Acute renal failure associated with inhaled tobramycin

CARRIE A. CANNELLA AND SAMANEH T. WILKINSON

Patients with an extended hospital stay are often at an increased risk of developing infections with multidrug-resistant pathogens. In this population, one of the more commonly identified organisms is *Pseudomonas aeruginosa*. When health care-associated pneumonia is suspected, double-antibiotic coverage for *P. aeruginosa* is recommended (usually an antipseudomonal β-lactam antibiotic plus an aminoglycoside). Nephrotoxicity associated with aminoglycoside therapy has traditionally led to decreased use of this antibiotic class. However, use of nebulized aminoglycosides, such as tobramycin inhalation solution, is thought to reduce the nephrotoxic potential of this agent. We report a case of nephrotoxicity possibly caused by tobramycin inhalation solution (TOBI, Chiron Pharmaceuticals).

Case report

A 62-year-old Caucasian woman was admitted to the surgical intensive care unit from an outside hospital for treatment of decreased urine output and sepsis secondary to *P. aeruginosa*. Her past medical history was significant for morbid obesity (weight at time of admission: 119 kg), diabetes mellitus, chronic renal insufficiency (baseline serum creatinine concentration [Scr] 2 mg/dL), gout, osteoarthritis, hypertension, hypothyroidism, and acute myocardial infarction. The patient was initially admitted to the transferring institution for a perforated diverticulum, status posthemolectomy. At the time of transfer, she

Purpose. A case of nephrotoxicity possibly caused by tobramycin inhalation solution is presented.

Summary. A 62-year-old Caucasian woman was admitted for treatment of decreased urine output and sepsis secondary to *Pseudomonas aeruginosa*. Her past medical history was significant for multiple diseases, including chronic renal insufficiency (baseline serum creatinine concentration [Scr] 2 mg/dL). One month postadmission, the patient was diagnosed with health care-associated pneumonia. The patient was initiated on piperacillin–tazobactam and tobramycin 2 mg/kg i.v. She was changed to imipenem–cilastatin with continuation of i.v. tobramycin. A month after discontinuation of her antibiotic regimen, the patient was diagnosed with *P. aeruginosa* pneumonia. The patient received imipenem–cilastatin, vancomycin, and inhaled tobramycin 300 mg twice daily. At that time, her Scr was 2 mg/dL. Inhaled tobramycin was continued for four weeks, and the patient’s Scr steadily rose to a peak of 4.5 mg/dL. During week 1 of treatment, multidrug-resistant *P. aeruginosa* and methicillin-resistant *Staphylococcus aureus* were diagnosed. The patient continued to receive i.v. imipenem–cilastatin, vancomycin, and inhaled tobramycin with an Scr of 1.9 mg/dL. However, at the end of week 2, the patient’s Scr began to slowly rise (2.3 mg/dL). At week 3, imipenem–cilastatin was discontinued; inhaled tobramycin was continued. The patient’s Scr continued to rise (3.2 mg/dL). At week 4, her Scr rose to 4.5 mg/dL, resulting in initiation of hemodialysis and discontinuation of inhaled tobramycin. The patient’s Scr never returned to baseline, and renal function was never regained.

Conclusion. Acute renal failure requiring dialysis occurred in a high-risk patient receiving an extended course of treatment with inhaled tobramycin.

Index terms: Aerosols; Aminoglycosides; Cilastatin; Dialysis; Drugs, adverse reactions; Imipenem; Kidney failure; TOBI; Tobramycin; Vancomycin

Am J Health-Syst Pharm. 2006; 63:1858-61
was receiving mechanical ventilation and was being treated with i.v. ciprofloxacin, piperacillin–tazobactam, and vancomycin; a 14-day course of this antibiotic regimen was completed. No aminoglycosides were given at the transferring institution.

