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Case Reports

Hypersensitivity to Inhaled TOBI® Following Reaction to Gentamicin

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Summary. Cystic fibrosis (CF) is the most common autosomal-recessive disease in Caucasians. Colonization with *Pseudomonas aeruginosa* (*P. aeruginosa*) of the CF airways causes deterioration of pulmonary status. TOBI® (Tobramycin solution for inhalation) is an inhaled antibiotic that can improve the pulmonary disease.

We report on a 9-year old boy with CF who developed a rash following a course of IV gentamicin. The rash resolved after its discontinuation. However, the rash returned all over his body, with the start of inhalation of TOBI® therapy. We desensitized the patient using escalating doses of inhaled TOBI®. He tolerated the procedure well, and continues to be on TOBI® 9 months after desensitization on a once-a-day regimen. **Pediatr Pulmonol. 2002; 33:311–314.**

Key words: allergy; cystic fibrosis; Tobramycin; TOBI®; aminoglycosides; hypersensitivity reaction; desensitization.

INTRODUCTION

Inhaled antibiotics have become a cornerstone of treatment for chronic pseudomonal infection of the airways in patients with cystic fibrosis. These treatments lead to a reduction in rate of lung function deterioration, which correlates with increased survival and decreased hospitalizations.[1,2]

In this report, we describe a 9-year-old boy with CF who developed a total body rash following the administration of intravenous gentamicin. This rash resolved, but returned upon resumption of inhaled tobramycin (TOBI®) therapy. He was subsequently desensitized using escalating dosages of inhaled tobramycin (TOBI®), and has been successfully maintained on that medication since that time. This type of case is, to our knowledge, unique and has not been reported in any pediatric or adult patient.

CASE REPORT

History

A 9-year-old boy with CF was admitted for a pulmonary exacerbation with increased cough and sputum production and worsening pulmonary function tests. He was initially treated with ceftazidime and was then changed to intravenous Zosyn® (piperacillin sodium/tazobactam sodium) and gentamicin prior to his discharge home. On day 13 of his course of therapy, he experienced the onset of a pruritic rash over his lower extremities, with fevers to 40°C. He was readmitted to the hospital. Gentamicin and Zosyn® were discontinued. Within 36 hr the rash began to resolve, and he had no further fevers. He was discharged home on his usual medications including Pancrease® capsules (Pancrelipase), ADEK vitamins, Pulmozyme® (rh DNAse), and albuterol nebulized-mist therapy. Following discharge, his rash resolved completely. Three days after discharge, he began inhaled tobramycin (TOBI®) therapy as part of a 300-mg, twice per day, 28 day on, 28 day off inhaled antibiotic regimen using a Pari LC Plus jet nebulizer with Pulmo-Aide compressor. Within the next 2 days he began to develop a rash. This rash began

