

AMERICAN ACADEMY OF PEDIATRICS

Technical Report: Precautions Regarding the Use of Aerosolized Antibiotics

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ABSTRACT. In 1998, the Food and Drug Administration (FDA) approved the licensure of tobramycin solution for inhalation (TOBI). Although a number of additional antibiotics, including other aminoglycosides, β -lactams, antibiotics in the polymyxin class, and vancomycin, have been administered as aerosols for many years, none are approved by the FDA for administration by inhalation.

TOBI was approved by the FDA for the maintenance therapy of patients 6 years or older with cystic fibrosis (CF) who have between 25% and 75% of predicted forced expiratory volume in 1 second (FEV₁), are colonized with *Pseudomonas aeruginosa*, and are able to comply with the prescribed medical regimen. TOBI was not approved for the therapy of acute pulmonary exacerbations in patients with CF nor was it approved for use in patients without CF. Currently, no other antibiotics are approved for administration by inhalation to patients with or without CF.

The purpose of this statement is to briefly summarize the data that supported approval for licensure of TOBI and to provide recommendations for its safe use. The pharmacokinetics of inhaled aminoglycosides and problems associated with aerosolized antibiotic treatment, including environmental contamination, selection of resistant microbes, and airway exposure to excipients in intravenous formulations, will be discussed. *Pediatrics* 2000;106(6). URL: <http://www.pediatrics.org/cgi/content/full/106/6/e89>; aerosolized antibiotics, tobramycin solution for inhalation; cystic fibrosis; *Pseudomonas aeruginosa*.

ABBREVIATIONS. TOBI, tobramycin solution for inhalation; CF, cystic fibrosis; FEV₁, forced expiratory volume in 1 second; FDA, Food and Drug Administration; MIC, minimal inhibitory concentration.

APPROVED INDICATION FOR TOBRAMYCIN SOLUTION FOR INHALATION (TOBI)

TOBI is approved for *maintenance* therapy of patients with cystic fibrosis (CF) who are known to be colonized with *Pseudomonas aeruginosa*. The results of 2 randomized, double-blind, placebo-controlled, multicentered, 24-week clinical studies demonstrated the favorable effects of this therapy.^{1,2} Each study enrolled subjects 6 years or older who had $\geq 25\%$ and $\leq 75\%$ of predicted forced expiratory volume in 1

second (FEV₁). Subjects with serum creatinine concentrations above 2 mg/dL and those colonized with *Burkholderia cepacia* were excluded. Study participants received alternating 28-day cycles of drug therapy. Two hundred fifty-eight patients received 300 mg of TOBI twice daily and 262 received inhaled saline placebo. Both drug and placebo were delivered by a PARI LC Plus nebulizer (PARI Respiratory Equipment Inc, Monterey, CA) with a Pulmo-Aide compressor (DeVilbiss Air Power Co, Jackson, TN). The drug recipients experienced significant improvement in pulmonary function compared with the placebo recipients; the average improvement in FEV₁ at the end of the study (week 24) relative to baseline (week 0) was 7% to 11% in the treatment group versus 0% to 1% in the placebo group ($P < .001$). Furthermore, TOBI resulted in a significant reduction in the number of *P aeruginosa* colony-forming units in sputum during the monthly periods of drug administration. Other evidence from these 2 studies that supported the possible benefit of chronic intermittent administration of TOBI included a reduction in the average number of hospitalization days during the 24-week study, from 8.1 days among the placebo recipients to 5.1 days among TOBI recipients ($P = .001$). The average number of days of parenteral antipseudomonal antibiotic treatment in the TOBI group also was reduced (9.6 vs 14.1 days; $P = .003$) during the 24-week study.

