Tobramycin (TOBI® or TOBI PODHALER®) in ventilator associated pneumonia: an overviewm

Despite the fact that Ventilator Associated Pneumonia (VAP) has a high death rate, it is not yet defined very well. Mortality in patients with lung injury on mechanical ventilation is estimated as 24% in persons 15-19 years and 60% in patients 85 years or older. Very few studies have reported the use of tobramycin (TOBI® or Tobi Podhaler®) in VAP management. However, the use of such antibiotics to treat VAP is equivocal and no clinical evidences reported. Tobi Podhaler® contains active substance of tobramycin, which is available as capsules (28 mg). Tobi Podhaler® can be used as a hand-held device which suppresses the chronic lung infections caused by P. aeruginosa in patients aged >6 years. The recommended dose is four capsules twice a day in adults and children older than 6 years of age. It can be also used to treat Cystic Fibrosis (CF). This review highlights the advantages of treatment with TOBI (Tobi Podhaler®) in VAP patients and also a note on inhaled antibiotics in management of chronic respiratory infections.

Keywords: tobramycin, ventilator associated pneumonia, pseudomonas spp., broad-spectrum antibiotics, TOBI®

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Introduction

Tobramycin is an aminoglycoside broad-spectrum antibiotic, which is effective against most of the gram-negative bacterial infections, especially, against *Pseudomonas* Spp., initially isolated from *Streptomyces tenebrarius* and identified (1967) as a complex and designated as factor 6 (10% of the complex), subsequently named as tobramycin [1,2]. It has been reported that in combination with other antibiotics tobramycin is effective in treatment of vast range of infections such as urinary tract infections, gynecologic infections, pneumonia, respiratory infections, soft tissue infections, etc. However, there are certain combinations (Tobraflex® (containing Fluorometholone, Tobramycin) not yet approved by United States Food and Drug Administration (USFDA) for safety and effectiveness whereas few combinations (Tobrasone® (containing Fluorometholone, Tobramycin) are not available in the markets due to safety concerns [3,4]. Tobramycin is an effective agent, used in the management of lung diseases in adult and pediatric populations with cystic fibrosis; furthermore, intravenous tobramycin plays major role in management of acute pulmonary exacerbations of cystic fibrosis [5,6]. Inhaled tobramycin in patients with CF and chronic *P. aeruginosa* infection enables the delivery of significant concentrations of antibiotic and shows bactericidal effect by which toxicity and systemic absorption is reduced [7]. An orally inhaled dry powder, Tobi® Podhaler®-Novartis (FDA Approved) is effective in management of *P. aeruginosa* pulmonary infection in cystic fibrosis patients' ≥ 6 years old; moreover, tobramycin is effective as inhalation solutions (TOBI®), which also have been reported to be an operational drug for this indication [8]. *P. aeruginosa* causes Ventilator Associated Pneumonia (VAP), a common lung infection, which associated with significant rates of mortality and recurrent rates in patients with acute respiratory distress syndrome. Studies have reported that aerosolized tobramycin is an effective drug for VAP treatment [9-11]. The drug action pathways of tobramycin involved at molecular level where protein synthesis is inhibited or misleading to derive inactive/incorrect protein by binding to the bacterial 30s ribosomal subunit protein and 16S rRNA to prevent the formation of initiation complex [12,13]. Many clinical studies reported that tobramycin is effective in treating many infections caused by G-ve bacteria. Clinical and experimental evidences reported that tobramycin is ototoxic and nephrotoxic and

it is said that not an ideal drug with narrow therapeutic index [14]. There are many studies showed that tobramycin is effective in all forms available and improve the patient satisfaction at recommended doses with scheduled duration. **TABLE 1** shows the recommended doses, frequency of administration, duration and clinical outcomes of TSI and TIP.

