Assessment of Detectable Serum Tobramycin Concentrations in Patients Receiving Inhaled Tobramycin for Ventilator-Associated Pneumonia

Christopher A Droege, Neil E Ernst, Madeline J Foertsch, Paige G Bradshaw, Andrew E Globke, Dina Gomaa, Betty J Tsuei, and Eric W Mueller

BACKGROUND: Inhaled tobramycin can be used for empiric or definitive therapy of ventilator-associated pneumonia (VAP) in mechanically ventilated patients. This is believed to minimize systemic exposure and potential adverse drug toxicities including acute kidney injury (AKI). However, detectable serum tobramycin concentrations have been reported after inhaled tobramycin therapy with AKI. METHODS: This retrospective, observational study evaluated mechanically ventilated adult subjects admitted to ICUs at a large, urban academic medical center that received empiric inhaled tobramycin for VAP. Subjects were separated into detectable (ie, ≥ 0.6 mg/L) or undetectable serum tobramycin concentration groups, and characteristics were compared. Independent predictors for detectable serum tobramycin concentration and new onset AKI during or within 48 h of therapy discontinuation were assessed. RESULTS: Fifty-nine inhaled tobramycin courses in 53 subjects were included in the analysis, of which 39 (66.1%) courses administered to 35 (66.0%) subjects had detectable serum tobramycin concentrations. Subjects with detectable serum tobramycin concentrations were older (57.1 y ± 11.4 vs 45.9 ±15.0, *P* = .004), had higher PEEP (9.2 cm H_2O [7.0–11.0] vs 8.0 [5.6–8.9], *P* = .049), chronic kidney disease stage ≥ 2 (10 [29.4%] vs 0 [0%], *P* = .009), and higher serum creatinine before inhaled tobramycin therapy (1.26 mg/dL [0.84–2.18] vs 0.76 [0.47–1.28], *P* = .004). Age (odds ratio 1.09 [95% CI 1.02–1.16], *P* = .009) and PEEP (odds ratio 1.47 [95% CI 1.08–2.0], *P* =.01) were independent predictors for detectable serum tobramycin concentration. Thirty-seven subjects had no previous renal disease or injury, of which 9 (24.3%) developed an AKI. Sequential Organ Failure Assessment score (odds ratio 1.72 [95% CI 1.07–2.76], *P* = .03) was the only independent predictor for AKI. CONCLUSIONS: Detectable serum tobramycin concentrations were frequently observed in critically ill, mechanically ventilated subjects receiving empiric inhaled tobramycin for VAP. Subject age and PEEP were independent predictors for detectable serum tobramycin concentration. Serum monitoring and empiric dose reductions should be considered in older patients and those requiring higher PEEP. *Key words: aminoglycosides; tobramycin; critical illness; pneumonia; ventilators; mechanical; acute kidney injury.* [Respir Care 2022;67(1):16–23. © 2022 Daedalus Enterprises]

Introduction

Ventilator-associated pneumonia (VAP) is a common hospital-acquired infection affecting between 10–27% of mechanically ventilated patients with an attributable mortality ranging 13–37%.[1-4] As the incidence of multidrug-resistant organisms (MDRO) continues to increase, aerosolized or inhaled aminoglycoside antibiotics are often used as empiric or definitive therapy to treat VAP in ICU patients.[5,6] Most recent guidelines support the use of inhaled aminoglycosides in addition to systemic therapy for the treatment of VAP due to MDRO.[7] Depending on the inhalation system used and the particle size of the medication, inhaled aminoglycosides may deliver significantly higher concentrations to the lung parenchyma compared to intravenous administration.[8] Another perceived benefit of inhaled aminoglycosides is minimizing systemic exposure, which can limit adverse effects such as ototoxicity with elevated serum concentrations and acute kidney injury (AKI) with lack of serum clearance.[5,9]

Tobramycin is an aminoglycoside frequently used as inhaled therapy. Inhaled tobramycin is FDA approved for use in patients with cystic fibrosis but is also used off-label in patients with VAP. Given the particle size of tobramycin, it is anticipated that inhaled tobramycin would not result in

significant systemic accumulation. Detectable serum tobramycin concentrations have been documented in patients receiving inhaled tobramycin or tobramycin instilled through the endotracheal tube.[10-13] Despite the risk of detectable serum tobramycin concentrations, reports of adverse effects are low.[14] Case reports have indicated subjects developed AKI and vestibular toxicity.[15-19]

SEE THE RELATED EDITORIAL ON PAGE 151

Risk factors associated with systemic absorption of inhaled tobramycin and subsequent development of adverse effects remain unclear. Systemic absorption following inhaled tobramycin is likely multifactorial and could be due to factors such as AKI, chronic kidney disease, positive-pressure ventilation, diminished acute or chronic lung function with or without structural lung pathologies, or airway obstructions (eg, mucous plugs).[20]

This retrospective cohort analysis observed critically ill, mechanically ventilated subjects that received inhaled tobramycin as part of VAP treatment. We aimed to investigate the rate of and assess risk factors for detectable serum tobramycin concentrations. The practical application of this study is to increase awareness among clinicians regarding the safety of inhaled tobramycin.

