Tobramycin Serum Concentrations in Tracheostomy-Dependent Children Receiving Inhaled Tobramycin

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Introduction: In recent years, administration of inhaled aminoglycosides has gained popularity in tracheostomy-dependent pediatric patients because of medication delivery to the target site of action while minimizing systemic absorption and adverse effects. A recent report of detectable serum tobramycin concentrations in critically ill children receiving inhaled tobramycin 300 mg every 12 h prompted our investigation in tracheostomy-dependent pediatric patients receiving inhaled tobramycin 80 mg every 8 h.

Methods: Serum tobramycin trough concentrations were obtained from tracheostomy-dependent pediatric patients receiving treatment with inhaled tobramycin 80 mg every 8 h for the treatment of tracheitis. Patient data, including demographic data, medical history, renal function, and serum concentrations, were collected.

Results: Twelve patients with a median age of 0.5 (0.3–6.1) years had serum tobramycin concentrations evaluated. Eleven of the 12 patients had undetectable trough concentrations (<0.6 mcg/mL). All of these patients had normal blood urea nitrogen (BUN) and serum creatinine (SCr) for age and no history of kidney disease. One patient had a detectable trough concentration of 2.1 mcg/mL. This patient was 11 months old and had polycystic kidney disease with an elevated BUN and SCr for age.

Conclusions: Detectable serum concentration from systemic absorption of inhaled tobramycin 80 mg every 8 h is unlikely in tracheostomy-dependent pediatric patients with normal renal function. However, in tracheostomy-dependent pediatric patients with a history of renal dysfunction or elevations in BUN or SCr, inhaled tobramycin should be used with caution. Monitoring serum concentrations to guide dose modification should be considered in these patients.

Keywords: child, gram-negative bacterial infections, kidney diseases, lung diseases, tracheostomy

Background

MEDICAL ADVANCES IN NEONATAL and pediatric critical care have greatly reduced neonatal and pediatric mortality, but with these lifesaving advances, there has been a rise in medically fragile children with significant morbidity. A subgroup of this population are children dependent on long-term mechanical ventilation via tracheostomy at home.^{1,2} Tracheostomy-dependent pediatric patients with chronic respiratory failure will often have respiratory infections that require treatment with antibiotic therapy.

Tobramycin is an aminoglycoside antibiotic with a narrow therapeutic window used to treat infections of gram-

negative bacteria. Systemic parenteral administration of tobramycin has long been associated with nephrotoxicity,³ and therefore, therapeutic drug monitoring is recommended. In recent years, oral inhaled administration has been used in the management of gram-negative infections in patients with cystic fibrosis (CF).⁴ As this treatment showed efficacy, administration of inhaled aminoglycosides gained popularity in patients with acute and chronic lung diseases not associated with CF.⁵ The inhaled route of administration has an advantage over the parenteral form of the drug as it can deliver medication to the target site of action while minimizing systemic absorption, therein decreasing the potential for adverse effects such as nephrotoxicity.⁵ A recent

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retrospective study reported detectable serum tobramycin concentrations in 10 of 22 critically ill children with serum trough concentrations measured while receiving inhaled tobramycin 300 mg every 12 h.⁶ The authors did not show statistical significance in age groups or gender, but patients with detectable tobramycin concentrations were younger with higher prevalence of tracheostomy than patients with undetectable tobramycin concentrations.⁶

This report illustrates concern for centers where inhaled tobramycin is used routinely for tracheostomy-dependent pediatric patients. The aim of this study was to determine if tracheostomy-dependent non-CF pediatric patients receiving inhaled tobramycin would have detectable trough concentrations and be at increased risk for nephrotoxicity.

Materials and Methods

This was initiated first as a quality improvement project at our institution and tobramycin serum concentrations were obtained due to clinical concern associated with this recent publication.⁶ Once this quality improvement was underway, institutional review board (IRB) approval was obtained for retrospective data collection to report our findings. No informed consent was required.