No data support the benefit of TOBI in the management of acute exacerbations of pulmonary disease in patients with CF; thus, the drug is not recommended for hospitalized patients with CF. Nonetheless, some centers are prescribing TOBI for patients with CF if they are hospitalized during months when they already have been scheduled to receive their maintenance therapy. Even in the absence of supportive data, some centers also are prescribing TOBI for patients who are hospitalized because they are critically ill and/or are awaiting lung transplantation. In addition to the lack of clinical research studies supporting these practices, the administration of TOBI in hospital environments raises concerns regarding development and spread of antibiotic-resistant bacteria among hospitalized patients with CF and other fragile, immunocompromised hosts.

A number of antibiotic agents, including other aminoglycosides, β -lactams, vancomycin, and antibi-

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otics in the polymyxin class, have been administered as aerosols for many years to patients with CF.³⁻¹⁷ However, none of these agents have been approved for inhalation and studies evaluating their efficacy have substantial problems in study design, including: small sample size, inadequate blinding of participants, lack of appropriate controls, and failure to consider potential carryover effects in crossover designs. Other aminoglycosides,¹⁸⁻²⁰ vancomycin,^{21,22} and polymyxin²³ also have been administered by inhalation in different circumstances to patients without CF. However, their efficacy has not been evaluated in any randomized, controlled trials and their use in aerosolized form has not been approved by the Food and Drug Administration (FDA).

DELIVERY AND PHARMACOKINETICS

Aerosolized antibiotics have been used since the 1950s. Although understanding of the science of this form of medication delivery has increased, much still remains to be studied. Understanding how to administer aerosolized medications to patients requires an appreciation of the physiologic, physical, chemical, and mechanical limitations of this form of delivery.

Delivery Considerations

Two devices are most commonly used to aerosolize antibiotics—ultrasonic and jet nebulizers. Ultrasonic nebulizers produce an aerosol from the shear force created by a vibrating piezoelectric crystal. This class of nebulizer produces the most consistent and efficient aerosol,²⁴ but has a number of limitations, such as: cost of the device, high maintenance needs, and the need to heat the aerosol solution, which may cause degradation of some drugs. Jet nebulizers produce an aerosol by forcing a compressed jet of gas over the medication solution. The source of compressed gas (eg, wall gas in institutions or a compressor), use of a T-tube, breath-enhanced design, and recirculating bag or face mask all affect delivery and, hence, dose of the medication delivered.²⁵

Once an aerosol is produced, the particle size created has a large impact on delivery. Particles in the range of 1 to 5 μm in diameter are most desirable for pulmonary delivery.²⁶ Within this range, the distribution of particles is regional. Smaller particles are deposited in alveoli and larger particles are deposited more proximally. Particles $>5 \mu\text{m}$ generally are delivered to the oropharynx and swallowed. Particles $<1 \mu\text{m}$ have too small a mass to adhere to the respiratory epithelium and thus deliver an insufficient quantity of drug.²⁷ The variation between the available nebulizers in mean size and range of particle sizes generated is wide.²⁷ Volume of fill, surface tension of the nebulizer solution, and nebulizing flow rate also have been shown to affect drug delivery.²⁸ Physiologic factors, including minute ventilation, pattern of breathing, age, and disease (obstruction or inflammation), also have some effect on efficiency of aerosol drug delivery.²⁸

Pharmacokinetics

Even with use of an optimal nebulizer, only approximately 10% of the total dose is delivered to the lung.²⁹ The rest of the dose is either delivered to the oropharynx and swallowed, is left in the dead space of the nebulizer or tubing, or is released into the environment.³⁰ Potentially, the portions of the drug swallowed and delivered to the lung are available for systemic absorption. Antibiotics are cleared from the lung by mucociliary action, coughing, and absorption into the blood with subsequent elimination.³¹ A number of chemical properties of the drug will influence drug absorption, including molecular weight, lipophilicity, and protein binding.³² Absorption appears to be highly variable between individuals.^{33,34} No clearly defined variables have been identified to increase absorption.