QUICK LOOK

Current knowledge

Inhaled tobramycin may be used as an adjunctive treatment in adult critically ill patients with ventilator-associated pneumonia (VAP). This route of administration is thought to lessen systemic tobramycin exposure and risk for acute kidney injury (AKI) relative to intravenous administration; however, the incidence of detectable serum tobramycin concentrations in adult critically ill patients without cystic fibrosis is unknown. Risk factors for detectable tobramycin concentrations and association with AKI are poorly characterized to support safe use of inhaled therapy.

What this paper contributes to our knowledge

A majority of critically ill subjects receiving inhaled tobramycin therapy without concomitant intravenous therapy for VAP were at risk for systemic exposure. Subject age and PEEP while receiving inhaled tobramycin were independent risk factors associated with detectable serum tobramycin concentration. New AKI was associated with severity of illness and not the presence of detectable serum tobramycin during inhaled therapy.

Methods

This single-center, retrospective, observational, safety analysis evaluated adult subjects on mechanical ventilation admitted to an ICU at the University of Cincinnati Medical Center that received inhaled tobramycin for empiric treatment of VAP per institutional protocol. The study was approved by the University of Cincinnati Institutional Review Board, and data collection was conducted August 2016 and July 2017. Data were being collected across all institutional ICUs (ie, medical, surgical, neuroscience, cardiovascular, burns) in which serum tobramycin concentrations were intended to be drawn after the third or fourth inhaled tobramycin dose in subjects receiving empiric therapy as part of a safety and quality analysis. The pursuance of this safety analysis was driven by 2 anecdotal observations in patients who subjects developed AKI had random serum tobramycin concentrations drawn and return detectable while receiving inhaled tobramycin. For the safety analysis, the first concentration was intended to be drawn 3 h after the third dose with an optional second concentration 10 h after the third dose. The formulation of inhaled tobramycin used for subjects without cystic fibrosis was sterilely compounded as 7.5 mL of tobramycin 40 mg/mL for injection, resulting in a final dose of 300 mg instilled into vibrating mesh nebulizer (Aerogen, Galway, Ireland) on the dry side of the humidified adult breathing circuit. The mesh nebulizer is set for a 30-min nebulization cycle with a maximum capacity of 6 mL. The remainder of the 7.5 mL is added once there is room in the nebulizer cup to avoid potential interruption to ventilation or the nebulization process.

Adult patients on mechanical ventilation were eligible for inclusion if they were initiated on inhaled

Drs Droege, Ernst, Foertsch, Bradshaw, and Mueller are affiliated with UC Health – University of Cincinnati Medical Center, Department of Pharmacy Services, Cincinnati, Ohio and University of Cincinnati James L. Winkle College of Pharmacy, Division of Pharmacy Practice and Administrative Sciences, Cincinnati, Ohio. Dr Globke is affiliated with United States Army, Blanchfield Army Community Hospital, Department of Pharmacy, Fort Campbell, Kentucky. Dr Tsuei and Ms Gomaa are affiliated with University of Cincinnati, Department of Surgery, Division of Trauma, Cincinnati, Ohio.

The authors have disclosed no conflicts of interest.

Dr Globke presented a version of this paper at the 2018 American College of Clinical Pharmacy Global Conference on Clinical Pharmacy held October 20–23, 2018, in Seattle, Washington.

Correspondence: Christopher A Droege PharmD, UC Health – University of Cincinnati Medical Center, Department of Pharmacy Services, 234 Goodman Street, Cincinnati, OH 45219. E-mail: christopher.droege@uchealth.com.

DOI: 10.4187/respcare.09412

tobramycin therapy for empiric antibacterial coverage of VAP and received at least three 300 mg doses twice daily and had at least one serum trough tobramycin concentration drawn after the third dose. Patients were excluded if they had a diagnosis of cystic fibrosis, received intravenous tobramycin within 48 h of the first inhaled tobramycin dose or during inhaled tobramycin therapy, were actively incarcerated, or were pregnant. Subjects were included more than once if they had inhaled tobramycin exposure > 7 d apart from one another. If subjects were included more than once, data such as age, sex, and race were only included in analyses once. Subject entries were separated into detectable and undetectable groups for analysis as determined by the first serum tobramycin concentration. A serum tobramycin concentration was considered detectable if it was above the laboratory lower limit of 0.6 mg/L at any time. Tobramycin assays used were a validated homogeneous enzyme immunoassay, which is an FDA-approved test to assess serum concentrations and aligns with package insert recommendations.

