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Commentary

Use of Tobramycin in Ventilator Associated Pneumonia

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Introduction

Tobramycin is an aminoglycoside antibiotic and used to treat various types of bacterial infections specifically Gram-negative infections. It is effective against species of Pseudomonas [1-5]. Tobramycin is indicated for the treatment of following clinical/pathological conditions:

- Acute and chronic lower respiratory tract infections
- Ventilator-Associated Pneumonia (VAP)
- Nosocomial Pneumonia (NP)
- Cystic Fibrosis (CF)
- Immunocompromised, such as with cancer and neutropenia and/or hypogammaglobulinemia
- Neuromuscular blockade
- Tracheostomy receiving short-term mechanical ventilation.

For the treatment and prevention of VAP, the efficacy of inhaled antimicrobial therapy and as an adjunct to systemic antibiotics is well established [6-17]. The inhaled antibiotic have some complexicities and misconceptions [8,9,11,14,18,19]. In acute or chronic lower respiratory tract infections, the inhaled antibiotics have the theoretical advantage of increasing drug levels in the bronchial secretions, without subjecting the patient to systemic side effects of the drug [20].

This paper summarizes the efficacy of antimicrobials and aerosolized antimicrobials especially tobramycin in ventilator-associated pneumonia (VAP).

Inhalation antibiotics

- Inhalation antibiotics have been popularly used in patients with cystic fibrosis and from the last few decades, their use in the treatment of VAP and emergence of VAP due to multiple-drug-resistance has increased [20].
- The clinical failure of treatments is due to the poor distribution of the IV antibiotics to atelectatic pulmonary regions and the failure to achieve therapeutic concentrations and emergence of resistant strains due to subtherapeutic concentrations [21].
- Inhaled administration of antibiotics is related to less systemic toxicity and a profound action on biolayers [22-24].
- Inhaled antibiotics are required to be used in combination with systemic antibiotics to overcome the problem of low absorption into the blood (2 - 4%) and it is not sufficient to treat the concomitant extrapulmonary infections and reach the alveoli [25].
- Clinical studies support effective monotherapy with inhaled tobramycin in a patient with severe allergic reaction to systemic antibiotics [25-30].

- The increased evidences of VAP due to MDR pathogens demands use of inhaled antibiotics to improve patient outcomes and reduce emergence of antimicrobial resistance [21].
- Most of the recent experience with inhaled antibiotics and *P. aeruginosa* infections comes from treatment of chronic infection in cystic fibrosis. Inhaled tobramycin (TOBI®, 300 mg vials, nebulized treatment twice a day for 28 days, with 28 days off) with repeated intermittent cycle has shown improved pulmonary function with diminished need for oral or parenteral antibiotics in adolescent patients with cystic fibrosis over a two year period of long-term intermittent therapy [31].
- TOBI® is a preservative-free preparation, developed and FDA-approved exclusively for suppressive, inhalation treatment [32].
- Frequently patients notice an initial increase in their cough at the beginning of a TOBI® month, as well as a change in their voice (more husky or hoarse-sounding). Inhaled tobramycin has minimal side effects (10% with bronchospasm), decreases the risk of hospitalization and *P. aeruginosa* density in sputum, and is well tolerated.
- Patients requiring tracheotomy tubes and chronic mechanical ventilation are frequently colonized with *P. aeruginosa,* making intermittent use of TOBI®, a reasonable consideration. The dose of 300 mg twice a day is the same regardless of age or size. Tobramycin levels are not recommended.
- Inhaled tobramycin has been successfully used for severe non-cystic fibrosis bronchiectasis with chronic bronchial *P. aeruginosa* infections [19,33]. Pulmonary function and quality of life were unaffected.
- In cystic fibrosis as long-term intermittent therapy, combination parenteral therapy for nosocomial pneumonia caused by MDR *P. aeruginosa*, nebulized colistin is cycled every other 28 days, often alternating with TOBI® therapy. The disadvantage of colistin is the lack of a preservative-free form for nebulization (the IV solution is used). Some patients may dislike the foamy, sticky nature of the solution when reconstituted; the solution may be irritating to the airway [32,34].
- Other antimicrobial agents, using the parenteral solution of the drug, have been attempted with limited success (i.e. colistin, gentamicin, ceftazidime) for inhalation. Lack of guidelines as to the frequency and dosage of these drugs are drawbacks to their clinical utility. Another major drawback to use of inhaled ceftazidime is the offensive taste and smell when this drug in placed into a nebulizer for inhalation [34].

