimen follows the most recent CFF treatment recommendations.[7]

Two clinical trials are published involving once daily IV aminoglycosides in children.[12,13] The first was a randomized clinical trial in 22 CF subjects, mean age 11 years old, comparing once daily IV tobramycin dosing to thrice daily dosing, both groups in combination with ceftazidime as the second agent. They reported clinical improvement in both groups without renal or ototoxicity with no statistically significant difference between groups. The authors concluded once daily tobramycin combined with ceftazidime was safe and effective for treatment of *P. aeruginosa* exacerbations in CF.[13] The next study compared the safety and efficacy of once daily IV tobramycin monotherapy to conventional thrice daily tobramycin coupled with ceftazidime IV for acute *P. aeruginosa* pulmonary exacerbations in CF.[12] A total of 51 subjects were randomized into two groups, mean age 16 years old in the conventional treatment group and 14 years in the tobramycin monotherapy group. They reported once daily tobramycin monotherapy to be as effective and safe as conventional thrice daily tobramycin/ceftazidime therapy.[12] Both of these studies demonstrated that once daily IV tobramycin is safe and as effective as traditional thrice daily dosing without significant differences in safety or efficacy.

Although not specific to CF, a meta-analysis of 24 studies examined extended interval aminoglycoside administration for children with a variety of conditions, 3 studies involving CF subjects. This meta-analysis concluded there were no significant difference in the failure rates, primary nephrotoxicity outcomes, or ototoxicity between ODD and multiple daily doses of IV aminoglycosides.[14]

The largest study to date evaluating once daily aminoglycoside dosing was the TOPIC study published by Smyth and colleagues in 2005. The TOPIC study was a large, multi-centered, randomized controlled trial that included 244 subjects. Of these, 125 were children. Subjects were randomized to receive either once daily or multiple daily doses of IV tobramycin with ceftazidime. They concluded that once daily IV tobramycin had equal efficacy for pulmonary exacerbations based on pulmonary function testing and that the once daily regimen might be less nephrotoxic in children.[5] The subjects enrolled in this study all received ceftazidime as the second anti-pseudomonal agent in combination with tobramycin, and no additional antibiotic agents were evaluated in combination with once daily tobramycin.

The previously mentioned studies all used clinical endpoints. Another group examined the safety of once daily IV tobramycin in 18 subjects with CF using pharmacokinetics. Subjects were older, with a mean age of 24.6 years and only included two pediatric subjects. They were administered IV tobramycin in doses ranging from 7 to 15 mg/kg/d (mean dose 11.9 mg/kg/d). Peak serum concentrations, mean total body clearance, volume of distribution, and elimination half-life were measured. No ototoxicity or nephrotoxicity was observed, and assessments were based on hearing screen and SCr, respectively. Using a combination of pharmacokinetic and clinical data, they concluded once daily IV tobramycin may be used safely to treat pulmonary exacerbations in subjects with CF. Investigators did not use a second anti-pseudomonal agent to treat subjects in this study.[15]

In 2012, the most recent Cochrane review regarding ODD versus MDD of IV aminoglycosides for CF was published.[4] They included four studies with a total of 328 subjects that evaluated the efficacy and toxicity of once versus thrice daily dosing of IV tobramycin for a pulmonary exacerbation in CF. Two of the studies are described above,[5,13] and the results of the other two are as follows. The first of these was performed only in adults. A total of 30 subjects received once daily IV tobramycin and 19 received thrice daily IV tobramycin. The second anti-pseudomonal agents included piperacillin, tazocin, aztreonam, azlocillin, meropenem, imipenem, or ceftazidime and were selected based on sputum cultures and sensitivity results. Both groups showed significant improvement in respiratory function as measured by pulmonary function testing without clinically significant changes in renal function. They concluded these were encouraging results, but suggested larger multi-centered studies to confirm the results.[16] The next study was designed to determine the efficacy of continuous versus thrice daily ceftazidime therapy in CF administered concomitantly with once daily IV tobramycin. This study included a total of 56 subjects, mean age 14.4 years. They concluded both regimens to be efficacious by clinical and pulmonary function measures, but did not report creatinine.[17] Cochrane concluded, based on review of the literature, that once daily and three-times daily dosing of IV aminoglycoside antibiotics appeared to be equally effective in the treatment of CF pulmonary exacerbations and based

on the TOPIC study that ODD may have less nephrotoxic effects in children.[4]

Although multiple groups have examined the safety and efficacy of once daily aminoglycoside dosing compared to thrice daily dosing in pulmonary exacerbations in subjects with CF, only a small pediatric CF population was represented. Also, the majority of these studies were performed with subjects on only ceftazidime as the second anti-pseudomonal agent. The only study that used a wider variety of anti-pseudomonal agents was in adults only and authors did not clearly specify the number of subjects receiving each antibiotic combination. There has been little work published showing the safety of once daily IV tobramycin in children with CF using additional anti-pseudomonal antibiotics, other than ceftazidime. This is an important gap as in clinical practice, a variety of anti-pseudomonal antibiotics may be used based on respiratory cultures and bacterial susceptibilities. In our study, we used an exclusively pediatric population and showed the use of multiple anti-pseudomonal agents in combination with once daily tobramycin was both safe and effective. This adds additional information previously missing from the literature.

A few limitations of our study exist. This was a retrospective review, thus the sample size was small. SCr was used as a marker of renal function. SCr is affected by muscle mass and therefore can be quite variable in children with CF. Glomerular filtration rate (GFR) may have been a better measure; however, GFR is not routinely measured at our institution. eGFR was used in place of measured GFR. IV fluid use may have contributed to nephrotoxicity avoidance; however, these data were not collected. BUN/Cr ratio was used as a surrogate indicator of hydration status. Culture and susceptibility data were not recorded; however, the practice at our institution is to choose antibiotics based on available sputum cultures and susceptibility data.

Conclusion

In conclusion, ODD of IV tobramycin in combination with a variety of second anti-pseudomonal antibiotics, mainly piperacillin-tazobactam, did not cause nephrotoxicity in children with CF and led to notable physiologic improvements in lung function. As the median age of survival of the CF population increases, delivery of IV antibiotic courses that are safe, effective, and decrease the risk of toxicity are important.

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Declaration of conflicting interests

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Ethical approval

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Informed consent

Informed consent was not sought for this study because it was a retrospective review with exempt status (no patient identifiers were recorded and the study made use of already existing data).

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