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Inhalation of Polymyxin B as a Bronchial Provocation Method

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Abstract. With the exception of allergen inhalation, current bronchial provocation tests do not elicit a reaction identical to an asthmatic attack because the first stage of the latter - degranulation of mast cells - does not occur. In order to detect bronchial hyperreactivity and to determine the role of mast cells, polymyxin B - a histamine releasing agent - was administered by inhalation to 49 asthmatic patients and the resulting bronchospasm compared with that induced by histamine and exercise. Inhalation of disodium cromoglycate (Intal®) inhibited the response to polymyxin B. Polymyxin B probably acts on mast cells in lung tissue. Inhalation of polymyxin B appears to be useful as a method for detection of bronchial hyperreactivity.

Key words: Polymyxin B - Mast cell degranulation - Airways obstruction - Bronchial asthma

In patients with asthma, we need to distinguish between bronchial hyperreactivity - not necessarily associated with clinical symptoms - and partially or fully reversible airway obstruction which may occur either periodically or continuously. In patients without airway obstruction, only allergen provocation tests elicit such obstruction by mechanisms similar to those in spontaneous asthmatic attacks. However, application of this method is limited because it depends on the specific allergens involved, and also because of the risk of delayed bronchial responses. Other bronchial provocation tests might provide information about bronchial hyperreactivity, but the mechanisms (e. g., induced airway constriction) are not the same as those which take place in spontaneous asthma.

A bronchial provocation test should be sensitive enough to reveal bronchial hyperreactivity and should also elicit airway constriction similar to that of an asthmatic attack. Prolonged and hazardous airway obstruction should be avoided. We believe that this can be accomplished by using polymyxin B in solution in very small doses. Polymyxin B, a polypeptide, is a histamine-releasing agent that nonspecifically degranu-

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lates mast cells [4, 9, 10, 12]. The aim of our present work is, therefore, to evaluate the applicability of polymyxin B to the detection of bronchial hyperreactivity, and we shall also attempt to explain the mechanism of bronchospasm as it relates to the involvement of mast cells.

Subjects and Methods

The study was performed using 49 patients with bronchial asthma who did not have attacks at the time of the study. The patients inhaled 1 ml of polymyxin B sulfate in saline solution, and then the dosage was gradually increased (0.5, 1.0, 2.5, 5.0 mg/ml), but even the maximum was more than ten times less than the therapeutic doses used in intramuscular or intravenous therapy. Airway obstruction was measured with a spirograph (Godart), and we assumed that a threshold response to polymyxin B was obtained when the FEV decreased more than 10%. Higher doses of the drug were not administered. All patients also inhaled a 0.9% saline solution, and those that reacted with airway obstruction to this inhalation were excluded from the trial. The control group consisted of 16 healthy persons who inhaled a 20 mg/ml solution of polymyxin B.

In 18 patients, we also studied the polymyxin B threshold doses after a three-week period during which disodium cromoglycate (Intal®) (80 mg/day) was inhaled. In this way we attempted to verify the hypothesis that the action of polymyxin B is related to mast cell degranulation. We also compared the time course of airway obstruction after inhalation of polymyxin B with that after inhalation of histamine hydrochloride (32 mg/ml) and with the time course of airway obstruction after exercise [3, 11].