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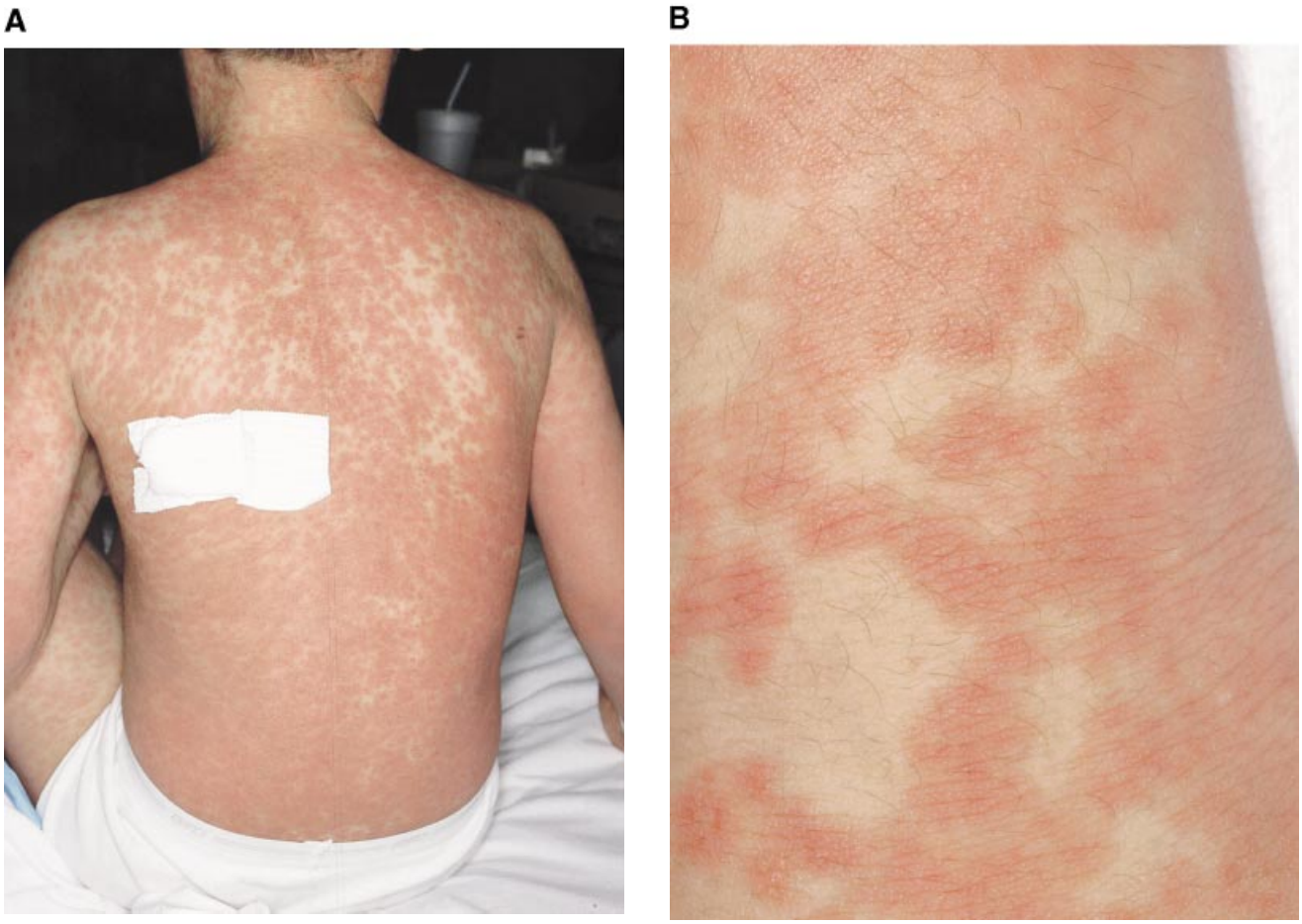

Fig. 1. A: Blanching erythematous papules coalescing into plaques involving the trunk, four extremities, and face. Bandage indicates biopsy site. B: Close-up of upper extremity, showing rash.

over his lower extremities and rapidly progressed to a generalized pruritic rash over his entire body, with a fever to 38.6°C orally. A review of systems revealed no increased cough or sputum production, chills, nausea, vomiting, or ill contacts at home.

Physical Examination

Following readmission, vital signs showed a temperature of 38.2°C, respiratory rate of 16/min, heart rate of 136/min, blood pressure of 111/54, and weight of 30.4 kg. The patient was a nontoxic-appearing boy. Pulmonary examination revealed coarse bilateral basilar crackles. Examination of the skin revealed multiple blanching, and erythematous papules coalescing into plaques involving the trunk and all four extremities as well as the face. No mucosal involvement or joint swelling were noted (Fig. 1A,B).

ABBREVIATIONS

CF	Cystic fibrosis
P. aeruginosa	*Pseudomonas aeruginosa*
TOBI®	Tobramycin solution for inhalation

Laboratory Analysis

A skin biopsy revealed superficial perivascular dermatitis with focal spongiosis and dyskeratosis, as well as eosinophils consistent with either a drug rash or viral exanthem. Epstein-Barr virus and cytomegalovirus titers were negative. Urinalysis demonstrated no hematuria.