Clinical outcomes

The outcomes of Tobramycin administration in ventilator-associated pneumonia (VAP) are discussed below:

- The study described effective use of aerosolized tobramycin as therapeutic strategy for *P. aeruginosa* VAP with acute respiratory distress syndrome (ARDS). A total of 44 patients who developed VAP by *P. aeruginosa* during the course of ARDS at the intensive care unit were selected. Aerosolized tobramycin inhalation solution (TIS, 240 mg) has been administered daily for 14 days along with systemic antibiotics. The TIS treated group and control group has shown no significantly different clinical characteristics. The recurrence of *P. aeruginosa* VAP and ICU mortality was found lesser in TIS group (22.7% and 22.7%, respectively) than the control group (52.4% and 63.6%, respectively). In TIS group, the bacterial concentration in tracheal aspirate was also found to be decreased as compared to the control group [35].
- TIP (administered via T-326 inhaler) has found to effectively control chronic pulmonary *P. aeruginosa* infection in cystic fibrosis patients as well as to alleviate the treatment burden. TIP has ease of use as total administration time is less, greater patient satisfaction and unlike nebulizers, the T-326 inhaler does not require disinfection [5].
- A three year study has been carried out to analyze development of resistant by Gram-negative pathogens associated with hospital-acquired and ventilator-associated pneumonia (VAP) to the available treatment options as well as requirement of combination antimicrobial therapy. Five medical centers in Vietnam provided 529 *P. aeruginosa* from affected patients from 2012-214 were verified and susceptibility testing has been carried out. Development of resistance for cephalosporins, β-lactam inhibitors, carbapenems and fluoroquinolones was evaluated. Among the aminoglycosides, Tobramycin has shown susceptibility of 58.0% [36].
- An online survey has been carried out worldwide (192 intensive care units) to assess the indications, dosages and recent patterns of use for nebulized antimicrobial agents in mechanically ventilated patients. Nebulized antimicrobial agents are most commonly used for the treatment of VAP (56/87) and most common nebulizing agents include tobramycin (36.7%), amikacin

(26.4%), and colistin methane sulfonate and sulphates (41.3% and 27.5%) at significantly higher dosage than ventilator-associated tracheobronchitis (VAT) [37].

- A study has been carried out to analyze occurrence of organisms isolated from pneumonias in US hospitalized patients (PHP) including VAP. Under the SENTRY Antimicrobial Surveillance Program (2012), 2,203 bacterial isolates (339 from VAP) were collected from 25 medical centers. For Tobramycin (MIC50, 4 µg/ml) the studies were found to significant [38].
- During clinical trial on a total 93 patients having *P. aeruginosa* or *Acinetobacter baumannii* infection effect of inhaled colistin (150 mg) or tobramycin (300 mg) was compared against IV antibiotics. Patients treated with colistin (n = 9) or tobramycin (n = 10) were more severely ill and had more MDR infections [27].
- The contribution of adjunctive aerosolized antibiotic treatment in VAP has been investigated clinically at a Level I trauma ICU on 49 patients (January 2001 - July 2007). Aerosolized tobramycin, amikacin, and colistimethate were administered in 44, 9 and 9 episodes, respectively and systemic antibiotics were used in 98% episodes. In critically ill trauma patients with VAP, good response rate was observed with adjuvant aerosolized antibiotic treatment [39].

Bibliography

1. Fogila E., *et al*. "Ventilator-associated pneumonia in neonatal and pediatric intensive care unit patients". *Critical in Microbiology Reviews* 20.3 (2007): 409-425.