Data regarding serum concentrations of aminoglycosides attained following aerosolization are summarized in Table 1.^{2,33-35} These studies demonstrate that patients with normal renal function, given the

TABLE 1. Pharmacokinetics of Aerosolized Aminoglycosides*

Drug	Number Subjects	Dose	Nebulizer	Disease	Level† ($\mu\text{g}/\text{mL}$)		Reference
					Mean	High	
Tobramycin	61	300 mg BID	Pari LC‡	CF	0.57	0.95	42
Tobramycin	61	300 mg BID	Sidestream§	CF	0.74	1.17	
TOBI	520	300 mg BID	Pari LC Plus‡	CF	0.98	3.41	40
Tobramycin	5	400 mg	Ultra Neb 99¶	CF	0.44	>20	41
	5	600 mg	Ultra Neb 99¶	CF	0.58	0.7	
Tobramycin	6	600 mg \times 1	Ultrasonic‡	CF	1.27	2.57	38
Tobramycin	5	300 mg \times 1	Not listed	Healthy	.27	NL	37
	5			Mechanical ventilation; no lung disease	1.07	1.6	
	5			Lung cancer	0.55	0.55	
Tobramycin	14	80 mg BID	Pariboy or Pari-Privat jet‡	CF	NL	0.4	43
Gentamicin	8	600 mg	Jet type	CF	2.48	4.2	39

* Does not include aminoglycosides given endotracheally. BID indicates twice daily; CF, cystic fibrosis; NL, not listed.

† Obtained at approximately 1 hour "peak" values.

‡ PARI Respiratory Equipment Inc, Monterey, CA.

§ Invacare, Elyria, OH.

¶ DeVilbiss Air Power Co, Jackson, TN.

|| Not clear if this value represents absorption or spurious contamination. Mean value does not include high value since not quantitated ($>20 \mu\text{g}/\text{mL}$).

currently recommended doses, rarely have significant drug accumulation. As this therapy is used in a greater number of patients with a variety of disease states, range of physiologic function, ages, nebulizers, concomitant medications (Pulmozyme [Genentech, San Francisco, CA], β -agonists), and dosing strategies, some individuals may achieve levels in the toxic range. Absorption appears to occur in a dose-dependent fashion as demonstrated in a study of 8 patients 6 to 20 years of age with CF who were given single doses (120, 360, and 600 mg) of gentamicin using an unspecified jet-type nebulizer. Systemic absorption increased as the dose was increased. At the highest dose (600 mg), the highest peak plasma concentration was 4.2 $\mu\text{g}/\text{mL}$ (mean, 2.48 $\mu\text{g}/\text{mL}$). At all doses, drug was undetectable after 8 hours. This was a single-dose study and steady state values may be higher. In the TOBI trial, serum concentrations were measured 1 hour after administration to approximate a "peak."² On day 1, the mean peak concentration was 0.94 $\mu\text{g}/\text{mL}$ (range: 0.18–3.62) and during week 20 of therapy, the mean peak concentration was 0.98 $\mu\text{g}/\text{mL}$ (range: 0.18–3.41). Because absorption of drug from this lung depot is variable, the actual peak may occur earlier or later.

Sputum concentrations attained after inhalation of antibiotics were highly variable. In addition to drug delivery variability, some of this variability may reflect differences in sampling technique and some may reflect the lack of standardization of bioassays for sputum specimens. Mean sputum concentrations of tobramycin in subjects participating in the phase III TOBI trials were approximately 1200 $\mu\text{g}/\text{mL}$ 10 minutes after dosing. Concentrations were more than 10 times the minimal inhibitory concentration (MIC) of the most resistant isolate in 98% of patients and more than 25 times the MIC of the most resistant isolate in 95% of patients.^{1,2}

ADVERSE EVENTS

The prolonged use and/or repetitive cycles of use of aerosolized antibiotics in patients with and without CF raise safety concerns with regard to possible toxicities of the antibiotic or other component(s) in the aerosol for the patient and the potential for selection of antibiotic-resistant organisms in the patient and the home or hospital environment.

