

Case report

Accelerated cell-mediated broncho-obstructive reaction to inhaled stepronin: a case report

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We describe the case of a 20-year-old man who developed an obstructive bronchial reaction accompanied by a maculopapular facial rash 8 h after an aerosol treatment with the mucolytic drug stepronin. The results of intradermal and patch testing with stepronin, together with those of bronchial challenge and histologic findings in patch-tested skin, indicate that the patient's reaction involved an accelerated cell-mediated mechanism of hypersensitivity. Bronchial challenges with methacholine demonstrated a transient increase in nonspecific bronchial hyperactivity.

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Stepronin, *N*-(2-mercaptopropionyl)glycine 2-thiophenecarboxylate, is a sulphydryl compound that appears to have mucolytic properties. It has been used to treat bronchitis, as well as acute and chronic forms of hepatitis, and is generally well tolerated. We recently observed a patient who had experienced an obstructive bronchial reaction accompanied by a facial maculopapular eruption during treatment with stepronin.

Case report

A 20-year-old white man was hospitalized for bronchospasm that had occurred approximately 8 h after inhalation of an aerosol product containing stepronin (Mucodil®, one 720-mg vial stepronin). The aerosol therapy (one vial bid) had been prescribed for acute bronchitis, and three treatments had already been administered before the attack occurred. The patient had used the same drug to treat a previous case of bronchitis 1 year earlier and had suffered no adverse effects.

At the time of admission, the patient presented a hacking cough, dyspnea, and wheezing, as well as a maculopapular eruption in the perioral region (the area that had been covered by the aerosol

mask) and conjunctival injection. Stepronin was discontinued and treatment with 6-methylprednisolone (40 mg i.v./day) and salbutamol aerosol (2 puffs qid) was started. The respiratory symptoms promptly improved, and 4 days later, all symptoms (respiratory and cutaneous) had completely disappeared. The patient reported that he suffered from perennial rhinitis that was more severe during the spring, and one of his brothers suffered from hay fever.

Allergologic studies

Allergologic testing for respiratory allergies was performed 3 months after the reaction described above. Prick tests were administered, according to the recommendations of the Subcommittee on Skin Tests of the EAACI (1), with the following airborne allergens: grasses; mugwort; *Plantago*, olive, beech, and plane-tree pollens; *Dermatophagoides pteronyssinus* and *D. farinae*; cat and dog dander; *Alternaria tenuis*; *Cladosporium herbarum*; *Aspergillus* mix; and *Penicillium* mix (Dome/Hollister-Stier-Bayropharm Italiana, Milan, Italy). Responses were compared with positive-control wheals produced by histamine

10 mg/ml, and positive reactions were noted for *A. tenuis* (++) and olive-tree pollen (+++).

Subsequent radioimmunologic assays for specific serum IgE (RAST, Pharmacia, Uppsala, Sweden) revealed levels of 13.3 kU/l (class 3) for *A. tenuis* and 2.3 kU/l (class 2) for olive-tree pollen. RAST was negative for *D. pteronyssinus*. The total serum IgE level (PRIST, Pharmacia) was 85 kU/l.

Prick and intradermal skin tests were then performed with stepronin (1.8 mg/ml in normal saline). A positive reaction was observed 8 h after intradermal injection of 0.02 ml. At 24 h, an indurated, erythematous zone 22 mm in diameter was present at the test site and persisted for 3 days. A patch test using 0.1 ml of a normal saline solution containing stepronin 180 mg/ml was also positive at the 48- and 72-h readings (2). Control intradermal and patch tests administered to five volunteers produced no reactions. Patch tests performed with the European standard series were negative.

A biopsy of the patch-tested skin revealed signs of epidermal and follicular spongiosis together with a dense inflammatory infiltrate within the reticular dermis. Higher magnification disclosed lymphocyte exocytosis as well, and some of these cells presented kidney-shaped nuclei. Marked exocytosis was noted within the hair follicles. At the margins of the leukocyte infiltrate, there were signs of intra- and extracellular edema (the cause of the spongiosis observed in the follicular stratum spinosum). Tissue eosinophils were rare, but there were a number of these cells along the walls of capillaries (Fig. 1).