One month postadmission to our facility, the patient developed a bilateral lower-lobe infiltrate and was diagnosed with health-care–associated pneumonia. Bronchial alveolar lavage (BAL) yielded multidrug-resistant \( P. \text{aeruginosa} \) susceptible only to aminoglycosides, piperacillin–tazobactam, and imipenem–cilastatin. The patient was initiated on piperacillin–tazobactam 2.25 g (combined total potency: piperacillin 2 g and tazobactam 0.25 g) i.v. every six hours and tobramycin 2 mg/kg i.v. Tobramycin dosing was conducted randomly with doses being given when trough serum concentrations dropped below 1 µg/mL. The patient developed a rash secondary to piperacillin–tazobactam and was changed to imipenem–cilastatin 250 mg (250 mg of anhydrous imipenem and 250 mg of cilastatin) i.v. every six hours with continuation of i.v. tobramycin. Treatment continued for 21 days with no increase in SCr throughout treatment.

An additional month after discontinuation of the previously described antibiotic regimen (three months’ postadmission), the patient again developed a multilobar infiltrate and was found to have multidrug-resistant \( P. \text{aeruginosa} \) pneumonia (see previous susceptibility). At this time, the patient began therapy with imipenem–cilastatin 250 mg i.v. every six hours, vancomycin 1 g i.v. random dosing based on serum vancomycin concentrations, and inhaled tobramycin 300 mg twice daily. Her SCr at the time was reported to be 2 mg/dL.

Inhaled tobramycin was continued for 27 days. Over the course of this four-week period, the patient’s SCr steadily rose to a peak of 4.5 mg/dL (Figure 1). She remained hemodynamically stable and was maintained on mechanical ventilation throughout the course of the infection. During week 1 of treatment, BAL yielded multidrug-resistant \( P. \text{aeruginosa} \) and methicillin-resistant \( S. \text{aureus} \). The patient continued therapy on i.v. imipenem–cilastatin, vancomycin, and inhaled tobramycin with an SCr of 1.9 mg/dL. However, at the end of week 2, the patient’s SCr began to slowly rise (2.3 mg/dL). The renal medicine service was consulted and recommended a serum vancomycin trough concentration between 10 and 15 µg/mL in an attempt to decrease the nephrotoxic potential of the combination therapy. Urine sediment was examined and found to be consistent with acute tubular necrosis (ATN).

At the start of week 3, imipenem–cilastatin was discontinued with continuation of inhaled tobramycin. A urinalysis before discontinuation of imipenem was negative for eosinophils, thereby decreasing the likelihood of interstitial nephritis secondary to this agent. The patient’s SCr continued to rise (3.2 mg/dL), and a renal ultrasound was performed showing no signs of obstruction. On day 20, a serum 12-hour tobramycin trough concentration of 0.7 µg/mL was reported. Finally, in week 4, a technetium-99m mercaptoacetyl triglycine (MAG-3) scan and a repeat urine sediment examination were performed, both consistent with ATN. The SCr rose to 4.5 mg/dL, resulting in initiation of hemodialysis and discontinuation of inhaled tobramycin on day 28. During this time, three additional random serum tobramycin concentrations were obtained on day 26, day 29, and day 30 and were 0.6, <0.5, and <0.5 µg/mL, respectively.

The patient’s SCr never returned to baseline, and renal function was never regained. The patient remained on hemodialysis until the time of her death, almost six months later. The patient never displayed any signs of ototoxicity while receiving aminoglycoside therapy, which was reinstated on multiple occasions throughout the admission.

Figure 1. Increased serum creatinine concentration over the course of one month in a patient receiving inhaled tobramycin.
Discussion

The patient’s Naranjo adverse drug reaction probability score was 3, indicating a possible association between the reaction and inhaled tobramycin. Supporting evidence includes a previously published report of tobramycin nebulized solution causing acute renal failure. In addition, a MAG-3 scan and urine sediment were consistent with ATN. The decreased Naranjo adverse drug reaction probability score may be explained by a recent study, in which it was postulated that application of Naranjo criteria to patients who are critically ill may not be reliable or valid. This is secondary to the fact that a higher score (indicating a more definitive relationship between medication and reaction) is unlikely in a critically ill patient for multiple reasons, including the inability to rechallenge a hemodynamically unstable patient, lack of placebo, and the fact that not all toxic drug reactions are dose dependent.

