CASE REPORT

Induced Tolerance to Nebulized Colistin After Severe Reaction to the Drug

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Abstract

Daily nebulized colistin therapy has been used as maintenance therapy for patients with chronic *Pseudomonas aeruginosa* infection and in treatment protocols aimed at eradicating early *P aeruginosa* infection. Colistin-induced nephrotoxicity and mild neurotoxic effects have been described but hypersensitivity reactions are rare. However, bronchial constriction has been reported associated with the inhalation of the antibiotic. We report the case of a 63-year-old man who had been diagnosed with bronchiectasis and bronchopleural fistula and who developed severe bronchospasm when using nebulized colistin. A skin prick test (80 mg/mL) with colistin was performed and was negative. An intradermal test was not performed due to its possible irritant effect. As our patient suffered from a tobramycin-resistant *P aeruginosa* infection, we started a procedure to induce tolerance to 80 mg colistin (8 mg, 16 mg, 24 mg, 32 mg, 40 mg, 80 mg) nebulized in 30-minutes-intervals. No changes in forced expiratory volume in 1 second values were observed and the patient continues on treatment twice daily after the tolerance induction with no new episodes of bronchospasm. We report the first successful procedure to induce tolerance to colistin after escalating doses of inhaled colistin.

Key words: Colistin. Bronchospasm. Desensitization procedure. Tolerance induction

Resumen

La nebulización diaria de Colistina se ha utilizado como terapia de mantenimiento en pacientes aquejados de infección crónica por *Pseudomonas aeruginosa* y como tratamiento erradicador de la infección por dicha bacteria. Se han descrito diferentes efectos adversos especialmente a nivel renal y neurotóxicos pero las reacciones de hipersensibilidad son raras. Sin embargo, sí está descrita la aparición de broncoespasmo asociado a la inhalación del antibiótico.

Presentamos el caso de un paciente de 63 años de edad, diagnosticado de bronquiectasias y fístula bronco-pleural, que presentó un broncoespasmo severo tras la inhalación de Colistina nebulizada. Las pruebas cutáneas en prick resultaron negativas. No se realizó prueba intradérmica por un posible efecto irritante del fármaco. Puesto que se trataba de una infección por *P aeruginosa* resistente a la tobramicina, se comenzó una pauta de inducción de tolerancia a la Colistina alcanzando la tolerancia de 80 mg (8 mg, 16 mg, 24 mg, 32 mg, 40 mg, 80 mg) nebulizados en intervalos de 30 minutos. No se objetivaron descensos en los valores espirométricos y el paciente ha continuado con su pauta de 80 mg cada 12 horas de modo diario sin nuevos episodios de broncoespasmo.

Presentamos el primer protocolo descrito, desarrollado con éxito, para inducir tolerancia a la Colistina nebulizada en un paciente que había desarrollado un broncoespasmo severo tras su inhalación.

Palabras clave: Colistina. Broncoespasmo. Inducción de tolerancia. Protocolo de desensibilización.

Introduction

Daily nebulized antibiotic therapy has been used frequently for the last 25 years. The antibiotic is delivered directly to the site of infection, thus maximizing its efficacy and reducing its potential for toxicity. The main indications of nebulized antibiotic use are as maintenance therapy for patients with chronic *Pseudomonas aeruginosa* infection and in treatment protocols aimed at eradicating early *P aeruginosa* infection [1]. Regular aerosolized antibiotic treatment results in improved respiratory function, fewer hospital admissions and respiratory exacerbations, thus contributing to prolonged

survival. Successful eradication of *P aeruginosa* has been reported with different nebulized antibiotics, including colistin (polymyxin) and tobramycin (aminoglycoside).

Polymyxins were discovered in 1947 from different species of *Bacillus polymixa* but only colistin and polymyxin B are currently used in clinical practice. However, they are only recommended for highly selected cases of serious infections caused by gram-negative bacilli resistant to currently available antibiotics [2]. Colistin is very poorly absorbed after oral administration and its use was abandoned because of concerns related to toxicity. It was reported that polymyxins induced nephrotoxicity and neurotoxicity. Neurotoxic effects have also been reported but these are usually mild and resolve after prompt discontinuation of the drugs [3]. Furthermore, bronchial constriction has been associated with the inhalation of the antibiotic, particularly in patients with co-existing cystic fibrosis or asthma [4] as well as in those with no clinical evidence of airway hyper-reactivity. In these cases, induction of tolerance could be a good therapeutic alternative in order to maintain the benefits of the treatment.