Ventilated associated pneumonia (VAP)

VAP defined as a type of lung infection that occur after 48-72 hospitalization, characterized by endotracheal intubation, systemic infection, changes in sputum characteristics. It has been reported that, nearly half of the hospitalized patients are prone VAP and estimated that VAP occur in 9-27 % of all mechanically ventilated patients. Bacteria, such as *Streptococcus pneumoniae*, antibiotic-sensitive enteric Gram-negative bacilli cause the early onset of VAP, whereas multidrug resistant bacteria are culprits of late VAP [15-17]. It has been reported that *Pseudomonas* spp. are predominant pathogenic agents, followed by *S. aureus* and *Enterobacteriaceae*. However, VAP has remarkable mortality rate; there is no universally accepted diagnosis method to identify the disease at early stage. None of the recommended clinical methods has sensitivity or specificity to accurately identify the disease; however, bedside valuation in conjunction with chest radiography is the most recommended method [18,19]. The clinical pulmonary infection score (CPIS) is used to predict the presence or absence of VAP based on clinical, physiological, microbiological and radiographic evidences [20].

As reports stated to treat late onset VAP >4 days required broad-spectrum antibiotic therapy whereas early onset ≤ 4 days can be treated with narrow spectrum antibiotics. Due to the high rates of resistance to the monotherapy; combinations therapy is always recommended. The role of inhaled antibiotics in management of VAP is not clear. The ideal duration to treat early onset VAP is vancomycin (15-20 mcg/ml), amikacin (<5 mcg/ml), gentamicin (<1 mcg/ml) and tobramycin (<1 mcg/ml is 8 days and may be longer in late onset VAP). The use of antibiotics in treatment of VAP associated with adverse events such as hepatic and renal failure. The review concluded that a gold standard criterion is required to diagnosis of VAP at early stages. The major goals of VAP management are early diagnosis, appropriate antibiotic therapy, dosage and duration to minimize the toxic effects/adverse events [15-20].

The causative agents for large portion of lower respiratory tract infections are gram-negative bacteria, mostly, hospital-acquired infection or nosocomial infections. The systemic administration of antibiotics is being reported poor effectiveness with significant toxicity. Maximization of target site concentration and optimization of pharmacokinetic / pharmacodynamic indices can be achieved by using inhaled antibiotics with minimal systemic exposure and toxicity. The formulation and drug delivery, pharmacokinetics /pharmacodynamics, clinical outcomes, safety and limitations of inhaled antimicrobials are important in treatment of VAP. Most of the clinical studies reported that there were no serious side effects and emergence of resistance of multi drug resistance G-ve bacteria. Therefore, patient undergone mechanical ventilation associated with significant risk for VAP, high rate of mortality and morbidity may be benefited

Table 1: Suggested doses, duration and clinical outcomes of tobramycin (Table courtesy: Maselli DJ, et al. 2017 [52])

Form of tobramycin	Dose	Frequency	Duration	Significant outcome
TIP	112 mg	Twice daily	I cycle (28 days on/off)	improvement in the lung function
TIP	112 mg	Twice daily	3 cycles (28 days on/off)	greater satisfaction
TSI	300 mg	Twice daily	3 cycles (28 days on/off)	greater satisfaction
TSI	300 mg	Twice daily	7 cycles (28 days on/off)	Decreased hospitalization rates
TSI	300 mg	Twice daily	28 days	reduced lower airway *P. aeruginosa* density
TSI	300 mg	Twice daily	24 weeks (28 days on/off)	Improved pulmonary function
TSI	600 mg	Three times daily	12 weeks (28 days on/off)	Improved pulmonary function
TSI	600 mg	Three times daily	12 weeks	Improved symptoms, decrease in bacterial density
TSI	80 mg	Three times daily	32 months	Stability in pulmonary function

from inhaled antibiotic therapy. However, the most available clinical data suggests that further studies are needed to assess the safety and efficacy of antibiotics. Moreover, to recommend inhaled antibiotics, development of drug delivery devices is also a remarkable challenge [21].

Gentamicin vs. Tobramycin

Gentamicin and Tobramycin are widely used antibiotics and reported that have similar antimicrobial activity. In vitro studies suggested that both are effective against most of the strains of *Enterobacteriaceae* and *Staphylococcus*; moreover, both the drugs have similar toxic effects. A clinical in vitro investigation compared the effectiveness of gentamicin and tobramycin in serious infections caused by Gram-negative bacteria. The study reported that in a clinical prospective both the drugs are similar in a series of urinary tract infections (66% of favorable responses and in pulmonary infections, septicemia, and meningitis 26% of favorable responses). The study concluded that the encountered adverse event frequency is also similar for both the drugs [22]. Other studies reported that both of them have significant ototoxicity and nephrotoxicity in animal and human models. However, it has been demonstrated that gentamicin is associated with frequent renal failure, which is three times more than that of tobramycin [23].

