Therapeutic Drug Monitoring of Inhaled Tobramycin in a Post–Hematopoietic Cell Transplant Patient With Bronchiolitis Obliterans and End-Stage Renal Disease

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There are no widely accepted dose alterations for inhaled tobramycin in the setting of renal dysfunction, and serum concentrations are not typically monitored. Herein we describe a case report of a 16-year-old female with a history of 2 hematopoietic cell transplants and a kidney transplant who received inhaled tobramycin for chronic *Pseudomonas aeruginosa* management. The patient developed chronic kidney disease, and tobramycin concentrations were monitored. Initially she received a reduced dose of inhaled tobramycin, with repeated doses based on serum concentrations. The dose was increased, but serum concentrations obtained the following day remained higher than desired, leading to a suspicion of delayed systemic absorption. Tobramycin administration was changed from immediately prior to dialysis to the evening prior to the next day's dialysis session, and serum concentrations were consistently <1 mg/L postdialysis. In conclusion, systemic absorption of inhaled tobramycin in non–cystic fibrosis (CF) patients may differ compared to that observed in CF patients. Renal dysfunction may lead to systemic accumulation of inhaled tobramycin, and the timing of inhaled tobramycin administration with respect to dialysis has a potentially significant influence on drug clearance. Thus, monitoring may be required. Further cases are required to verify these observations.

ABBREVIATIONS CF, cystic fibrosis; FDA, US Food and Drug Administration; HCT, hematopoietic cell transplant; IHD, intermittent hemodialysis

KEYWORDS administration, bronchiolitis obliterans; inhalation; renal dialysis; therapeutic drug monitoring; tobramycin

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Introduction

Tobramycin is an aminoglycoside with concentration-dependent bactericidal activity against Gram-negative bacilli, including *Pseudomonas aeruginosa*.¹ Although trough concentrations are routinely obtained when tobramycin is administered systemically, concentrations after administration of inhaled tobramycin are not commonly assessed because of assumed low levels of systemic exposure. We present the first known case describing the experience of therapeutic drug monitoring of tobramycin following administration by inhalation in a post–hematopoietic cell transplant (HCT) patient with bronchiolitis obliterans and end-stage renal disease.

Case

A 16-year-old black female (40 kg) with a past medical history significant for 2 HCTs (4 years prior), bronchiolitis obliterans requiring overnight oxygen support, and renal insufficiency status post–kidney transplant (1 year prior) was admitted to the pediatric intensive care unit with respiratory distress secondary to multiorganism necrotizing pneumonia requiring vasopressors and

invasive respiratory support. Baseline laboratory values were within normal limits on admission, except for an elevated cystatin C of 2.13 mg/L (normal: 0.55–1.15 mg/L) and a serum creatinine of 1.38 mg/dL (baseline: 0.75 mg/dL), indicating worsening renal dysfunction. It was ruled out via biopsy that the worsening renal dysfunction was secondary to rejection of her transplanted kidney.

An infectious workup via bronchoalveolar lavage was positive for *P aeruginosa*, *Cladisporium* species, and Aspergillus antigen. The patient completed treatment with intravenous posaconazole for 28 days (subsequently transitioned to oral posaconazole for fungal prophylaxis indefinitely) along with systemic tobramycin and extended infusion meropenem for 21 days.

Upon completion of treatment, cultures from a repeat bronchoalveolar lavage remained positive for *P aeruginosa* despite resolution of the patient's clinical signs and symptoms. The care team concluded that the patient was colonized with this bacterium. Alternating 28-day treatment with inhaled tobramycin, followed by inhaled colistin, was initiated in an attempt to reduce the bacterial burden and the risk of invasive infection.

The patient had presented on admission with acute

Figure. Time in days to tobramycin serum concentration of <1 mg/L when given immediately prior to intermittent hemodialysis (IHD) vs the night before IHD.

kidney injury that progressed into chronic kidney disease requiring continuous renal replacement therapy. Eventually, the patient was transitioned to intermittent hemodialysis (IHD) 3 to 4 times weekly. Inhaled tobramycin was administered immediately before IHD to maximize the amount of systemic tobramycin removed by IHD. Initially she received a reduced dose of inhaled tobramycin (90 mg). The decision to empirically reduce the dose was based on several case reports^{2–8} discussing evidence of systemic tobramycin accumulation and associated toxicities when inhaled tobramycin was administered to patients with renal dysfunction. The tobramycin was administered intermittently based on serum concentrations, which were periodically assessed to ensure adequate clearance (i.e., serum tobramycin concentrations < 1 mg/L). If the patient displayed adequate clearance, the dose was gradually increased until she reached the recommended dose of 300 mg.