The primary aim of this pilot analysis was to compare clinical characteristics between detectable and undetectable groups. Secondary aims included assessment of factors associated with and independent predictors for detectable tobramycin concentrations and, for those with detectable concentrations, new onset AKI during therapy or within 48 h of inhaled tobramycin discontinuation, as determined by the Kidney Disease: Improving Global Outcomes (KDIGO) criteria.[21] Subjects were only included in this analysis if they did not have a history of end-stage renal disease (ESRD) or AKI prior to inhaled tobramycin initiation. AKI prior to inhaled tobramycin was determined with the same KDIGO criteria used for new onset AKI. For the purpose of evaluations focused on AKI, subjects were separated into new onset AKI and no AKI groups. Data collected included age, weight, race, sex, serum creatinine before inhaled tobramycin initiation, serum creatinine closest to inhaled tobramycin completion, whether the subject was on a pressure or volume ventilator mode during the first dose of inhaled tobramycin, ventilator settings including F_{IO_2} and PEEP during inhaled tobramycin therapy, P_{aO_2}/F_{IO_2}, Sequential Organ Failure Assessment (SOFA) score,[22] mechanical ventilation duration, days of mechanical ventilation prior to inhaled tobramycin initiation, a diagnosis of COPD, ESRD, or chronic kidney disease stage 2 or greater (as identified per chart history and physical), AKI during treatment and within 48 h of cessation, renal replacement therapy mode (eg, continuous renal replacement therapy [CRRT], intermittent hemodialysis) received during inhaled tobramycin therapy, and diagnosis of septic shock or ARDS during or within 7 d of inhaled tobramycin therapy. Due to the piloted, safety analysis approach of this project, a convenience sample was used including collection of data for all subjects in any ICU receiving inhaled tobramycin identified and monitored during the prespecified period.

Continuous variables were evaluated by Student *t* test or Wilcoxon rank-sum, whereas categorical variables were evaluated by chi-square test or Fisher exact test as appropriate. To identify factors associated with detectable serum tobramycin concentrations and AKI, univariate analyses were performed. Variables with a $P < .2$ on univariate analysis were included in multivariate logistic regression analyses to identify independent predictors for each outcome. Variables identified a priori for inclusion in the multivariate logistic regression for detectable serum tobramycin concentrations included age, PEEP during inhaled tobramycin therapy, diagnosis of ARDS within 7 d of treatment, SOFA score, CRRT or intermittent hemodialysis use within 2 d of inhaled tobramycin therapy initiation, and AKI or ESRD before inhaled tobramycin therapy initiation. Variables identified a priori for inclusion in the multivariate logistic regression for new onset AKI included age, SOFA score, first serum tobramycin detectable (ie, ≥ 0.6 mg/L), and total daily dose of inhaled tobramycin per subject actual body weight. The Hosmer-Lemeshow goodness-of-fit test statistic was reported for each multivariate logistic regression analysis performed. Statistical analyses were performed using SigmaPlot 14.0 software (Systat, San Jose, California).

Results

Fifty-three subjects representing 59 inhaled tobramycin courses were included. Thirty-nine (66.1%) courses administered to 35 (66.0%) subjects had detectable serum tobramycin concentrations. The median time to first serum tobramycin concentration in the detectable group was 3.84 h (3.34–4.54) with a corresponding median serum concentration of 1.0 mg/L (0.73–1.48; range: 0.60–3.50). The median time to second serum tobramycin concentration ($n = 26$ [22 detectable, 4 undetectable]) in the detectable group was 9.82 h (9.40–10.70) with a corresponding median serum concentration of 1.0 mg/L (0.90–1.60; range: 0.70–2.80) (for subjects with detectable second concentrations). In contrast, the median time to first serum tobramycin concentration in the undetectable group was 3.44 h (3.11–5.13) with undetectable serum concentrations (< 0.6 mg/L) for all 20 courses.

Subjects with detectable serum tobramycin concentrations were older, had higher median serum creatinine upon inhaled tobramycin initiation and at inhaled tobramycin discontinuation, had longer duration of mechanical ventilation after starting inhaled tobramycin, had higher PEEP during inhaled tobramycin therapy, more often had AKI or ESRD prior to inhaled tobramycin therapy, and had a higher incidence of at least chronic kidney disease stage > 2 (Table 1). Age and PEEP were found to be independent

Table 1. Demographics and Clinical Characteristics of Subjects With Detectable and Undetectable Serum Tobramycin Concentrations While Receiving Inhaled Tobramycin

