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CASE REPORT

# Elevated Tobramycin Concentrations Following Endotracheal Administration in a Premature Infant

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The following case report describes a 1-month-old, 34-week-gestation premature neonate who had compromised renal function. The neonate received endotracheally administered tobramycin (300 mg every 12 hours) via a PARI PLUS reusable nebulizer to treat a documented Gram-negative tracheostomy infection. The patient also received systemic tobramycin (2.5 mg/kg intravenously every 18 hours). The tobramycin serum concentration obtained 45 hours after the last intravenous dose and 11.5 hours after the second nebulized dose was 17.6 mg/L. The tobramycin nebulizations were stopped.

**KEYWORDS** endotracheal, neonate, tobramycin

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Patients with tracheostomies have a higher incidence of bronchopulmonary infections, which can be attributed to inadequate secretion of drainage from the lung caused by decreased mucociliary movement and insufficient cough reflex.[1-4] These patients are often colonized or infected with Gram-negative rods, most commonly *Pseudomonas aeruginosa*. These organisms are often resistant to many antibiotics and can cause persistent episodes of pneumonia.[4]

Although intravenous (IV) aminoglycosides are used to treat tracheostomies colonized with *Pseudomonas* species, this class of drugs penetrates poorly into bronchial secretions following systemic administration.[5,6] Hagerman and colleagues extrapolated MIC data from *P aeruginosa* broth cultures and found that minimum inhibitory concentrations of gentamicin may be increased 10- to 25-fold in purulent sputum of patients with cystic fibrosis. This may require sputum gentamicin concentrations of 40 to 100 mg/L for bacterial eradication.[7]

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**ABBREVIATIONS** BUN, blood urea nitrogen; CLCR, creatinine clearance; ET, endotracheal; IV, intravenous; NICU, neonatal intensive care unit; SCR, serum creatinine; UOP, urine output

In order to increase sputum concentration at the site of infection or colonization and reduce systemic drug exposure, aerosolized antibiotics were introduced as a therapeutic option.[7] Although gentamicin sputum concentrations have been reported to exceeded 100 mg/L following aerosolized administration,[8] only about 10% of the dose is deposited in the lung when antibiotics are given via face mask or mouthpiece. Decreased deposition can be explained by many different factors including the size of the drug particle, the diameter of the bronchial tree, drug exhalation by patient, inspiratory flow rate of the patient, nebulizer wastage, drug trapping within the nebulizer, and the type

**Table.** Clinical and Laboratory Data

| NICU Day # | BUN | SCR | UOP (mL/kg/hr) | Dosage Form | Serum Concentration (mg/L) | Time After IV Dose (hr) | Time After ET Dose (hr) |
|---|---|---|---|---|---|---|---|
| 6 | 9 | 0.5 | 2.6 | IV | | | |
| 12 | 11 | 1.1 | 1.6 | IV | | | |
| 16 | 23 | 1.1 | 2.9 | IV | 4.9 | 18 | |
| 17 | 24 | 1.2 | 3.4 | ET x 2 | 8.8/17.6 | 32/45 | 9/11.5 |
| 18 | 24 | 1.3 | 1.6 | | | | |
| 19 | 28 | 1.6 | 0.2 | | 8.9 | 82 | 48 |
| 20 | 33 | 2.2 | 0.7 | | | | |
| 21 | 36 | 2.6 | 3 | | 4.6 | 127 | 94 |
| 22 | 39 | 2.3 | 4.1 | | | | |

*BUN, Blood Urea Nitrogen; ET, endotracheal; IV, intravenous; NICU, neonatal Intensive Care Unit; UOP, urine output*

of nebulizer used.[9,10] A variety of approaches have been used to enhance drug deposition into the lung. New technologies such as ultrasonic nebulizers are able to decrease a drug's particle size and thereby enhance lung deposition. A commercially available nebulization product (TOBI; Tobramycin Inhalation Solution, USP; Novartis Pharmaceuticals Corporation, East Hanover, NJ) has been improved so that the pH is similar to airway epithelium and is chemically stable, preservative free, and isotonic.[11,12] Safety and efficacy trials performed on patients given TOBI nebulizations attained mean peak sputum concentrations of 1237 μg/g of sputum following one 300-mg dose.[11] These concentrations were above the bacteria's MIC.[13]

The patient's mode of breathing also influences drug distribution. Infants tend to breathe through their noses, which significantly reduces the amount of drug delivered to the lung. For this reason, face mask administration can be less efficient than oral inhalation.[7] In fact, when compared to face mask or mouthpiece delivery, endotracheal (ET) administration is associated with more adequate drug delivery.[5,6]

In order to increase antibiotic efficacy through enhanced lung penetration, IV and ET administered aminoglycosides are often given concurrently for the treatment of tracheostomy colonizations and infections. Two studies found that concurrently administered IV and ET aminoglycoside therapy was safe and resulted in clinical improvement.[14,15] We report a premature infant with renal impairment who initially received IV followed by ET tobramycin to treat a tracheostomy infection and developed markedly elevated systemic concentrations.