A serum concentration drawn the day following an IHD session showed that there was no appreciable change in concentration compared with concentrations before IHD, which led the clinical team to postulate that systemic absorption was delayed. To allow more time for absorption of the drug, tobramycin administration was changed to the evening prior to IHD. In addition, the clinical team hypothesized that this change in the timing of tobramycin administration with respect to IHD would lead to elimination of the drug in a manner analogous to that associated with normal kidney function. The goal of this change was to optimize the frequency of inhaled tobramycin. Because tobramycin exhibits concentration-dependent bactericidal activity, more frequent dosing is desired to adequately and more rapidly eradicate *P aeruginosa* while avoiding

resistance.¹

When tobramycin was administered approximately 12 hours before dialysis, all post-IHD serum tobramycin concentrations fell from >1mg/dL to <1 mg/dL. With post-IHD concentrations now consistently < 1 mg/L, the time to re-dosing the inhaled tobramycin decreased from a median of 1.7 days to 0.7 days (Figure). The frequency of inhaled tobramycin administration could be increased from 2 to 3 times weekly to 3 to 4 times weekly, depending on IHD frequency. Once this dosing scheme was established, tobramycin serum and sputum concentrations were obtained 1 hour post-inhalation administration and were 1.7 mg/L and 2745 mg/L, respectively. These concentrations are consistent with those found to be safe and effective in other publications.^{9,10}

Eradication of *P aeruginosa* was achieved after approximately 5 months of inhaled therapy. Shortly thereafter, the patient was discharged from the hospital but continued indefinitely on inhaled therapy (i.e., alternating months of aztreonam and tobramycin) because of the severity of her infection.

Discussion

Inhaled tobramycin is FDA approved for patients at least 6 years of age with cystic fibrosis (CF).¹ In patients with CF, chronic infection with *P aeruginosa* correlates with poorer outcomes, including a 2.6 times higher 8-year risk of death than is seen in those without positive respiratory cultures.¹¹ Inhaled tobramycin has been an essential part of therapy for eradication of *P aeruginosa* in this patient population to improve morbidity and mortality.¹²

Most studies designed for the approval of inhaled

tobramycin were conducted in patients with CF, including pharmacokinetic and dose-finding studies. The recommended dosing regimen for patients with CF is 300 mg inhaled twice daily.¹ Very few studies have looked specifically at dosing regimens in non-CF patients; a Cochrane review¹³ that included studies in which tobramycin was used for bronchiectasis in non-CF patients with *P aeruginosa* reported that dosing regimens of 300 mg twice daily were used. In addition, there is variable evidence^{13,14} demonstrating that inhaled tobramycin decreases exacerbations, improves quality of life, and improves long-term outcomes in non-CF patients.

Previous studies^{9,10} reported that a regimen of tobramycin 300 mg inhaled twice daily reached sputum concentrations of greater than 25 times the minimum inhibitory concentration, thereby achieving bactericidal activity in most patients with CF. Pharmacokinetic studies^{9,10} suggested that peak sputum concentrations occurred shortly after administration of the inhaled medication (within an hour), with peak serum concentrations occurring 1 to 2 hours after administration. In addition, these studies^{9,10} demonstrated that peak serum concentrations did not accumulate in CF patients and remained below levels that could potentially cause toxicity. Thus, monitoring serum concentrations is not routinely recommended for CF patients receiving inhaled tobramycin.

It is well known that the clearance and volume of distribution of aminoglycosides, including tobramycin, is increased in CF patients as compared with non-CF patients.¹⁵ This likely explains, in part, the observed differences in absorption and clearance of inhaled tobramycin in CF patients as compared with non-CF patients. However, these observations do not apply to non-CF patients with renal dysfunction, and the dosing of inhaled tobramycin in the patient with renal dysfunction has not been well studied. Case reports²⁻⁸ have suggested that systemic accumulation of inhaled tobramycin may occur in patients with renal dysfunction. Several patients in these case reports developed toxicities due to elevated serum trough concentrations, including 2 patients with vestibular injury and one with hearing loss.^{3,4,7}

The case presented above represents a patient with non-CF pulmonary complications who demonstrated unique pharmacokinetic properties and required an innovative dosing regimen with inhaled tobramycin for *P aeruginosa* eradication. To our knowledge, this is the first case report of a pediatric patient receiving inhaled tobramycin while concomitantly requiring long-term IHD. It was evident in this patient that timing the administration of the inhaled tobramycin with respect to IHD sessions played a significant role in its clearance. More specifically, administering inhaled tobramycin

immediately prior to IHD resulted in the patient requiring 2 sessions of IHD to obtain serum concentrations of <1 mg/L. When tobramycin was administered approximately 12 hours before dialysis, the frequency of inhaled tobramycin administration could be increased, thus, drug efficacy was maximized for suppression of *P aeruginosa*.

This case report demonstrates that tobramycin pharmacokinetic characteristics, including time to peak serum concentration, may vary when the inhaled drug is used outside of CF patients with normal renal function. To prevent drug accumulation and associated toxicities, therapeutic monitoring of serum concentrations during the administration of inhaled tobramycin should be considered in patients with renal dysfunction, especially in patients requiring renal replacement therapy or medication dose adjustments because of a reduced glomerular filtration rate. The timing of inhaled tobramycin administration, especially with respect to IHD sessions, may also affect the clearance characteristics of this drug. Further studies are necessary to verify these observations.

ARTICLE INFORMATION

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Ethical Approval and Informed Consent Given the nature of this study, the project was exempt from institution review board/ethics committee review and informed consent was not required.

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