Characteristic	Detectable ($n = 39$)	Undetectable ($n = 20$)	P
Age,* y	57.1 ± 11.4	45.9 ± 15.0	.004
Weight, kg	95.7 ± 25.1	96.3 ± 20.7	.93
Male sex*	22 (62.9)	12 (63.2)	.79
White*	29 (82.9)	15 (78.9)	.73
Inhaled tobramycin length of therapy, d	2.0 (2.0–3.0)	2.0 (1.0–3.0)	.13
Smoking history*	15 (42.9)	6 (31.6)	.60
SOFA score, median	7 (6–9)	8 (5–9)	.72
CKD stage > 2*	10 (29.4)	0	.009
ICU LOS,* d	31 (17–46)	24 (18–33)	.34
AKI or ESRD prior to inhaled tobramycin	19 .0 (48.7)	2.0 (10.5)	.01
History of COPD*	11.0 (32.4)	2.0 (10.5)	.10
Septic shock during treatment	15.0 (38.4)	6.0 (30.0)	.72
ARDS during or within 7 d treatment	15.0 (38.5)	4.0 (20.0)	.25
Hospital LOS,* d	34 (22–50)	27 (23–34)	.18
6-mo mortality from first inhaled tobramycin dose*	10.0 (28.6)	3.0 (15.8)	.34
Baseline serum creatinine (mg/dL)	1.12 (0.89–1.27)	0.99 (0.72–1.13)	.14
Serum creatinine before first dose inhaled tobramycin (mg/dL)	1.26 (0.84–2.18)	0.76 (0.47–1.28)	.004
Serum creatinine after discontinuing inhaled tobramycin (mg/dL)	1.79 (0.69–2.71)	0.70 (0.46–1.16)	< .001
Ventilator duration before inhaled tobramycin, d	10.0 (6.0–14.0)	9.0 (6.0–13.5)	.92
Mechanically ventilated d after starting inhaled tobramycin	19.0 (8.0–34.0)	8.5 (4.2–16.5)	.02
PEEP during therapy (cm H_2O)	9.2 (7.0–11.0)	8.0 (5.6–8.9)	.049
Maximum PEEP during therapy (cm H_2O)	10.4 ± 3.8	8.7 ± 2.4	.07
P_{aO_2} at initiation of inhaled tobramycin therapy, mm Hg	69.0 (62.0–80.0)	77.5 (67.5–91.5)	.10
F_{IO_2} at initiation of inhaled tobramycin therapy, %	51.0 (45.0–71.0)	58.0 (42.0–71.7)	.99
P_{aO_2}/F_{IO_2} at inhaled tobramycin initiation	129.1 (98.3–150.9)	166.7 (86.8–223.9)	.31
Pseudomonas aeruginosa or Gram-negative MDRO	12.0 (30.8)	7.0 (35.0)	.97
CRRT at inhaled tobramycin initiation	13.0 (33.3)	3.0 (15.0)	.23
CRRT/HD within 2 d inhaled tobramycin initiation	14.0 (35.9)	3.0 (15.0)	.17

Data are expressed as n (%), median (interquartile range), or mean ± standard deviation.
* Variables counted only once; detectable: $n = 35$; undetectable: $n = 19$.
SOFA = Sequential Organ Failure Assessment score
CKD = chronic kidney disease
LOS = length of stay
AKI = acute kidney injury
ESRD = end-stage renal disease
MDRO = multidrug-resistant organisms
CRRT = continuous renal replacement therapy
HD = hemodialysis

Table 2. Independent Risk Factors for Detectable Serum Tobramycin Concentrations

Characteristic	P	Odds Ratio (95% CI)
Age	.009	1.09 (1.02–1.16)
AKI/ESRD prior to inhaled tobramycin	.15	4.83 (0.57–40.70)
Mean PEEP during therapy (cm H_2O)	.01	1.47 (1.08–2.00)
SOFA score at inhaled tobramycin initiation	.14	0.79 (0.58–1.08)
ARDS within 7 d of treatment	.80	0.79 (0.13–4.89)
RRT within 2 d of inhaled tobramycin initiation	.74	1.44 (0.17–11.9)

Hosmer-Lemeshow goodness-of-fit statistic: $P = .39$.
AKI = acute kidney injury
ESRD = end-stage renal disease
SOFA = Sequential Organ Failure Assessment
RRT = renal replacement therapy

Table 3. Demographics and Clinical Characteristics of Subjects With New Onset AKI and no AKI While Receiving Inhaled Tobramycin

Characteristic	AKI ($n = 9$)	No AKI ($n = 28$)	P
Age, y	54.7 ± 8.9	49.4 ± 16.3	.36
Weight, kg	102.0 ± 26.8	94.1 ± 23.1	.40
Male sex	5 (55.6)	16 (57.1)	> .99
White	8 (88.9)	23 (82.1)	> .99
ICU LOS, d	27.0 (22.5–59.0)	22.5 (15.0–28.0)	.10
Hospital LOS, d	31.0 (23.5–64.5)	25.5 (19.0–33.7)	.17
SOFA score	8.0 (7.0–10.5)	6.0 (5.0–8.0)	.03
6-mo mortality from first dose	3.0 (33.3)	3.0 (10.7)	.14
Detectable concentration measured	6.0 (66.7)	14.0 (50.0)	.46
First serum tobramycin concentration, mg/L*	0.75 (0.68–1.30)	0.90 (0.68–1.10)	.73
MAP at inhaled tobramycin initiation, mm Hg	72.0 (63.5–81.5)	78. (68.0–95.5)	.18
Mechanical ventilation d before inhaled tobramycin	9.0 (6.5–13.5)	7.5 (5.25–10.0)	.40
Mechanical ventilation d after starting inhaled tobramycin	17.0 (14.5–34.0)	8.5 (5.0–20.0)	.056
ARDS during or within 7 d of inhaled tobramycin	5.0 (55.6)	4.0 (14.3)	.02
Septic shock during inhaled tobramycin	4.0 (44.4)	8.0 (28.6)	.43
Pseudomonas aeruginosa or Gram-negative MDRO	5.0 (55.6)	7 (25.0)	.12
First serum tobramycin concentration detectable	6.0 (66.7)	14.0 (50.0)	.46
Total daily dose of tobramycin, mg/kg	6.00 (4.95–7.30)	6.65 (5.55–7.48)	.37