## CASE REPORT

A 1-month-old, 34-week-gestation, 2.67-kg ventilator-dependent African American female infant born to an insulin dependent diabetic mother was admitted to our neonatal intensive care unit (NICU) from an outlying hospital. The past medical history was significant for respiratory distress syndrome, multiple genetic anomalies, and hyaline membrane disease. On NICU day 6, the patient was started on vancomycin 10 mg/kg/dose IV every 12 hours and gentamicin 2.5 mg/kg/dose IV every 12 hours for presumed sepsis. The patient's serum creatinine was 0.5 mg/dL (Table). Subsequent positive cultures included: urine - *Enterococcus faecalis* Group D β-lactamase negative; central venous line—*Staphylococcus epidermidis*; and tracheostomy—*Pseudomonas aeruginosa*.

On NICU day 12, the serum creatinine increased to 1.1 mg/dL and a vancomycin trough serum concentration obtained 11.5 hours after a dose was 20.4 mg/L. A gentamicin concentration was not obtained. The vancomycin and gentamicin dosing intervals were increased to every 18 hours. Later that day the gentamicin was changed to tobramycin secondary to increased susceptibility of the *Pseudomonas aeruginosa* cultured.

On NICU day 16, a tobramycin concentration obtained 18 hours after a dose was 4.9 mg/L (Figure). The IV tobramycin and vancomycin doses were stopped and tobramycin nebulization 300 mg every 12 hours via ET tube was begun. The first ET dose was given 22 hours after the last IV tobramycin dose. The ET aerosolized antibiotic was administered via a PARI PLUS reusable nebulizer, which used central

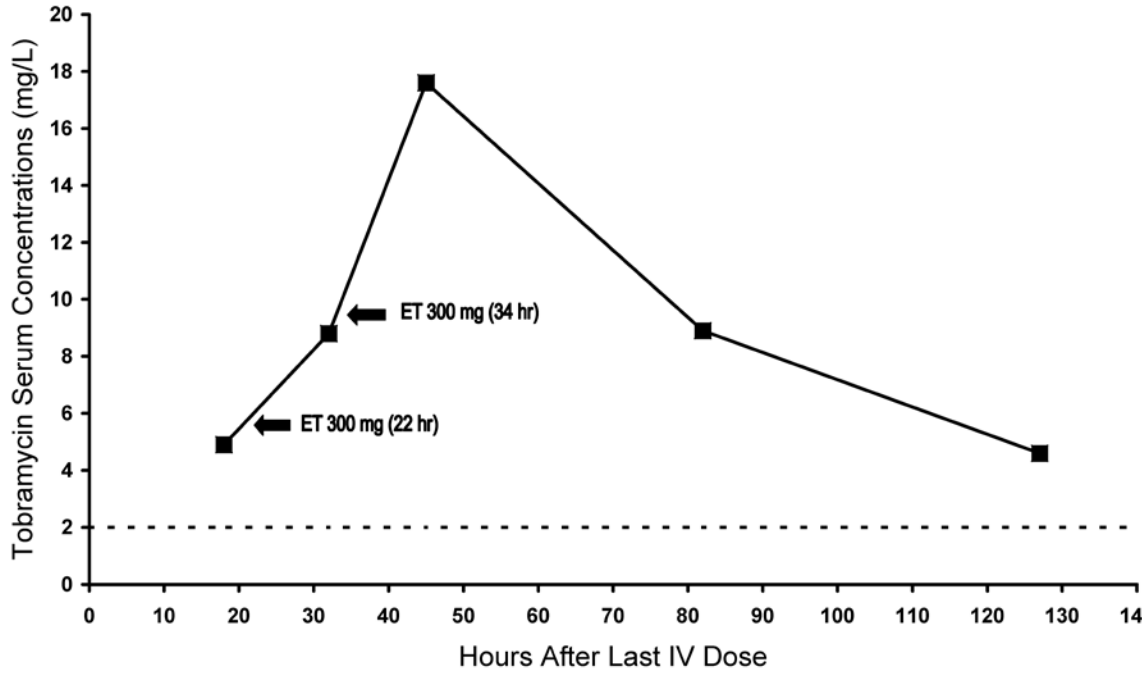


**Figure.** Tobramycin serum concentrations. Time zero is when the last dose of IV tobramycin was given. The first concentration (4.9 mg/L) was obtained on NICU Day 16, 18 hours after the last IV dose of tobramycin. The arrows are the times of ET tobramycin administration. The line at 2 mg/L represents the usual maximum nadir tobramycin serum concentration.

air supply as its compressor. A furosemide infusion was also started at a rate of 3 mg/kg/day because of decreased urine output.

