Inhaled Tobramycin for Treatment of Ventilator-Associated Pneumonia: The Interplay of Patient, Drug, and Device

Inhalation of antibiotics has had a long and checkered history. After their introduction in the 1940s, the use of inhaled antibiotics was abandoned for many decades because indiscriminate and inappropriate use led to excess mortality due to pneumonia with multidrug-resistant (MDR) organisms.[1] Several factors contributed to a renewed interest in use of inhaled antibiotics for treatment of ventilator-associated pneumonia (VAP), including improved understanding of aerosol delivery in mechanically ventilated patients and the availability of more efficient aerosol-generating devices, reported success with use of inhaled antibiotics in patients with cystic fibrosis, and the emergence of MDR organisms that failed to respond to systemically administered antibiotics.[2] Currently, inhaled antibiotics are frequently employed as adjuncts to systemic antibiotics for treatment of VAP.[3]

The potential benefits of inhaled antibiotics in patients with VAP are that aerosolization through the artificial airway ensures direct delivery to the site of infection, with high lung concentrations but low plasma concentrations, which minimizes the risk of systemic toxicity.[4,5] The ability of inhaled antibiotics to penetrate biofilms and limit Quorum sensing is thought to be an advantage over systemically administered antibiotics.[6,7]

In contrast, systemically administered antibiotics have a narrow therapeutic window, and combining the use of inhaled antibiotics with systemic antibiotics has the potential to reduce overall use and duration of systemic antibiotic therapy.[4,5] The combined use of inhaled and systemic antibiotics could also reduce selection pressure for emergence of MDR organisms.[8] However, combining inhaled and systemic antibiotics has not been shown to provide clinical superiority to systemic antibiotics alone in prospective clinical trials in subjects with VAP due to Gram-negative organisms.[9,10] Thus, recommendations to use inhaled antibiotics are limited; the American Thoracic Society/Infectious Diseases Society of America guidelines for treatment of VAP recommend inhaled antibiotics as adjunctive therapy in patients with Gram-negative organisms susceptible only to aminoglycosides and polymyxins who are not responding to systemic therapy alone.[11]

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The safety of antibiotics administered by inhalation is predicated on the belief that absorption of drugs from the lungs is limited and low plasma levels could avoid systemic adverse reactions such as acute kidney injury (AKI). In this issue of the Journal, Droege and colleagues[12] report their experience with inhaled tobramycin as empiric treatment for VAP at a large, urban medical center. Inhaled tobramycin was administered to 53 subjects (total 59 courses), and the characteristics of subjects who had detectable serum concentrations ($\geq$ 0.6 mg/L) were compared with subjects with undetectable serum levels (ie, $<$ 0.6 mg/L). In this retrospective analysis, detectable serum concentrations were noted in older subjects, those with chronic kidney disease stage $\geq$ 2, subjects with higher serum creatinine levels, and those who were receiving higher PEEP.[12] On multivariate logistic regression analysis, older age and higher PEEP were independent predictors of detectable serum tobramycin levels. In 37 subjects with no previous history of renal disease or injury, the Sequential Organ Failure Assessment (SOFA) score was the only independent predictor for development of AKI in 9 subjects.[12] The authors concluded that serum monitoring and empiric reduction of inhaled tobramycin dose should be considered in older patients and those requiring higher PEEP levels.[12]

The distribution of antibiotics after inhalation depends on a host of factors. Pharmacokinetic and pharmacodynamic characteristics could be influenced by changes in cardiac output, fluid balance, need for organ support, and renal/hepatic dysfunction among others. These factors could lead to uncertainty in antibiotic dosing. Faster or slower rates of metabolism among patients may lead to underdosing or overdosing. Although rare, systemic toxicity may result in patients with renal dysfunction, and therapeutic drug monitoring and/or dosing adjustments may be needed in patients with renal failure or those receiving dialysis support.[13] The interaction of these factors could explain the observation of Droege and

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colleagues that older subjects and those requiring a higher level of PEEP had higher odds of having detectable levels of tobramycin in serum.[12]

Two aspects of the study by Droege and colleagues[12] deserve further consideration. First, the investigators aerosolized the intravenous formulation of tobramycin. The specially formulated tobramycin solution for inhalation (TOBI, Novartis Pharmaceuticals, Basel, Switzerland) is a preservative-free, nonpyrogenic, pH 6.0 solution and is salinity adjusted for use with a nebulizer. It contains 300 mg of tobramycin and 11.25 mg sodium chloride in 5 mL sterile water.[14] Although not specifically stated in the accompanying paper, Droege and colleagues[12] probably used a generic, sterile, preservative-free intravenous tobramycin (PFIT) solution (X-Gen Pharmaceuticals, Horseheads, New York) that is made to order by pharmacy sterile products to a concentration of 40 mg/mL. The recommended dose for both solutions is 300 mg of tobramycin twice daily. The therapeutic substitution of TOBI with PFIT is perceived as being efficacious and safe. However, there are limited data regarding the use of either product, mostly in subjects with cystic fibrosis.[15,16] The substitution of TOBI for PFIT is associated with significant cost savings and has not been associated with any safety concerns.[14]

The second consideration is that subjects included in the study by Droege and colleagues received at least 3 doses of inhaled tobramycin (300 mg twice daily). The serum trough level of tobramycin was drawn after the third dose. The dose of tobramycin employed was based on doses employed to treat *Pseudomonas* infection in patients with cystic fibrosis.[15,16] Nebulizers are commonly employed for aerosolization of antibiotics in patients with VAP. Whereas TOBI is recommended for use with a jet nebulizer and compatible compressor (a PARI LC Plus nebulizer and Pulmo-Aide 5650D compressor are recommended) in patients with cystic fibrosis,[17] the European Society of Clinical Microbiology and Infectious Diseases recommends the use of vibrating mesh nebulizers over jet and ultrasonic nebulizers for delivery of inhaled antibiotics.[18,19] The various nebulizers differ in their drug delivery efficiency depending on fill volumes, placement in the ventilator circuit, bias flow, mode of nebulization, and gas flow used to operate the nebulizer.[20] In their report, Droege and coworkers[12] employed a high-efficiency vibrating mesh nebulizer placed on the dry side of the humidified adult breathing circuit. This configuration of the nebulizer could deliver a higher dose of tobramycin to the lungs of patients with VAP. For example, in a bench model of mechanical ventilation, placement of the vibrating mesh nebulizer on the dry side of the humidifier delivered a 2–4-fold higher dose to the airway compared to a jet nebulizer.[21] Thus, a higher-than-expected frequency of detectable serum levels in subjects reported by Droege and colleagues[12] could be explained on the basis of higher deposition of tobramycin in the lungs, and the nominal dose may need adjustment when a high-efficiency vibrating mesh nebulizer is used versus a jet nebulizer.

In summary, we do not yet have an accurate estimate of the dose of nebulized tobramycin delivered to the lungs of patients with VAP. Further studies are needed to determine the appropriate dose and other patient-related factors before making a universal requirement for monitoring serum levels in mechanically ventilated patients receiving inhaled tobramycin. There can be no argument, however, that patients with preexisting AKI or chronic kidney disease should have their serum levels assessed while receiving inhaled tobramycin, and adjustment to the inhaled dose should be made accordingly. Such investigations are needed because inhaled antibiotics are being employed with increasing frequency for empiric treatment of VAP.

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