Data are expressed as n (%), median (interquartile range), or mean ± standard deviation.
* This analysis only included 20 patients, all of which were from the detectable group. Seventeen patients (of which 3 developed AKI) had undetectable concentrations and were not included in this analysis.
AKI = acute kidney injury
LOS = length of stay
SOFA = Sequential Organ Failure Assessment
MAP = mean arterial pressure
MDRO = multidrug-resistant organisms

Table 4. Independent Predictors for New Acute Kidney Injury in Subjects Receiving Inhaled Tobramycin

Characteristic	P	Odds Ratio (95% CI)
Age	.35	1.04 (0.96–1.13)
SOFA score	.03	1.72 (1.07–2.76)
First serum tobramycin concentration detectable	.23	4.00 (0.42–38.10)
Total daily dose of tobramycin	.22	0.65 (0.33–1.29)

Hosmer-Lemeshow goodness-of-fit statistic: $P = .58$.
SOFA = Sequential Organ Failure Assessment

predictors for serum tobramycin accumulation with inhaled tobramycin therapy (Table 2).

Of the 53 subjects included in the primary aim analysis, 37 (9 new onset AKI, 28 no AKI) were included in the AKI analysis. Clinical characteristics and demographics were similar between groups except for incidence of ARDS during or within 7 d of inhaled tobramycin therapy and SOFA score at inhaled tobramycin initiation (Table 3). Only SOFA score was found to be an independent predictor for new AKI during inhaled tobramycin therapy or within 48 h of discontinuation (Table 4).

Discussion

This is the first evaluation beyond case reports or series of critically ill, mechanically ventilated subjects without cystic fibrosis treated with empiric inhaled tobramycin for VAP. Out of a total of 59 separate subject entries, 39 (66.1%) had at least one detectable serum tobramycin concentration while on inhaled therapy. This observation challenges a perceived advantage of inhaled therapy rather than systemic administration to obtain high drug concentrations at the infection site while minimizing adverse effects such as AKI or vestibular toxicity. This study found that subjects with detectable serum tobramycin concentrations while receiving inhaled tobramycin were older, had a higher serum creatinine prior to inhaled tobramycin initiation, and had higher PEEP throughout therapy. Patient age and PEEP during inhaled tobramycin therapy were identified as independent predictors of detectable serum tobramycin concentrations. Regarding age, for every increase in age by 1 y the odds of observing a detectable serum tobramycin concentration increased by 9%, whereas PEEP increased odds by 47% for every 1 cm H_2O increase > 5 cm H_2O. This occurred despite severity of illness or disease states such as ARDS being no different between groups. These findings provide insight on patients to either consider monitoring serum tobramycin concentrations while on

inhaled tobramycin therapy or administering the therapy less frequently.

When assessing the literature for serum tobramycin concentrations with inhaled tobramycin use, data are primarily limited to case reports or series in subjects with cystic fibrosis and/or history of solid-organ transplantation > 20-y old.[13,18,23,24] These occurrences happened in children with and without a history of renal disease, much like observed in the data reported in the present study. One case report by Hoffman et al[18] in a 20-y-old patient with cystic fibrosis confirmed aminoglycoside-induced changes via renal biopsy. The largest case series was performed at a single academic center in 40 children < 18-y old with cystic fibrosis receiving inhaled tobramycin over a 6.5-y time frame.[23] Twenty-two (55%) of the subjects had serum tobramycin trough concentrations obtained, of which 10 (45.5%) were detectable. The authors observed no differences between detectable and nondetectable groups regarding age, sex, or administration technique. In contrast to the current study, subjects in the detectable group tended to be younger but did display a significant decrease in glomerular filtration rate. Case reports in older adult subjects parallel to our groups also report AKI or vestibular toxicity with inhaled tobramycin.[25-27] The age range for these 4 case reports was 41–75-y old and involved subjects with a history of cystic fibrosis, solid-organ transplant, or had extensive comorbidities. The first case was a 41-y-old woman with a history of renal failure requiring hemodialysis that was on inhaled tobramycin 300 mg twice daily for *Pseudomonas aeruginosa* in her sputum.[19] After 16 d of therapy, the subject had a serum tobramycin trough concentration drawn predialysis that returned at 19.2 mg/L with a subsequent concentration drawn a week later that remained at 19.5 mg/L. This subject did develop vestibular toxicity. Interestingly, the oldest subject at 75-y old developed isolate vestibular toxicity after 2 weeks of inhaled tobramycin but no evidence of renal toxicity.[27] No serum concentrations were reported. To note, serum concentrations of inhaled aminoglycosides are not isolated to inhaled tobramycin as it has also been reported with amikacin.[28]