2. Vidaur L., *et al*. "Clinical approach to the patient with suspected ventilator-associated pneumonia". *Respiratory Care* 50.7 (2005): 965-974.

3. Nseir S., *et al*. "Nosocomial tracheobronchitis in mechanically ventilated patients: incidence, aetiology and outcome". *European Respiratory Journal* 20.6 (2002): 1483-1489.

4. Richards MJ., *et al*. "Nosocomial infections in medical intensive care units in the United States. National Nosocomial Infections Surveillance System". *Critical Care Medicine* 27.5 (1999): 887-892.

5. Hamed K and Debonnett L. "Tobramycin inhalation powder for the treatment of pulmonary Pseudomonas aeruginosa infection in patients with cystic fibrosis: a review based on clinical evidence". *Therapeutic Advances in Respiratory Disease* 11.5 (2017): 193-209.

6. Greenfield S., *et al*. "Prevention of gram-negative bacillary pneumonia using aerosol polymyxin as prophylaxis. I. Effect on the colonization pattern of the upper respiratory tract of seriously ill patients". *Journal of Clinical Investigation* 52.11 (1973): 2935-2940.

7. Klastersky J., *et al*. "Endotracheally administered gentamicin for the prevention of infections of the respiratory tract in patients with tracheostomy: a double-blind study". *Chest* 65.6 (1974): 650-654.

8. Klick JM., *et al*. "Prevention of gram-negative bacillary pneumonia using polymyxin aerosol as prophylaxis. II. Effect on the incidence of pneumonia in seriously ill patients". *Journal of Clinical Investigation* 55.3 (1975): 514-519.

9. Feeley TW., *et al*. "Aerosol polymyxin and pneumonia in seriously ill patients". *The New England Journal of Medicine*293.10 (1975): 471-475.

10. Lode H., *et al*. "Systemic and endotracheal antibiotic prophylaxis of nosocomial pneumonia in ICU". *Intensive Care Medicine* 18.1 (1992): S24-S27.

11. Wood GC., *et al*. "Aerosolized ceftazidime for prevention of ventilator-associated pneumonia and drug effects on the proinflammatory response in critically ill trauma patients". *Pharmacotherapy.* 22.8 (2002): 972-982.

12. Falagas ME., *et al*. "Administration of antibiotics via the respiratory tract for the prevention of ICU-acquired pneumonia: a meta-analysis of comparative trials". *Critical Care* 10.4 (2006): R123.

13. Stoutenbeek CP., *et al*. "Nosocomial gram-negative pneumonia in critically ill patients: a 3-year experience with a novel therapeutic regimen". *Intensive Care Medicine* 12.6 (1986): 419-423.

14. Brown RB., *et al*. "Double blind study of endotracheal tobramycin in the treatment of gram-negative bacterial pneumonia. The endotracheal tobramycin study group". *Antimicrobial Agents and Chemotherapy* 34.2 (1990): 269-272.

15. Le Conte P., *et al*. "Administration of tobramycin aerosols in patients with nosocomial pneumonia: a preliminary study". *Presse Médicale* 29.2 (2000): 76-78.

16. Sobieszczyk ME., *et al*. "Combination therapy with polymyxin B for the treatment of multidrug-resistant Gram-negative respiratory tract infections". *Journal of Antimicrobial Chemotherapy* 54.2 (2004): 566-569.

17. Michalopoulos A., *et al*. "Aerosolized colistin for the treatment of nosocomial pneumonia due to multidrug-resistant Gram-negative bacteria in patients without cystic fibrosis". *Critical Care* 9.1 (2005): R53-R59.

18. Palmer LB., *et al*. "Aerosolized antibiotics in mechanically ventilated patients: delivery and response". *Critical Care Medicine* 26.1 (1998): 31-39.

19. Drobnic ME., *et al*. "Inhaled tobramycin in non-cystic fibrosis patients with bronchiectasis and chronic bronchial infection with Pseudomonas aeruginosa". *Annals of Pharmacotherapy* 39.12 (2005): 39-44.

20. Dhand R. "The role of aerosolized antimicrobials in the treatment of ventilator-associated pneumonia". *Respiratory Care* 52.7 (2007): 866-884.