A bronchial aerosol challenge was administered with 360 mg stepronin after inhalation of 45 µl of normal saline. The aerosol was administered with a

Table 1. Results of bronchial aerosol challenge with stepronin

	Basal (%pred)	4 h after stepronin
Forced vital capacity (l)	3.38 (80)	2.92 (-14%)
Forced expiratory volume in 1 s (l/s)	3.05 (83)	2.05 (-33%)
Thoracic gas volume (l)	2.75 (83)	2.80 (+2%)
Total lung capacity (l)	5.17 (90)	4.58 (-12%)
Airway resistance (kPa × s/l)	0.13	0.20 (+49%)
Specific airway conductance (l/kPa × s)	2.86	1.84 (-36%)

De Vilbiss 646 nebulizer attached to a Pulmocare dosimeter (Meccanoterapeutica, Salvas, Biella, Italy) regulated to generate a pressure of 1.5 kg/cm² for 0.5 s. Pulmonary function parameters were measured with a 2800 body plethysmograph (Gould Medical BV, Bithoven, The Netherlands), according to recommendations published by the American Thoracic Society (3).

Baseline values and those observed 4 h after the challenge are shown in Table 1. Baseline findings were within normal limits. There were no significant changes after the normal saline challenge. After challenge with stepronin, there was a progressive decrease in the FEV₁ (-7% after 1 h; -16% after 2 h; -33% after 4 h). By 4 h after the challenge, the patient began to complain of dyspnea and moderate weakness. The blood pressure dropped from 120/70 to 90/50 mmHg. Facial erythema, conjunctival injection, and fever (axillary temperature 37.7°C) developed. Wheezing, previously absent, could be heard over all lung fields. The patient was treated with fenoterol (400 µg) and ipratropium bromide (160 µg) by aerosol, methylprednisolone (60 mg i.v.), and volume replacement (normal saline 1500 ml), leading to gradual improvement of the symptoms. A chest radiograph performed approximately 1 h after treatment was within normal limits. By 8 h after the challenge, FEV₁ had increased to 92% of the baseline value, the blood pressure had risen to 100/60 mmHg, and the temperature was 37.2°C. By 24 h after the challenge, FEV₁ was 2.96 l/s (-3% vs baseline), and a nonspecific bronchial challenge was performed with methacholine. PC₂₀ FEV₁ (i.e., the methacholine concentration that provoked a 20% decrease in the FEV₁) was 8 mg/ml, indicating mild nonspecific bronchial hyperreactivity. Pulmonary function was reevaluated 1 month later, and the findings were again in the lower ranges of the norm with no signs of obstruction. The repeat methacholine challenge was normal with PC₂₀ FEV₁ of 32 mg/ml.

Discussion

This patient suffered an obstructive bronchial reaction with a maculopapular eruption and conjunc-



Fig. 1. Skin biopsy of patch-tested skin shows epidermal and follicular spongiosis. Dense inflammatory infiltrate within reticular dermis contains primarily lymphocytes. Rare eosinophils are scattered among collagen fibers. Intense lymphocyte exocytosis is present within infundibular and epidermal epithelia.

tival injection on day 2 of aerosol therapy with streptococci. The reaction occurred 8 h after the third treatment. These findings, combined with the delayed reaction to the intradermal test, the patch-test positivity, the histologic findings, and the response to the aerosol challenge, strongly suggest delayed hypersensitivity to streptococci.

This episode has the characteristics of the accelerated cell-mediated reactions described by Warrington et al. (4) in two patients with penicillin allergy. These reactions, like the one described here, included a maculopapular rash that appeared roughly 24 h after initiation of treatment (i.e., earlier than classical delayed immune reactions), and both cases were characterized by late (9–12-h) intradermal reactivity. Delayed responses to intradermal (4–6) or patch (7) tests or to both (8, 9) have been reported in patients who developed maculopapular eruptions during treatment with beta-lactam antibiotics, and the histologic features of skin biopsies taken from the test sites in these cases were also typical of cell-mediated immune responses. In some cases (5, 6, 8, 9), positivity was confirmed with challenges. We therefore believe that the reaction experienced by our patient represents primarily a type IV hypersensitivity mechanism.