Potential Toxicity for Patients

The occurrence of ototoxicity and nephrotoxicity have been carefully assessed in a number of prospective, randomized controlled studies of both prolonged use and repetitive cycles of use of aerosolized tobramycin. No toxicity has been detected.^{1,6,8,9,36–38} Even aerosolized doses of 600 mg of tobramycin administered 3 times per day for 12 weeks in a small study of 22 patients were not associated with demonstrable ototoxicity or nephrotoxicity.³⁷ This lack of toxicity probably is related to the low and unsustained (<8 hours) serum concentrations achieved.

Both aerosolized tobramycin and gentamicin have been associated with acute bronchial constriction^{39,40} when the intravenous preparation of aminoglycoside

has been used for aerosol administration. These preparations contain antioxidants and preservatives that may contribute to bronchospasm. The aerosol preparation of tobramycin licensed by the FDA is preservative free, and in clinical studies has been found to be less irritating than the parenteral formulation administered by aerosol, although bronchospasms were observed occasionally.^{2,9}

In order to ensure correct delivery and evaluate drug tolerance, the first dose of TOBI should be given in the presence of a trained health professional. During this administration, patients or their caregivers should be trained to monitor for bronchospasm, urticaria, and/or perioral and periorbital edema. Patients or their caregivers should be advised to stop the medication and contact their physician if any of these adverse reactions occur.

Potential for Selection of Antibiotic-Resistant Organisms: Patient Risk; Environmental Risk

The most serious concern about prolonged use of aerosolized antibiotics is selection of resistant organisms from the primary microbial population or overgrowth of genera intrinsically resistant to the administered antibiotic. For patients with CF in whom eradication of *P aeruginosa* from the respiratory tract usually is not possible, even with aggressive therapy, emergence of multiply resistant organisms is a well-recognized problem associated with multiple courses of parenteral antibiotics administered for pulmonary exacerbations.^{41–43}

Development of tobramycin-resistant *P aeruginosa* during prolonged use or with repetitive cycles of aerosolized tobramycin has been reported. For example, after 3 months of continuous use of 600 mg of tobramycin 3 times daily by aerosolized administration, the percentage of patients having *P aeruginosa* with a tobramycin MIC ≥ 8 $\mu\text{g}/\text{mL}$ increased from 29% to 73%.³⁷ Furthermore, among patients with CF in the phase III TOBI trials, who received 300 mg of tobramycin by aerosol twice daily in 4-week cycles on drug, followed by 4 weeks off drug, the proportion of patients with *P aeruginosa* having a tobramycin MIC ≥ 16 $\mu\text{g}/\text{mL}$ was significantly higher in the TOBI group than the placebo group at week 20 (26% vs 17%; $P = .03$) and week 24 (23% vs 8%; $P < .001$).⁴⁴ The tobramycin MIC₉₀ for *P aeruginosa* isolates increased from 8 to 16 $\mu\text{g}/\text{mL}$ in the TOBI group whereas it decreased from 8 to 4 $\mu\text{g}/\text{mL}$ in the placebo group. Although the effects of more prolonged therapy are not known, preliminary analysis of 145 patients who have received inhaled tobramycin for 9 cycles demonstrates continued efficacy despite an increase in MIC₉₀ to 32 $\mu\text{g}/\text{mL}$.³⁷

In addition to a transient increase in the MIC of *P aeruginosa* isolates, treatment with inhaled tobramycin was associated with an increased isolation rate of *Candida albicans* and *Aspergillus* species from sputum.³⁷ Treatment-emergent *C albicans* was isolated in 22% of patients in the tobramycin group, compared with 16% in the placebo group ($P = .06$). Treatment-emergent *Aspergillus* species was isolated in 18% and 8%, respectively ($P = .001$). Fortunately, the increased rate of isolation of fungal species was not

associated with any recognized, clinically relevant adverse effects (eg, allergic bronchopulmonary aspergillosis or fungal pneumonia). Inhalation of tobramycin did not increase the isolation of multiply resistant *P aeruginosa*, *B cepacia*, *Stenotrophomonas maltophilia*, or *Alcaligenes xylosoxidans*.