We report the case of severe bronchospasm resulting from the use of nebulized colistin and describe the first successful procedure to induce tolerance to colistin after escalating doses of the inhaled drug.

Case Description

We describe the case of a 63-year-old man who had been diagnosed with bronchiectasis and bronchopleural fistula in 1990. He suffered from a chronic multi-resistant *P aeruginosa* infection with several recurrences. In January 2005, he started intermittent (28-day on / 28-day off) treatment with 1 million of International Units (mIU) (80 mg) of sodium colistimate twice daily. In March 2006, he had to reinitiate the treatment. He experienced mild difficulty breathing some minutes after the first nebulized dose of colistin but the clinical picture abated some hours later. When the patient inhaled the second nebulized dose at night, he developed an acute episode of dyspnea at rest, a breathing rate of 28 and cyanosis with low level of consciousness. He required emergency in-hospital medical care and was admitted to the Intensive Care Unit where he was endotracheally intubated for assisted ventilation. Salbutamol and intravenous corticoids were administered. He had never presented any similar episodes and he denied the involvement of viral infections, exercise or the intake of any other drugs.

A skin prick test (80 mg/mL) with colistin was performed and was negative. A histamine control was positive (wheal 8 × 8 mm). An intradermal test was not performed due to its possible irritant effect.

As our patient suffered from a tobramycin-resistant *P aeruginosa* infection, we started a procedure to induce tolerance to colistin, reaching tolerance to 80 mg of the drug (8 mg, 16 mg, 24 mg, 32 mg, 40 mg, 80 mg) nebulized at 30-minute-intervals. No changes in forced expiratory volume m 1 second values were observed and the patient continues on treatment twice daily after desensitization with no new episodes of bronchospasm. Recently, in May 2006, the procedure was repeated in a ambulatory setting and tolerance to 80 mg was successfully acheived.

Discussion

Although hypersensitivity reactions to polymyxins are extremely rare, intolerance to the drugs seems to be more frequent. It must be remembered that up to the 10% of the patients treated with nebulized colistin may develop pulmonary symptoms (cough, chest pain or bronchospasm). In these cases, the method of action of the drug remains unknown but it has been suggested the drug exerts a local irritant effect on the mucosa during prolonged treatment and induces bronchial hyper-responsiveness. We cannot explain the mechanism responsible in this case since an immunoglobulin (Ig) E-mediated mechanism could not be demonstrated and we reached the diagnosis on the basis of clinical history taking. We did not consider it ethically correct to perform a challenge test directly with the drug due to the extreme severity of the described reaction even though the patient did not suffer from other causes of bronchial hyper-responsiveness such as bronchial asthma or viral infections. However, the development of acute symptoms after the inhalation of the drug, and the previously asymptomatic status of the patient, seem to point to a direct relationship between the clinical picture and the previous use of nebulized colistin.

A good alternative for drug-allergic or drug-intolerant patients is a “desensitization procedure”. To induce clinical tolerance, progressive doses of a drug are administered in intervals until the full therapeutic dose is reached. The way in which clinical tolerance is induced is complex but depends fundamentally on achieving mast cell desensitization [5]. Oral tolerance induction has been widely used with some drugs, especially penicillin, acetyl salicylic acid, allopurinol [6], sulfasalazine or sulfamethoxazole-trimethoprim. We found no references to tolerance induction to polymyxins but, as it was a useful antibiotic in this case, we decided to carry out a protocol for drug desensitization in order to maintain the quality of the patient’s life.

Finally, good tolerance to the drug was acheived twice following a successful desensitization protocol. These novel procedures show great potential as a therapeutic safeguard in some patients and would especially help in avoiding recurrent infections, respiratory morbidity or the use of other potentially harmful drugs.

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Manuscript received June 20, 2006; accepted for publication September 8, 2006

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