Tobramycin trough concentrations were obtained from tracheostomy-dependent pediatric patients receiving treatment with inhaled tobramycin 80 mg administered every 8 h given via nebulizer by a respiratory therapist from December 2017 to November 2018. All patients received tobramycin 80 mg/2 mL for injection (Mylan, California). All tracheostomy-dependent pediatric patients receiving treatment with inhaled tobramycin 80 mg every 8 h (the standard dose for tracheostomy-dependent patients at our institution) were included and the only reason for exclusion was the inability or contraindication for drawing blood. No eligible patients were excluded. Trough concentrations were drawn after a minimum of 3 doses of the regimen and timed with other laboratory orders to mitigate an increase in blood draws. For example, if the fourth dose was in the evening, the trough was drawn before the fifth dose with scheduled morning laboratories; in addition, if inhaled tobramycin was

initiated on a weekend, the ordering of the trough concentration may have been delayed until the primary team returned on Monday. If a patient had 1 undetectable trough concentration and his/her renal function was normal, no other trough concentrations were drawn. In the event of a detectable trough concentration, the dose was adjusted and further serum concentrations were monitored. Patient data, including demographic data, medical history, current renal function (within 1 week of starting tobramycin), presence of concurrent nephrotoxic medications (including acyclovir, amphotericin B, calcineurin inhibitors, iodinated contrast agents, nonsteroidal anti-inflammatory drugs (NSAIDs), piperacillin/tazobactam, vancomycin, systemic aminoglycosides), and tobramycin regimen, including dose, timing, and serum concentrations, were collected.

Results

Twelve tracheostomy-dependent pediatric patients with a median age of 0.5 (0.3–6.1) years, who were hospitalized at our institution, had serum tobramycin concentrations evaluated. The duration of treatment was 7.9 ± 2.6 days and trough concentrations were drawn after 4.1 ± 1.5 doses (mean $\pm$ standard deviation). Eleven of the 12 patients had undetectable trough concentrations, defined as <0.6 mcg/mL at our institution. One patient had a steady-state trough concentration of 2.1 mcg/mL after 5 doses of inhaled tobramycin. This patient was 11 months old with baseline blood urea nitrogen (BUN) of 37 mg/dL (normal range 5–20 mg/dL) and serum creatinine (SCr) of 0.95 mg/dL (normal range 0.2–0.6 mg/dL), both elevated for age and polycystic kidney disease. Once this elevated trough was identified, the dose was changed to 80 mg every 24 h and a repeat level was drawn 24 h after the next dose. This repeat trough concentration was 1.2 mcg/mL and the patient remained on inhaled tobramycin for a total of 6 days. All of the patients with undetectable troughs had normal BUN and SCr for age and no history of kidney disease. However, 2 patients had concurrent therapy with nephrotoxic medications (vancomycin). Refer Table 1 for further clinical details.

TABLE 1. PATIENT DATA

Patient	Sex	Age (years)	Weight (kg)	History of kidney disease or hypertension	BUN (mg/dL)	SCr (mg/dL)	Concurrent nephrotoxic medications	Doses before level	Serum concentration (mcg/mL)	Total length of therapy (days)
1	M	0.5	7.3	None	11	<0.2	None	4	<0.6	9
2	F	6.1	13.4	Hypertension	6	<0.2	Vancomycin	3	<0.6	5
3	F	0.6	5.2	Hydronephrosis	9	0.22	None	3	<0.6	6
4	M	0.6	6.1	None	16	0.23	None	4	<0.6	9
5	M	0.3	7.4	None	5	<0.2	None	3	<0.6	11
6	F	3.6	14.1	Hypertension	6	<0.2	None	5	<0.6	10
7	M	0.4	7.3	Hypertension	3	0.23	None	6	<0.6	6
8	M	0.7	6.25	None	12	0.21	None	3	<0.6	11
9	M	0.6	5	None	9	<0.2	None	3	<0.6	7
10	F	4.7	14.2	None	8	<0.2	Vancomycin	4	<0.6	3
11	M	0.3	5.5	Hypertension	9	0.37	None	8	<0.6	9
12	M	0.9	8.8	Polycystic kidneys	37	0.95	None	3	Initial: 2.1 After change: 1.2	6

BUN, blood urea nitrogen; F, female; M, male; SCr, serum creatinine.