A prospective randomized study conducted with a total of 194 patients of to compare the toxicity of gentamicin and tobramycin. Patients were divided into 2 groups (97 each) and received the gentamicin and tobramycin with no significant difference of total dose, duration and blood levels. The study observed that possible nephrotoxicity and definite nephrotoxicity occurred due to gentamicin in 8 (7.8%) patients and 10 (9.8%), respectively, whereas in 7 patients (6.8%) possible nephrotoxicity and in 8 (7.8%) patients definite nephrotoxicity occurred due to tobramycin. This indicates that there are significant toxicological differences found in this study even after completion of serial audiological and vestibular studies [24].

Bauer et al. compared the pharmacokinetic values of gentamicin or tobramycin in patients with pseudomonas pulmonary infection (Cystic Fibrosis (CF)). Total of 31 patients out of 69 were received gentamicin sulfate, 38 received tobramycin sulfate, and dose interval was 6 h. Serum concentrations of both the drugs determined by radioimmunoassay. Half-lives were 1.2 ± 0.5 for tobramycin and 1.4 ± 0.4 h for gentamicin. The average volume of distribution and clearance values for the tobramycin patients were 0.33 ± 0.20 l/kg and 2.98 ± 0.80 ml/min/kg. For the patients received gentamicin the values were 0.35 ± 0.15 liters/kg and 2.79 ± 0.75 ml/min/kg. The studies concluded that there is no significance deference between the kinetic variables in the patients receiving gentamicin or tobramycin [25].

Nebulized and inhaled Tobramycin in VAP

Tobramycin is available in various forms such as nebulizer, PulmoSphere formulation (PStob), inhaled solution (TIS) and inhaled powder (TIP). Among all available forms of tobramycin, studies reported that inhaled powder has showed significant decrease in mortality and morbidity rates in mechanically ventilated patients. Le Conte et al. [26] conducted a study on 5 healthy patients and 5 mechanically ventilated patients. The healthy group has administrated with 300 mg of tobramycin and 1 ml of 99mTc-DTPA via a pneumatic nebulizer; in the other group of patients who underwent thoracic surgery, 300 mg of tobramycin alone were administered. The study showed that, similar half-life of tobramycin in both the groups; however, aerosolization of tobramycin produced high lung concentrations and low serum levels [26]. The serum concentrations, whole lung depositions, efficiency and reproducibility of pulmonary delivery of tobramycin PulmoSphere formulation (PStob) by a passive powder inhaler are significantly high when compared with nebulized tobramycin. In addition, tobramycin inhalation powder allows delivery of large doses with low side effects. Newhouse et al. [27] conducted a nonrandomized five period open label cross over study with 14 healthy volunteers (12 completed). The subjects inhaled contents of a single capsule (72 L/min) containing 25 mg of (99 m) Tc-labeled PStob (13.5 mg of tobramycin freebase) in periods 1 to 3. In period 4, subjects received (99 m) Tc nebulized tobramycin, approximately 2.5 mL of 300 mg/5 mL in order to identify the whole lung deposition. The results showed that the whole-lung deposition of PStob was 34 ± 6% and nebulized tobramycin was 5 ± 2%. The Cmax values were 0.6 μ/ml and 0.28 μ/ml with PStob

and after nebulized tobramycin, respectively. The results suggested that aerosol doses of PStob (25 mg and 150 mg) were well dispersed and tolerated and serum drug concentrations are about twice than that of nebulized tobramycin [27].

Some prospective, randomized studies reported that instilled and imipenem obtained higher concentrations in respiratory secretions than nebulized; however, tobramycin showed equally high concentrations when nebulized or instilled. In some cases, it has been showed that TOBI patients had clinical resolution of VAP and more ventilator-free days than treated with other antibiotics. In respiratory diseases, it has been reported that instillation of the antibiotics is safe and showed significantly high drug concentrations. Another prospective, open-label study conducted on medical, surgical, and trauma patients with TOBI and reported that there was low to undetectable systemic absorption and no apparent effect on renal function [28-31].