An even greater concern than the potential for emergence of resistant organisms in the patient is the potential for antibiotic contamination of the local environment resulting in selection of multiply resistant organisms both in hospitals and in communities. A recent study by Jones et al⁴⁵ demonstrated that antibiotic contamination of the environment occurs easily and often. Although delivery to the lungs is enhanced by aerosolization, so is delivery to the local environment, an effect that does not occur with intravenous or oral delivery. Furthermore, the antibiotic accumulates in the local environment as more doses are given. Presence of tobramycin on patients' skin also was observed, resulting in spuriously high serum concentrations attributable to needle contamination at the time of skin puncture.⁴⁵

Environmental contamination with aminoglycosides is potentially problematic in hospitals where multiply resistant gram-negative organisms already represent a serious problem. The potential for a substantial increase in tobramycin resistance is large and measures to minimize environmental contamination, such as the use of nebulizer exhaust circuit filters and vent-free nebulizers, should be identified and used if this problem is to be prevented. Although data are not available concerning environmental contamination through use of other aerosolized antibiotics, local environmental contamination is inherent in the usual aerosol technique and is not a function of the specific antimicrobial agent.

A further area of concern for patients receiving aerosolized antibiotics is the potential for microbial contamination of the nebulizer equipment. Inadequate cleansing, improper drying, and reuse of disposable equipment can lead to nebulization of microbes as well as the aerosol antibiotic.^{46,47} Although nebulizers are recognized as potential sources for nosocomial infection in hospitals,⁴⁸ home use with less experienced caregivers operating the equipment can further aggravate the risk.

SUMMARY

1. TOBI has been approved and may be considered for maintenance therapy of patients with CF who are 6 years or older.
2. TOBI is the only antibiotic that has been approved by the FDA for administration by inhalation to patients with or without CF. The safety and effectiveness of antibiotics other than TOBI, when delivered by this route, have not been proven and many of these formulations may contain ingredients that can cause adverse effects when administered by inhalation.
3. Because only small amounts of aerosolized tobramycin reach the systemic circulation and drug accumulation has not been demonstrated, routine monitoring of serum tobramycin concentrations is unnecessary if the patient is receiving

the recommended dose of TOBI and has normal renal function.

4. Patients with CF who are receiving TOBI should be monitored for renal tubular toxicity (urinalysis, blood urea nitrogen, and creatinine) and eighth nerve toxicity (audiogram at 500-8000 Hz range) if they are receiving concomitant therapy with other nephrotoxic or ototoxic agents or have preexisting renal or auditory dysfunction, or recognized predisposition to toxicity (eg, family history of aminoglycoside intolerance). In addition, any patient receiving TOBI who develops signs or symptoms of auditory toxicity, such as tinnitus, should have an audiogram performed.
5. The initial dose of TOBI should be given in the presence of a trained health care professional who will monitor the patient for wheezing and respiratory distress, and instruct the patient in the proper technique of delivery.
6. Patients or their caregivers should be trained to monitor for bronchospasm, urticaria, and perioral or periorbital edema, and be advised to stop the medication and consult their physician if any of these or other adverse reactions to therapy occur.
7. When aerosolized TOBI administration is maintained, evaluation of long-term efficacy is recommended within 6 to 12 months of initiating therapy. Monitoring factors such as reduction in the frequency of hospitalization and intravenous antibiotic administration, sense of well-being, work or school performance and absenteeism, and cough frequency is recommended.
8. To minimize microbial contamination of nebulizer equipment, centers should develop policies for aerosolized antibiotic use in the home, clinic, and inpatient facility. Such a policy should address barrier techniques, filters, exhaust, environmental contamination, disposal of unused product, and cleaning of nebulizers.
9. Monitoring of antibiotic resistance patterns for specific pathogens and specific patient populations is recommended for institutions caring for patients who receive aerosolized tobramycin.
10. Strict adherence to infection control policies to minimize transmission of resistant organisms within the hospital environment is recommended for institutions caring for patients who receive aerosolized tobramycin.

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