21. Dimopoulos GT., *et al*. "Aerolized antibiotics for the treatment of ventilator associated pneumonia: A new era!". *PNEUMON* 27.1 (2014): 87-93.

22. Sievert DM., *et al*. "Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009-2010". *Infection Control and Hospital Epidemiology* 34.1(2013): 1-14.

23. Kiem S and Schentag JJ. "Interpretation of antibiotic concentration ratios measured in epithelial lining fluid". *Antimicrobial Agents and Chemotherapy* 52(2008): 24-36.

24. Ioannidou E., *et al*. "Administration of antimicrobials via the respiratory tract for the treatment of patients with nosocomial pneumonia: a meta-analysis". *Journal of Antimicrobial Chemotherapy* 60.6 (2007): 1216-1226.

25. Le J., *et al*. "Consensus summary of aerosolized antimicrobial agents: application of guideline criteria. Insights from the Society of Infectious Diseases Pharmacists". *Pharmacotherapy* 30.6 (2010): 562-584.

26. Korbila IP., *et al*. "Inhaled colistin as adjunctive therapy to intravenous colistin for the treatment of microbiologically documented ventilator-associated pneumonia: a comparative cohort study". *Clinical Microbiology and Infection* 16.8 (2010): 1230 -1236.

27. Arnold HM., *et al*. "Use of adjunctive aerosolized antimicrobial therapy in the treatment of Pseudomonas aeruginosa and Acinetobacter baumannii ventilator-associated pneumonia". *Respiratory Care* 57.8 (2012): 1226-1233.

28. Moroz VV., *et al*. "Inhaled tobramycin in treatment of severe nosocomial pneumonias". *General Reanimatology* 8 (2012): 5-10.

29. Polovnikov S., *et al*. "Administration of inhaled tobramycin in severe nosocomial pneumonia (case report)". *Pulmonology* 2 (2011): 109-112.

30. Kuzovlev AN. "Inhaled tobramycin in the treatment of nosocomial pneumonia in severe sepsis". *Journal of Pulmonary and Respiratory Medicine* 4.1 (2013): e132.

31. Fujitani S., *et al*. "Pseudomonas aeruginosa. Infectious Disease Antimicrob Agents". (2017).

32. Ramsey BW., *et al*. "Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group". *The New England Journal of Medicine* 340.1 (1999): 23-30.

33. Scheinberg P and Shore E. "A pilot study of the safety and efficacy of tobramycin solution for inhalation in patients with severe bronchiectasis". *Chest* 127.4 (2005): 1420-1426.

34. Gunderson BW., *et al*. "Synergistic activity of colistin and ceftazidime against multiantibiotic-resistant Pseudomonas aeruginosa in an in vitro pharmacodynamic model". *Antimicrobial Agents and Chemotherapy* 47.3 (2003): 905-909.

35. Migiyama Y., *et al*. "Aerosolized tobramycin for Pseudomonas aeruginosa ventilator-associated pneumonia in patients with acute respiratory distress syndrome". *Pulmonary Pharmacology and Therapeutics* 45 (2017): 142-147.

36. Biedenbach DJ., *et al*. "Antimicrobial-resistant Pseudomonas aeruginosa and Acinetobacter baumannii From Patients with Hospital-acquired or Ventilator-associated Pneumonia in Vietnam". *Clinical Therapeutics* 38.9 (2016): 2098-105.

37. Solé-Lleonart C., *et al*. "Global survey on nebulization of antimicrobial agents in mechanically ventilated patients: a call for international guidelines". *Clinical Microbiology and Infection* 22.4 (2016): 359-364.

38. Sader HS., *et al*. "Arbekacin activity against contemporary clinical bacteria isolated from patients hospitalized with pneumonia". *Antimicrobial Agents and Chemotherapy* 59.6 (2015): 3263-3270.

39. Czosnowski QA., *et al*. "Adjunctive aerosolized antibiotics for treatment of ventilator-associated pneumonia". *Pharmacotherapy* 29.9 (2009): 1054-1060.

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