Discussion

This is the first study to evaluate serum tobramycin concentrations in tracheostomy-dependent non-CF pediatric patients with chronic respiratory failure receiving inhaled tobramycin. In the first published study evaluating safety and efficacy of inhaled tobramycin in CF patients, both nephrotoxicity and ototoxicity were evaluated, but tobramycin serum concentrations were not monitored.⁷ In a follow-up study of 520 patients with CF receiving inhaled tobramycin 300 mg every 12 h, tobramycin serum concentrations were monitored at week 0 and 20.⁸ The mean serum concentration was 0.94 $\mu\text{g/mL}$ at week 0 and 0.98 $\mu\text{g/mL}$ at week 20, yet the study does not provide the timing of these levels in accordance with the doses. Although the reported serum concentrations were below a standard detectable level that would raise concern, 9 patients did have a transient increase of SCr by 50% or more during the 20-week study.⁸

Although there does not seem to be concern with accumulation with inhaled tobramycin in the CF population, our population of tracheostomy-dependent pediatric patients likely has significant pharmacokinetic differences compared with children with CF. Children with CF typically have increased clearance, larger volume of distribution, and lower body fat percentage thereby increasing lean body weight when compared with healthy children.^{9,10} Another point of distinction with the CF population is that inhaled tobramycin is typically administered by a specific nebulizer device approved for home use, and many of the CF studies with inhaled tobramycin used this device. In contrast, hospitalized patients (both our patients and CF patients) would receive doses administered by a respiratory therapist with whichever nebulizer utilized at that institution.

Our initiative for monitoring tobramycin trough concentrations was prompted by the 2017 study revealing elevated tobramycin concentrations in critically ill children receiving inhaled tobramycin, but this was not the first report.⁶ In 2008, authors reported elevated tobramycin serum concentrations in an 80 day-old tracheostomy-dependent infant that received 80 mg every 12 h for 5 doses and then 300 mg every 24 h for 3 doses. A concentration obtained 11 h after the third 300 mg dose was reported as 10.6 mcg/mL and tobramycin was discontinued.¹¹ Like our patient who had a detectable trough concentration, this patient also had an elevated BUN and SCr at the initiation of inhaled tobramycin. In addition, this patient also had received vancomycin in the days just before the start of inhaled tobramycin.

This is also the first study to demonstrate safety of inhaled tobramycin 80 mg every 8 h in a pediatric population. Many dosing strategies and delivery devices for inhaled tobramycin have been evaluated in clinical trials.^{12,13} The standard dose in CF patients is tobramycin 300 mg every 12 h,⁸ but little evidence exists to support the optimal dose of tobramycin in the in children without CF. At our institution, we standardly dose tobramycin 80 mg every 8 h in tracheostomy-dependent pediatric patients. One of the major drivers for this dosing strategy is that this dose is typically covered by insurance for outpatient administration, whereas the higher dose of tobramycin 300 mg every 12 h is not typically covered.

Although this is a small study, this is a very heterogeneous group of tracheostomy-dependent pediatric patients

that illustrated inhaled tobramycin 80 mg every 8 h is unlikely to cause detectable serum trough concentrations. A limitation of this study is that tobramycin trough concentrations were not obtained with strict timing with regard to the number of previous doses of tobramycin received before drawing the level. This ranged from 3 to 8 doses, but presumed to be at steady state. This was due to timing the level with scheduled morning laboratories, or if the dose was started on the weekend, a level may not have been ordered until the primary team returned on Monday. Although the number of doses before obtaining a trough varied, all concentrations were true trough concentrations drawn immediately before the next tobramycin dose. While only 1 patient had a detectable tobramycin concentration, this patient did have a history of renal disease and an elevated SCr and BUN at baseline. Based on our experience, we would strongly recommend monitoring tobramycin trough concentrations once steady-state concentrations are achieved in patients who have a history of renal disease or a significant rise in SCr or BUN while receiving inhaled tobramycin. In addition, if a patient has a significant change in renal function while receiving inhaled tobramycin, this may also warrant obtaining a trough concentration. In our patient population, concomitant nephrotoxic medications did not result in detectable tobramycin concentrations, but due to our small sample size further investigation is needed. Given the increased risk for acute kidney injury in these patients, it may also be appropriate to initiate therapeutic drug monitoring in these patients as well to avoid further adverse events.

Author Disclosure Statement

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