Hospital Course

Given the temporal development of the rash with resumption of TOBI® as well as the recent rash during treatment with gentamicin, coupled with a lack of any recent viral exposure and an up to date immunization status, it was felt that the most likely diagnosis was drug rash. As such, TOBI® was discontinued and treatment was undertaken with 1% triamcinolone cream topically twice daily and ranitidine (H_2 receptor antagonist). Antipruritic measures, including Atarax® (hydroxyzine HCl), were initiated and the rash slowly resolved while the boy was hospitalized. He was subsequently discharged on his usual home medications. Arrangements were made for readmission for further testing and desensitization.

TABLE 1—Skin Test Results[1]

Test medium	Epicutaneous (scratch) testing result	
TOBI® (60 mg/mL)	–	
Tobramycin (40 mg/mL)	–	
Saline (negative control)	–	
Histamine (positive control)	+++	3-mm wheel, 1.4-cm flare
Test medium	**Intracutaneous (subcutaneous) testing result**	
TOBI® (0.6 mg/mL)	–	
TOBI® (6 mg/mL)	–	
TOBI® (60 mg/mL)	–	
Tobramycin (0.4 mg/mL)	++++	6-mm wheel, 25 × 12 mm flare
Saline control	–	Done with each injection above

[1]Tobramycin was prepared from Abbot Pharmaceuticals (Chicago, IL) commercially available IV solution. TOBI was prepared from a commercially available mist treatment solution.

Allergy Testing

Following readmission, skin testing was done with TOBI® (PathoGenesis, Seattle WA) at 60 mg/mL and tobramycin sulfate (IV preparation, Abbot Pharmaceuticals, Chicago, IL) 40 mg/mL. This was accomplished using dilutions of commercially available agents, as there are no commercially available skin test reagents (Table 1). Prick tests were applied to the back and were negative, with a histamine control being positive (a 3-mm wheal and 1.4-cm flare). Intracutaneous testing with the tobramycin sulfate intravenous preparation was positive, with a 6-mm wheal with pseudopods and a 25 × 12 mm flare. TOBI® at 6 mg/mL and at 60 mg/mL (full strength) was skin tested on the arms and was negative.

Desensitization

A desensitization graded challenge protocol was devised, employing progressively increasing doses of inhaled TOBI®. The first dose was a 0.3 mg in 5-mL normal saline. The dose in mg was gradually increased in a 5-mL normal saline total volume. Each dose was nebulized on an every 2 hr schedule, until the full dose of 300 mg was given (Table 2). There were no complications with this protocol. He was able to complete the desensitization protocol and subsequently has been maintained on a standard TOBI® dose (300-mg inhalation treatment) on a twice-daily basis and was transitioned to once-daily dosing after 1 month. In the 12 months following presentation and 9 months following desensitization, there have been no further episodes of rash or temperature elevations.

Pulmonary function testing was not performed during either allergy testing or desensitization, as the patient did not exhibit any respiratory symptoms on his initial presentation. If there had been concerns for respiratory involvement, expiratory spirometry would have been conducted.

DISCUSSION

Adverse reactions to drugs (ADR) occur in 15–30% of hospitalized patients, with no more than 10% due to drug allergy. ''Allergic reactions'' can take the form of known immunologic responses to an administered drug or can be ''pseudoallergic'' reactions.[3] In many instances of pseudoallergic adverse drug reaction, immunologic mechanisms cannot be identified or implicated. This is often the case for cutaneous drug reactions associated with antibiotic administration. Age-related and illness-related abnormalities in drug metabolism may contribute to adverse drug reactions. An example of the latter is the frequent occurrence of drug reactions in HIV-infected

TABLE 2—TOBI Desensitization Protocol[1]

Treatment number	Dose
1	0.3 mg
2	0.6 mg
3	0.9 mg
4	1.2 mg
5	1.5 mg
6	3 mg
7	6 mg
8	12 mg
9	24 mg
10	48 mg
11	96 mg
12	150 mg
13	200 mg
14	250 mg
15	300 mg