Many studies have reported that the use of inhaled tobramycin as an adjuvant in mechanically ventilated patients is safe in majority of the cases studied and there was no incidence of Nosocomial Pneumonia observed [31]. A randomized multicenter, open-label, parallel-group study evaluated safety profiles of TIP and TIS. The study reported that there was grater patient satisfaction in all subjects with TIP and had efficacy outcomes compared with TIS [32]. Migiyama et al. [11] conducted a retrospective analysis was performed to evaluate the efficacy of aerosolized Tobramycin for *P. aeruginosa* VAP in acute respiratory distress syndrome patients. The results found that there is significant decrease in recurrence of *P. aeruginosa* VAP and ICU mortality in TIS Group that the control group. This study concluded that, aerosolized tobramycin could be an effective treatment strategy for *P. aeruginosa* VAP patients with acute respiratory distress syndrome [11]. Nebulizers are most common tobramycin delivering system; however, there are significant drawbacks and time is also a challenge. Wee et al. aimed to quantify the amount of aerosolized tobramycin delivered to the lungs of in vitro tracheostomized pediatric models with TOBI® Podhaler™ and PARI LC Plus®. In this study, 6 and 12-year-old trachea were created in vitro and tobramycin aerosol delivered by using TOBI® Podhaler™ and PARI LC Plus® and colorimetric tobramycin assay performed to quantify the amount. The results showed that Podhaler™ is more efficient than the competitor LC Plus® [33].

Discussion

Inhaled antibiotics are being used for treatment of chronic airway infections since early 1940s, due to the hyperosmolarity formulations and preservatives, inhaled antibiotics caused bronchial irritation. In 1990 remarkable clinical outcomes were reported when two large clinical trials with aerosolized tobramycin demonstrated improvement in lung function in CF patients. In 1997 USFDA approved inhaled tobramycin for treatment of airway infections. The advances in development of inhaled antipseudomonal therapies for management of cystic fibrosis contributed to significant patient outcomes. There are many inhaled antibiotics, dry powder inhalers developed that are advanced in accurate drug delivery and improving adherence compared with nebulized therapies [34,35].

Tobramycin is one of the first inhaled antibiotics studied in CF patients. The systemic absorption of many antibiotics is low because most of the aminoglycosides binds to the mucins of sputum and reduce availability of drug; hence, the available drug concentrations are not effective in killing of *P. aeruginosa*. Administration of inhaled of inhaled tobramycin overcome the barrier, since the drug available in various forms of including tobramycin solution for inhalation (TSI) and tobramycin inhalation powder (TIP) that can penetrate the mucous layers. Cyclic TIS administrated with jet or electronic nebulizer (twice daily) improved pulmonary function, decreased sputum density, and decreased need for systemic antibiotics. TIP has been recommended in the 2013 CF Foundation and the 2014 European guidelines as a therapy in CF for the maintenance of lung health. TIP offers therapeutic advantages over the traditional formulations [36-40]. Spray-dried formulation and engineered Tobramycin Inhalation Powder (TIP) designed through composition and process parameters. Characterization of TIP on both the particle and molecular levels using multiple orthogonal physical characterization techniques such Differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD), electron spectroscopy for chemical

analysis (ESCA), and Raman measurements was done. The report highlighted that IP enables highly efficient delivery of fine particles to the respiratory tract and particle engineering has enabled development of TOBI Podhaler, which is an approved inhaled drug product [41].