On NICU day 18, a tobramycin concentration obtained approximately 32 hours after the last IV dose and 10 hours after the first nebulized dose was 8.8 mg/L. The patient received one additional tobramycin nebulization prior to reporting of the tobramycin serum concentration. The tobramycin concentration obtained 45 hours after the last IV dose and 11.5 hours after the second nebulization was 17.6 mg/L; the tobramycin nebulizations were stopped. Subsequent tobramycin concentrations obtained 49 and 94 hours after the last nebulization dose were 8.9 mg/L and 4.6 mg/L, respectively (Figure).

## DISCUSSION

The infant described in this case received tobramycin ET via a closed system, thereby allowing a larger dose of the drug to be delivered to the lung. Several case reports have highlighted elevated serum tobramycin concentrations following ET administration in adults.[16-18] The first report involved a 20-year-old patient with cystic fibrosis who received inhaled tobramycin 300 mg twice daily.[16] This patient developed acute nonoliguric renal failure after 1 week of inhalation therapy. The tobramycin concentration 24 hours after the last dose was 2.8 mg/L. The next case described a 19-year-old woman experiencing acute rejection of a heart transplant and acute renal failure requiring dialysis.[17] Ten days after a second heart transplant she was begun on ET tobramycin for an endotracheal *Acinetobacter baumanii* infection. On day 25 post-transplant, two tobramycin concentrations obtained 2.5 hours after the dose and prior to the next dose were both 2.5 mg/L, suggesting drug accumulation. A third case described a 41-year-old patient undergoing hemodialysis, who was treated with 300 mg twice daily inhaled tobramycin to reduce *Pseudomonas aeruginosa* in her sputum.[18] This patient developed reversible vestibular toxicity and had a serum tobramycin concentration of 19.5 mg/L. This report did not state how the inhaled tobramycin was given nor the timing of the tobramycin concentration. These cases suggest that systemic aminoglycoside concen-

trations should be monitored in patients with renal dysfunction receiving ET aminoglycoside to determine if drug accumulation is occurring.

Our patient had decreased renal function. Few studies describe the use of ET aminoglycoside in patients who are renally compromised[19,20]; none of these studies included infants. The ET administration of gentamicin and/or tobramycin with a concurrent IV aminoglycoside was reported in 10 adult patients with pneumonia who had creatinine clearances greater than 40 mL/min.[19] Two patients had aminoglycoside trough concentrations greater than 2 mg/mL. Accumulation did not occur, however, caution was suggested when creatinine clearances were less than 40 mL/min. In another investigation, elevated trough tobramycin serum concentrations were described in 3 of 12 mechanically ventilated patients receiving ET tobramycin; only 2 patients had concentrations above 2 mg/mL.[20] The concentration in the third patient was 1.9 mg/L. These 3 patients had renal failure suggesting accumulation can occur with decreased renal function.

Our case report also raises questions about the use of a standardized dose of tobramycin in infants receiving ET administration. Clinical studies on the use of aerosolized antimicrobials have been limited to small sample sizes of patients that received short durations of therapy making it difficult to recommend routine use of nebulized antibiotics in patients outside of cystic fibrosis.[8] There have been no studies in infants evaluating the appropriate dose or safety of ET administered aminoglycosides in infants. Lung tissue of a neonate or infant may not be as fully developed and may allow more of the drug to be absorbed systemically. The lung is initially developed in the human fetal stage, but its maturation progresses even through adolescence.[21] Premature neonates, such as the one discussed in this case, will have an elevated risk of respiratory disease and altered respiratory function at all stages of postnatal life due to improper lung development before birth.

Two separate publications have noted falsely elevated tobramycin "serum" concentrations due to contamination of the blood sample obtained from patients receiving aerosolized tobramycin.[22,23] All of the elevated tobramycin concentrations were attributed to skin contamination that resulted from improper sample site cleaning with alcohol prior to venipuncture or fingerstick. Although the drug concentrations in our patient were obtained through phlebotomy via heelsticks, the tobramycin was given via a closed system which would not allow for contamination; hence, the method of serum sampling is not an explanation of the elevated concentrations noted in our patient.

The purpose of this case report is to make clinicians aware that ET administered tobramycin can result in elevated systemic concentrations. ET tobramycin is truly meant to be used adjunctively with IV therapy in patients with ET colonization or infection. If ET administration is used the practitioner should consider a reduced dose and obtain tobramycin trough serum concentrations to ensure proper clearance is occurring in the presence of renal dysfunction. Until clinical information regarding efficacy and pharmacokinetics is available, widespread use of this mode of antibiotic delivery cannot be advocated.

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