The association between positive-pressure ventilation and detectable serum tobramycin concentrations is consistent with previously published literature.[13] This case reports of a 19-y-old woman status post a second heart transplant that was receiving inhaled tobramycin for an *Acinetobacter baumannii* pneumonia. Her course of therapy started 10 d after transplantation and was continued up through 89 d. Multiple serum tobramycin peak and trough concentrations were evaluated and returned elevated. She was on maintenance hemodialysis and positive-pressure ventilation for the first 36 d. Dose reductions for inhaled tobramycin were made at day 30 (to 80 mg twice daily) and day 61 (to 300 mg every 24 h). Concentrations notably improved after she was weaned off ventilation. This observation is further supported by evidence that an increase in positive pressure leads to a significant decrease in an aerosol's aerodynamic diameter.[29] This could potentially result in an increased molecular penetrability into the deeper, more vascular alveolar regions of the lungs, leading to increased penetration into systemic circulation.[30] Combined with the data presented in the current study, patients receiving inhaled tobramycin requiring higher PEEP may warrant serum concentration monitoring and dose reductions to minimize likelihood of systemic absorption.

Our findings further confirmed the risk for new onset AKI in subjects receiving inhaled tobramycin without a previous history of renal disease. Of the 37 subjects evaluated in this secondary aim, 9 (24.3%) developed new onset AKI. Subjects that developed AKI had a higher incidence of ARDS during or within 7 d of inhaled tobramycin therapy and had a higher SOFA score. This is in comparison to an estimated 25% of all subjects who develop nephrotoxicity when receiving aminoglycoside therapy, although extended-interval dosing strategies have displayed an even lower incidence of 0–5% as this strategy allows for serum clearance and post-antibiotic effect.[31-33] It is important to note these observations were not focused in critically ill subjects being treated for VAP. Only the SOFA score was identified as an independent predictor of new onset AKI in subjects receiving inhaled tobramycin, with an increase of 72% for every 1-point increase in score. This finding aligns with previously reported literature of 333 critically ill noncardiac surgical subjects with elevated SOFA score predicting severe AKI within 7 d of ICU admission.[34] The authors reported specifically on SOFA nonrenal scores on admission with a score range of 2–5 having an odds ratio of 2.69 (95% CI 1.87–3.87, $P < .001$) and a score range of ≥ 6 having an odds ratio of 7.39 (95% CI 4.90–11.16, $P < .001$). Similar findings were reported in a systematic review and meta-analysis regarding risk factors for AKI in subjects on extracorporeal membrane oxygenation.[35] The authors reported a higher risk of severe AKI related to increasing SOFA scores with a weighted mean difference of 2.68 (95% CI 1.73–3.62, $P < .001$). As such, it is also important to recognize that AKI is multifactorial in critically ill patients, and variables such as sepsis or septic shock increase the risk for organ dysfunction with or without inhaled tobramycin.

Several limitations of this study should be acknowledged. The was a single-center, retrospective, observation study that initially started as a quality improvement project. As such, a convenience sample was employed with the intent of including all subjects with serum tobramycin concentrations drawn. There were subjects in which serum tobramycin concentrations were missed, further limiting reportable data and overall sample size. Our institutional lab cutoff for serum tobramycin concentrations of 0.6 mg/L may have resulted in potentially missing subjects with

detectable concentrations. The multivariate logistic regression models were performed with 6 variables for 59 subject entries and 4 variables for 37 subjects, respectively. Based on the observed goodness-of-fit statistics of the multivariate models, larger cohorts may be needed to improve the precision of the risk factor assessments. Additionally, the 95% CI of all variables included would suggest no overtly underpowered interactions. As a modest proportion of subjects included in the analysis was in the surgical ICU that includes trauma at a level 1 trauma center, some of these findings may not be immediately valid to centers that do not take care of those patients. Lastly, this analysis focused on subjects receiving inhaled tobramycin as empiric therapy only. However, these findings would likely remain applicable for longer, definitive use of inhaled tobramycin as well if risk factors were present.