A MEDLINE search for the period 1980 to November 2005 (key search terms were tobramycin, nephrotoxicity, and inhaled) revealed one case report of nephrotoxicity secondary to tobramycin nebulization. A 20-year-old cystic fibrosis patient received tobramycin inhalation (300 mg twice daily) in addition to ciprofloxacin 750 mg by mouth twice daily. After one week of therapy, the patient developed severe azotemia, hypobcarbonatemia, and widened anion gap. Her SCr rose to 9 mg/dL with a blood urea nitrogen of 71 mg/dL. Her serum tobramycin concentration at that time was found to be 2.8 µg/mL (24 hours after previously administered inhaled tobramycin dose). Histopathology studies were consistent with ATN. Two weeks after discontinuation of ciprofloxacin and tobramycin inhalation, the patient’s renal function returned to baseline. As discussed in this report, ciprofloxacin is not likely to be the cause of renal failure as there was no evidence of tubulointerstitial nephritis (the hallmark of fluoroquinolone-induced renal dysfunction) in the patient. Inhaled tobramycin is the most likely culprit for the observed deterioration in renal function in this case.

However, a small number of reports have indicated that tobramycin nebulization does not carry a risk for nephrotoxicity. A double-blind, crossover study was conducted with 71 cystic fibrosis patients. Treatment consisted of tobramycin inhalation 200 mg three times daily for 28 days or placebo inhalation for 28 days. Each patient received both placebo and tobramycin in a crossover fashion. To measure nephrotoxicity, SCr and urinalysis were evaluated during weeks 1, 3, 4, and 5. A transient rise in SCr was observed in six patients during tobramycin therapy and five patients during placebo administration. Urinalysis did not reveal any cellular casts in any patients with either therapy.

Similar to a European study conducted at 16 different cystic fibrosis centers evaluated with regard to inhaled tobramycin or colistin inhalation. Patients were randomized to parallel treatment regimens consisting of inhaled tobramycin 300 mg twice daily or 80 mg inhaled colistin twice daily for four weeks. Blood urea nitrogen, SCr, and protein dipstick were conducted at the time of screening and end of treatment visits. No clinically significant changes in renal function were observed in either treatment group over the course of the 28-day treatment.

In a Phase 2 study of 74 bronchiectasis patients, tobramycin inhalation or placebo was administered in a double-blind, randomized fashion. Patients self-administered therapy for a total of 28 days with a two-week drug-free period upon completion of therapy. Clinically significant increases in blood urea nitrogen and SCr were not observed in either treatment group. Serum tobramycin concentrations ranged from 0.18 to 2.64 µg/mL with an average of 0.54 µg/mL, 30 to 60 minutes after administration of treatment.

Finally, in a double-blind, placebo-controlled, crossover study, 20 noncystic fibrosis bronchiectasis patients received inhaled tobramycin 300 mg twice daily or placebo for a six-month period with a one-month washout period between crossover. Although not thoroughly discussed, SCr measurements remained within normal limits throughout the duration of the study period.

The majority of literature describing inhaled tobramycin therapy attests to the safety of this mode of administration. However, the majority of safety data exclude patients with decreased renal function on initiation of treatment. Our patient had a number of risk factors for renal failure, including age, diabetes, prior aminoglycoside therapy, prior sepsis, computed-tomography scan with contrast, chronic renal insufficiency, and concomitant administration of nephrotoxic agents (vancomycin, imipenem–cilastatin, furosemide). No temporal relationship could be established regarding the administration and discontinuation of these nephrotoxic agents and the decline in renal function. Patients with multiple risk factors for nephrotoxicity should perhaps be monitored more closely for any signs of worsening renal function when initiated on inhaled tobramycin therapy.

In addition, cystic fibrosis patients comprise the largest study population evaluated with regard to inhaled tobramycin. Cystic fibrosis patients exhibit altered pharmacokinetics, which may allow for increased drug clearance, thereby leading to a decreased incidence of nephrotoxicity. In the clinical setting, however, patients without cystic fibrosis are receiving inhaled tobramycin for pulmonary ailments including but not limited to health care-associated pneumonia. As inhaled tobramycin use extends into the noncystic...
fibrosis population, an increase in renal effects may be noted. While conclusive evidence of tobramycin as the offending agent in our patient does not exist, tobramycin cannot be eliminated as a possible etiologic agent.

Conclusion

Acute renal failure requiring dialysis occurred in a high-risk patient receiving an extended course of treatment with inhaled tobramycin.

References