Aminoglycoside antibiotics are effective in management of infections such as airway infections, cystic fibrosis, pneumonia and other complications caused by gram-negative bacteria. Inhaled antibiotics have been used to treat chronic airway inflammations **(TABLE 2).** Tobramycin inhalation powder has optimized the treatment of cystic fibrosis; the dry powder inhalation device reduces the administration time and improves the adherence with no significant risk of bacterial contamination [42]. Tobramycin inhalation powder improves the ease of use compared to Tobramycin inhalation solution and the efficacy of the treatment; however, it may vary by age of the patients, TIP had greater efficacy, safety and patient satisfaction. Moreover, studies have demonstrated that TIP had high patient tolerance and improved adherence compared with traditional formulations [43,44]. Compared to TSI, TIP showed similar efficacy in lung infection and sputum *P. aeruginosa* density; however, TIP delivered mush faster than that of TSI. In addition, overall satisfaction and quality of life scores are reported higher in patients assigned to dry-powder formulation [44,45]. Podhaler's Tobramycin delivery is a feasible option in tracheostomized pediatric patients [46]. Increasing prescriptions of inhaled Tobramycin from 2007 to 2015 in the OPDP with approximately half of these claims being for off-label use, mostly among patients with COPD [47]. TOBI Podhaler enables delivery of high doses of drug per inhalation, a feature critical for dry powder delivery of anti-infective for treatment of cystic fibrosis [41]. Therapeutic substitution of TOBI® with PFIT can produce immediate and sustained savings with an acceptable safety profile. However, there are no specific and sensitive criteria or definition to VAP, animal model studies have been proved that absorption of Tobramycin was dose dependent [36-48].

Despite the availability of several systemic antipseudomonal agents, many bacterial species developed resistance to the antimicrobial agents; therefore, alternative therapeutic strategies have drawn interest of many researchers. And also combination therapy failed in treatment of such airway infections due to the lack of high quality evidences and clear benefits of the approach. Systemic antibiotics are associated with severe toxicological events [49]. Most of the systemic antibiotics are failed to penetrate the sputum and the low level concentrations are not effective against bacterial species. Another significant adverse event is IV administration of broad spectrum antibiotics disrupts the normal gut flora and increases the risk of secondary infections and may promote the drug resistance [50,51]. On the other hand the inhaled antibiotics pose many advantages in treating the lower airway infections. Inhaled therapy is advanced in delivering high drug concentrations at target sites and the absorption and toxicity are significantly lower. Never the less, inhaled antibiotics reduce the frequency of exacerbations and airway bacterial density, and improve pulmonary function and quality of life [35,52-54]. Owing to the many advantages

Table 2: Tobramycin for Varity of infections (Table courtesy: Maselli DJ, et al. 2017 [53] and Quon BS, et al. 2014 [54])

Infection Type	Preparation	Potential Indication	Additional Information
Post–lung transplant infections	Inhaled Tobramycin	Post-transplant prophylaxis in patients with pretransplant infection with multidrug-resistant organisms (*P. aeruginosa* or *B. cepacia*)	Typically used for 3 months
Non–cystic fibrosis bronchiectasis	Inhaled Tobramycin	Chronic pulmonary *P. aeruginosa* in fection, Frequent infectious exacerbations, *P. aeruginosa* eradication	Not rigorously studied but might reduce more severe exacerbations and eradicate Pseudomonas in one-third of cases
cystic fibrosis	Tobramycin solution	Management of patients with CF with *P. aeruginosa* infection >6 yr of age	Alternating-month use
cystic fibrosis	Tobramycin dry powder	Management of patients with CF with *P. aeruginosa* infection >6 yr of age	Alternating-month use Not currently used for *P. aeruginosa* eradication

of inhaled antibiotics such as TOBI® or TOBI PODHALER, these drugs are considered as standard care for management of chronic management of pulmonary diseases.

Conclusion

Aminoglycosides are novel and effective antibiotics against Gram-negative organisms. Cellular uptake of modified aminoglycosides such as kanamycin, tobramycin and neomycin are reported to have significant effectiveness in patients with bacterial infections. It is also proven that the administration of tobramycin was safe in terms of nephrotoxicity in cystic fibrosis patients and mechanically ventilated patients. The clinical trials and randomized trials were found successful in patient outcomes and improved quality of life in VAP patients and other Pseudomonas infections; however, most of the clinical studies performed with inadequate sample sizes. Therefore, it is necessary to test tobramycin and tobramycin combinations with adequate sample sizes to measure the outcomes and adverse events, and also further research to develop more tobramycin combinations for the treatment of infections due to gram negative bacteria such as *Enterobacteriaceae, Pseudomonas* is warranted.

Conflict of interest

This is a literature review and no clinical study was conducted. The survey is based on selected biomedical databases (PubMed, PMC) and search words include Tobramycin, Tobi®, and ventilator Associated Pneumonia. No potential financial or commercial conflicts to disclose.

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This special issue on Current Trends in Clinical Research was edited by Dr. Mohamed Elsayed.