After completing a thorough literature review, this study appears to be the largest patient population reported regarding characteristics around inhaled tobramycin therapy and detectable serum concentrations. As inhaled tobramycin is an alternative to systemic tobramycin therapy in our institutional VAP protocols, this approach is standard of care at our institution, which enhances familiarity. The potential benefit of including all subjects receiving inhaled tobramycin therapy was to enhance external validity of the data reported. Variables included in the multivariate logistic regression models were identified a priori by the authors in effort to reduce potential bias. The findings from this study provides valuable insight to enhance awareness around implications of inhaled tobramycin use and may provide a foundation for larger, prospective studies to evaluate these impacts.

Conclusions

This study sought to describe subject characteristics that developed detectable serum concentrations of tobramycin while receiving inhaled tobramycin therapy. Whereas inhaled aminoglycosides can be considered due to the perceived advantages over intravenous administration such as obtaining high drug concentrations at the infection site and minimizing systemic exposure, we observed most subjects exhibiting detectable serum tobramycin concentrations. Both age and PEEP were identified as independent predictors of detectable serum tobramycin concentrations. These observations occurred despite no difference in severity of illness or ARDS incidence between detectable and undetectable groups. AKI also occurred in subjects with no history of renal disease prior to receiving inhaled tobramycin. Finally, the SOFA score was identified as an independent predictor for new onset AKI. Clinicians should consider serum tobramycin concentration monitoring and empiric dose reductions in older patients with higher PEEP requirements receiving inhaled tobramycin.

ACKNOWLEDGMENTS

The authors would like to acknowledge Jessica B Winter PharmD BCPS BCCCP, Shaun P Keegan PharmD BCPS, Nicole Harger Dykes PharmD BCCCP, and Kristen E Carter PharmD BCPS BCCP, for their aid in capturing subject data.

REFERENCES

1. Magill SS, Edwards JR, Bamberg W, Beldavs ZG, Dumyati G, Kainer MA, et al; Emerging Infections Program Healthcare-Associated Infections and Antimicrobial Use Prevalence Survey Team. Multistate point-prevalence survey of health care–associated infection. N Engl J Med 2014;370(13):1198-1208.
2. Bouadma L, Sonneville R, Garrouste-Orgeas M, Darmon M, Souweine B, Voiriot G, et al. Ventilator-associated events: prevalence, outcome, and relationship with ventilator-associated pneumonia. Crit Care Med 2015;43(9):1798-1806.
3. Rello J, Ollendorf DA, Oster G, Vera-Llonch M, Bellm L, Redman R, et al. Epidemiology and outcomes of ventilator-associated pneumonia in a large US database. Chest 2002;122(6):2115-2121.
4. Melsen WG, Rovers MM, Groenwold RH, Bergmans DC, Camus C, Bauer TT, et al. Attributable mortality of ventilator-associated pneumonia: a meta-analysis of individual patient data from randomized prevention studies. Lancet Infect Dis 2013;13(8):665-671.
5. Schreiber MP, Shorr AF. Inhaled antibiotics for the treatment of pneumonia. Curr Opin Pulm Med 2019 May;25(3):289-293.
6. Ehrman S, Roche-Campo F, Bodet-Contentin L, Razazi K, Dugernier J, Trenado-Alvarez J, et al; Reva Research Network. Aerosol therapy in intensive and intermediate care units: prospective observation of 2808 critically ill patients. Intensive Care Med 2016;42(2):192-201.
7. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis 2016;63(5):e61-e111. Epub 2016 July 14. Erratum in: Clin Infect Dis 2017;64(9):1298. Erratum in: Clin Infect Dis 2017;65(8):1435. Erratum in: Clin Infect Dis 2017;65 (12):2161.
8. Le J, Ashley ED, Neuhauser MM, Brown J, Gentry C, Klepser ME, et al Society of Infectious Diseases Pharmacists Aerosolized Antimicrobials Task Force. Consensus summary of aerosolized antimicrobial agents: application of guideline criteria. Pharmacotherapy 2010;30(6):562-584.
9. Wood GC, Swanson JM. An update on aerosolized antibiotics for treating hospital-acquired and ventilator-associated pneumonia in adults. Ann Pharmacother 2017;51(12):1112-1121.
10. Le Conte P, Potel G, Peltier P, Horeau D, Caillon J, Juvin ME, et al. Lung distribution and pharmacokinetics of aerosolized tobramycin. Am Rev Respir Dis 1993;147(5):1279-1282.
11. Geller DE, Pitlick WH, Nardella PA, Tracewell WG, Ramsey BW. Pharmacokinetics and bioavailability of aerosolized tobramycin in cystic fibrosis. Chest 2002;122(1):219-226.
12. Badia JR, Soy D, Adrover M, Ferrer M, Sarasa M, Alarcón A, et al. Disposition of instilled versus nebulized tobramycin and imipenem in ventilated intensive care unit (ICU) patients. J Antimicrob Chemother 2004;54(2):508-514.
13. Kahler DA, Schowengerdt KO, Fricker FJ, Mansfield M, Visner GA, Faro A, et al. Toxic serum trough concentrations after administration of nebulized tobramycin. Pharmacotherapy 2003;23(4):543-545.
14. Restrepo MI, Keyt H, Reyes LF. Aerosolized antibiotics. Respir Care 2015;60(6):762-773.