A slight decrease (–7%) in FEV₁ was already apparent 1 h after aerosol challenge with streptococci, although the patient himself did not experience dyspnea until FEV₁ had dropped by 33% 4 h after the challenge. The subsequent increase in non-specific airway reactivity suggests edema of the bronchial mucosa. The decreases in vital capacity and total lung capacity indicate that the reaction probably included an alveolar exudative component that was not detectable on the chest radiograph.

The early changes in FEV₁ might suggest the presence of a type I allergic mechanism with predominantly late-phase expression or perhaps a combined types I and IV response. However, the cutaneous findings (both clinical and histologic) were quite different from those associated with cutaneous late-phase responses that characteristically follow immediate allergic reactions. The latter response peaks 4–8 h after antigen exposure and may persist for up to 48 h. The intradermal reaction observed in our patient did not appear until 8 h after injection, reached maximal intensity at 24 h, and was still evident 72 h after the test (as was the patch-test reaction). The biopsy results in this case (i.e., a lymphocytic infiltrate with no polymorpho-

nuclear leukocytes) are also consistent with a cell-mediated response rather than a cutaneous late-phase response, which typically produces a mixed cellular infiltrate containing eosinophils, basophils, and possibly neutrophils, as well as some lymphocytes.

This is the second patient we have observed with an obstructive bronchial reaction and perioral maculopapular rash that developed on the second day of streptococci aerosol therapy. The first case was characterized by symptom onset more than 24 h after initiation of treatment, patch-test positivity, weak intradermal reactivity first noted at 36 h, and marked reduction in FEV₁ beginning 6 h after streptococci aerosol challenge (10). These findings are more unequivocally suggestive of classical cell-mediated reactivity than those of the present case.

Patch testing is a useful tool for evaluation of adverse drug reactions, particularly those manifested by maculopapular rashes. Patch-test positivity has the same significance as that of an indurated, erythematous reaction appearing 4–6 h or more after an intradermal injection of the culprit drug. This approach may eliminate the need for bronchial challenge, which can produce unpleasant symptoms.

References

1. Dreborg S. Skin tests used in type I allergy testing. Position paper. *Allergy* 1989;44 Suppl 10:22–30.
2. Wilkinson DS, Fregert S, Magnusson B, et al. Terminology of contact dermatitis. *Acta Dermatovener* 1970;50:287–92.
3. American Thoracic Society Statement. Snowbird workshop on standardization of spirometry. *Ann Rev Respir Dis* 1979;119:831–8.
4. Warrington RJ, Silvii-Dan F, Magro C. Accelerated cell-mediated immune reactions in penicillin allergy. *J Allergy Clin Immunol* 1993;92:626–8.
5. Terrados S, Blanca M, Garcia J, et al. Nonimmediate reactions to beta-lactams: prevalence and role of the different penicillins. *Allergy* 1995;50:563–7.
6. Vega JM, Blanca M, Carmona MJ, et al. Delayed allergic reactions to beta-lactams. *Allergy* 1991;46:154–7.
7. De Haan, Bruynzeel DP, van Ketel WG. Onset of penicillin rashes: relation between type of penicillin administered and type of immune reactivity. *Allergy* 1986;41:75–8.
8. Martin JA, Alonso MD, Lazaro M, Parra F, Compaired JA, Alvarez-Cuesta E. Delayed allergic reaction to cefonicid. *Ann Allergy* 1994;72:341–2.
9. Romano A, Di Fonso M, Papa G, et al. Evaluation of adverse cutaneous reactions to aminopenicillins with emphasis on those manifested by maculopapular rashes. *Allergy* 1995;50:113–18.
10. Romano A, Pietrantonio F, Di Fonso M, Pocobelli D, Venuti A. Delayed hypersensitivity to streptococci: a case report. *Contact Dermatitis* 1993;29:166.

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