[1]Doses were administered on a strict 2–hr basis, with continuous pulse oximetry and vital signs being followed every 2 hr. Anaphalaxis emergency treatment kit (Ana-Kit®; epinephrine injection and chlo-Amine®, chlorpheniramine maleate tablets) and intubation supplies were present at bedside throughout the entire protocol and beyond. Dilutions were made from TOBI® using preservative-free diluent to make up a 5-mL nebulized-mist treatment solution.

individuals, perhaps related to a deficiency of glutathione, which detoxifies hydroxylamines.[3] Protocols for trimethoprim sulfamethoxazole desensitization have been employed with moderate success in HIV patients sensitive or intolerant to this combination antibiotic.[4]

Drug allergy to aminoglycosides has been reported in the literature, typically to gentamicin and less commonly to tobramycin.[5–8] There is one example of an adult with CF who experienced a hypersensitivity reaction to intravenous tobramycin and was successfully desensitized.[7] Estimates of reaction to intravenous aminoglycoside antibiotics are reported to complicate 1–2% of treatment courses,[9] but no data exist for inhaled aminoglycosides. Cross-reactivity throughout the class of aminoglycosides has also been reported.[10]

We postulate that the initial skin reaction was a drug reaction to gentamicin. This resolved following the withdrawal of the aminoglycoside. The reappearance of a rash followed reintroduction of TOBI® (tobramycin for inhalation), which had been tolerated without difficulty in the past. Upon cessation of TOBI®, the rash again resolved. This rash was likely initiated by gentamicin therapy and maintained by cross-reactivity to the tobramycin in TOBI®.

We observed a markedly positive reaction to tobramycin but not to TOBI® in our skin test assay. One explanation for this observation is the 5% phenol in the intravenous tobramycin, which might have caused the skin rash, since TOBI® is phenol-free. This might support the possibility that this was not an IgE-mediated skin reaction. This also points out a potential pitfall of using intravenous tobramycin as a skin test agent.

Mechanistically, we are unable to explain why the TOBI® preparation of tobramycin did not elicit a positive skin test. It is possible that only the intravenous form of the antibiotic stimulated skin histamine release, to form a wheal-and-flare reaction in this patient. Histamine release may not have been responsible for the adverse reaction previously experienced with the inhaled antibiotic, but the effectiveness of the desensitization procedure and subsequent tolerance of the drug are still reasonable to assume. Our patient did not have a serum-sickness-like reaction to previous antibiotics or to TOBI®, although a ''priming mechanism'' for sensitivity to aminoglycoside antibiotics from previous exposure cannot be dismissed.

Desensitization was undertaken to allow ongoing treatment with TOBI® in order to help preserve lung function and prevent hospitalizations for this patient. The desensitization protocol (Table 2) was chosen for ease of administration and availability of TOBI® inhalation solution. The initial half-life of tobramycin is short; however, the terminal half-life is long. Unlike the intravenous administration, the peak serum level following aerosol administration occurs at about an hour and plateaus for 2 or 3 hr. Therefore, the desensitization protocol with every-2-hr dosing probably slowly increases the systemic exposure compared to episodic exposure. The blood level usually does not exceed 2 μg/mL.[1] This is the first documented description of desensitization using the inhalational route, rather than the more typical IV methods.[11] In Earl and Sullivan,[11] neither IgE-mediated reaction nor serum-sickness-like syndrome were likely the cause for the adverse drug reaction. There is a documented maintenance of desensitization with inhaled tobramycin following desensitization with IV tobramycin.[7] An extensive MEDLINE search was undertaken, which did not reveal any reported episodes of reaction to inhaled tobramycin or TOBI® compared to placebo. To our knowledge, this is the first reported case of a generalized systemic reaction to tobramycin in inhaled form. Review of the original TOBI® clinical trials did not reveal any hypersensitivity reactions.[1,2,12] Both groups showed a minimal degree of bronchospasm, which was not statistically significantly different between the TOBI® and the placebo group.

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