15. Cannella CA, Wilkinson ST. Acute renal failure associated with inhaled tobramycin. Am J Health Syst Pharm 2006;63(19):1858-1861.
16. Langley A, Cottingham L. Detectable serum tobramycin concentrations in a patient with renal dysfunction receiving tobramycin by inhalation. Am J Health Syst Pharm 2011;68(15):1385-1386.
17. Izquierdo MJ, Gomez-Alamillo C, Ortiz F, Calabia ER, Ruiz JC, de Francisco AL, Arias M. Acute renal failure associated with use of inhaled tobramycin for treatment of chronic airway colonization with Pseudomonas aeruginosa. Clin Nephrol 2006;66(6):464-467.
18. Hoffmann IM, Rubin BK, Iskandar SS, Schechter MS, Nagaraj SK, Bitzan MM. Acute renal failure in cystic fibrosis: association with inhaled tobramycin therapy. Pediatr Pulmonol 2002;34(5):375-377.
19. Edson RS, Brey RH, McDonald TJ, Terrell CL, McCarthy JT, Thibert JM. Vestibular toxicity due to inhaled tobramycin in a patient with renal insufficiency. Mayo Clin Proc 2004;79(9):1185-1191.
20. Zhang C, Berra L, Klompas M. Should aerosolized antibiotics be used to treat ventilator-associated pneumonia? Respir Care 2016;61(6):737-748.
21. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int Suppl 2012;2(1):1-138.
22. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the working group on sepsis-related problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996;22(7):707-710.
23. Miller JL, Lepa TM, Ranallo C, Chaaban H, Skrepnek GH, Johnson PN. Detectable concentrations of inhaled tobramycin in critically ill children without cystic fibrosis: should routine monitoring be recommended? Pediatr Crit Care Med 2017;18(12):e615-e620.
24. de Velde F, Emonts M, Verbruggen S, van der Sijs H. High tobramycin serum concentrations after tobramycin inhalation in a child with renal failure. J Antimicrob Chemother 2014;69(11):3163-3164.
25. Miller T, Pastuch C, Garavaglia L, Gannon K, Parravani A. Unknown renal impairment: a rare case of inhaled tobramycin-induced acute kidney injury in a cystic fibrosis patient. Antibiotics (Basel) 2021; 10(4):424.
26. Ahya VN, Doyle AM, Mendez JD, Lipson DA, Christie JD, Blumberg EA, et al. Renal and vestibular toxicity due to inhaled tobramycin in a lung transplant recipient. J Heart Lung Transplant 2005;24(7):932-935.
27. Kaufman AC, Eliades SJ. Vestibulotoxicity in a patient without renal failure after inhaled tobramycin. Am J Otolaryngol 2019;40(3):456-458.
28. Luyt CE, Eldon MA, Stass H, Gribben D, Corkery K, Chastre J. Pharmacokinetics and tolerability of amikacin administered as BAY41-6551 aerosol in mechanically ventilated patients with Gram-negative pneumonia and acute renal failure. J Aerosol Med Pulm Drug Deliv 2011;24(4):183-190.
29. Clay MM, Pavia D, Newman SP, Clarke SW. Factors influencing the size distribution of aerosols from jet nebulizers. Thorax 1983;38 (10):755-759.
30. Sakagami M. In vivo, in vitro, and ex vivo models to assess pulmonary absorption and disposition of inhaled therapeutics for systemic delivery. Adv Drug Deliv Rev 2006;58(9-10):1030-1060.
31. Lopez-Novoa JM, Quiros Y, Vicente L, Morales AI, Lopez-Hernandez FJ. New insights into the mechanism of aminoglycoside nephrotoxicity: an integrative point of view. Kidney Int 2011;79 (1):33-45.
32. Rybak MJ, Abate BJ, Kang SL, Ruffing MJ, Lerner SA, Drusano GL. Prospective evaluation of the effect of an aminoglycoside dosing regimen on rates of observed nephrotoxicity and ototoxicity. Antimicrob Agents Chemother 1999;43(7):1549-1555.
33. Murry KR, McKinnon KR, Mitrzyk B, Rybak MJ. Pharmacodynamic characterization of nephrotoxicity associated with once-daily aminoglycoside. Pharmacotherapy 1999;19(11):1252-1260.
34. Trongtrakul K, Patumanond J, Kongsayreepong S, Morakul S, Pipanmekaporn T, Akaraborworn O, Poopipatpab S. Acute kidney injury risk prediction score for critically ill surgical patients. BMC Anesthesiol 2020;20(1):140.
35. Mou Z, Guan T, Chen L. Risk factors of acute kidney injury in ECMO patients: a systematic review and meta-analysis. J Intensive Care Med 2021:088506662110034. [Epub ahead of print].