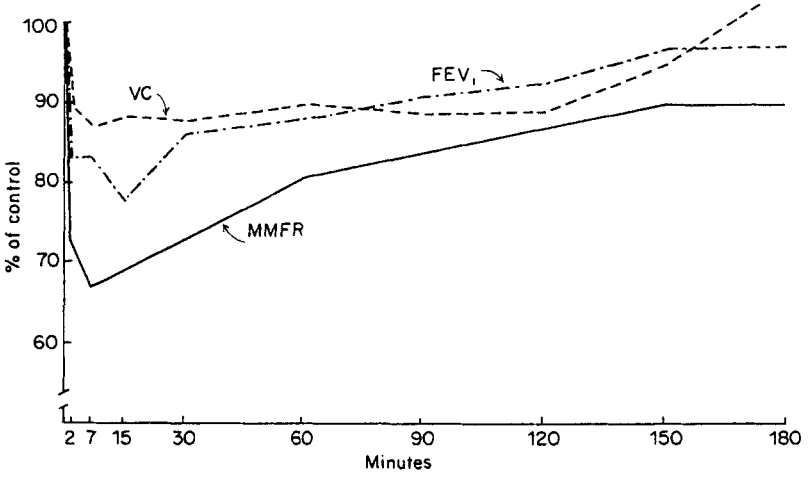

Fig. 1. The spirometric parameters VC, MMFR, and FEV_1 after polymyxin B inhalation at the threshold concentration.

Results

Airway obstruction induced by polymyxin B (Fig. 1) occurred somewhat later than that induced by histamine aerosol but lasted longer. After polymyxin B inhalation as well as exercise, maximal bronchoconstriction occurred between 7 and 17 min after the end of inhalation or exercise, and the polymyxin-induced airway obstruction lasted longer (Figs. 2, 3). None of the control subjects reacted to polymyxin B with significant airway obstruction, even at a dosage of 20 mg/ml.

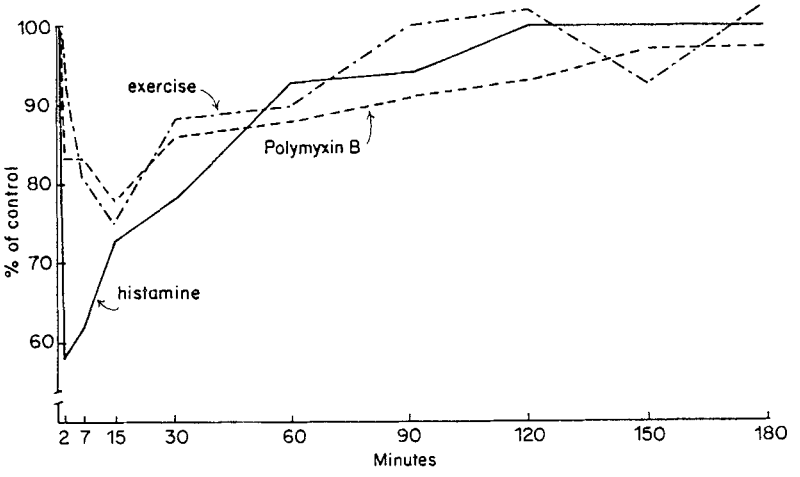

Fig. 2. FEV_1 after polymyxin B inhalation at the threshold concentration, histamine at the concentration 32 mg/ml, and the exercise provocation.

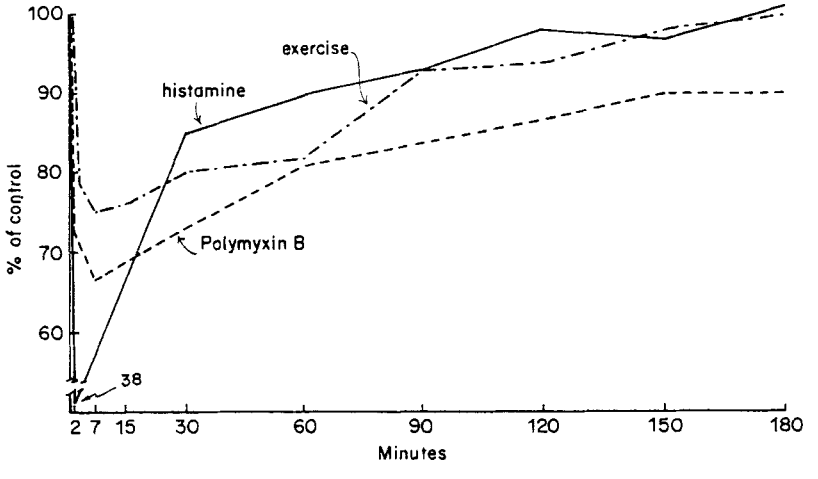

Fig. 3. MMFR after polymyxin B inhalation at the threshold concentration, histamine at the concentration 32 mg/ml, and the exercise provocation.

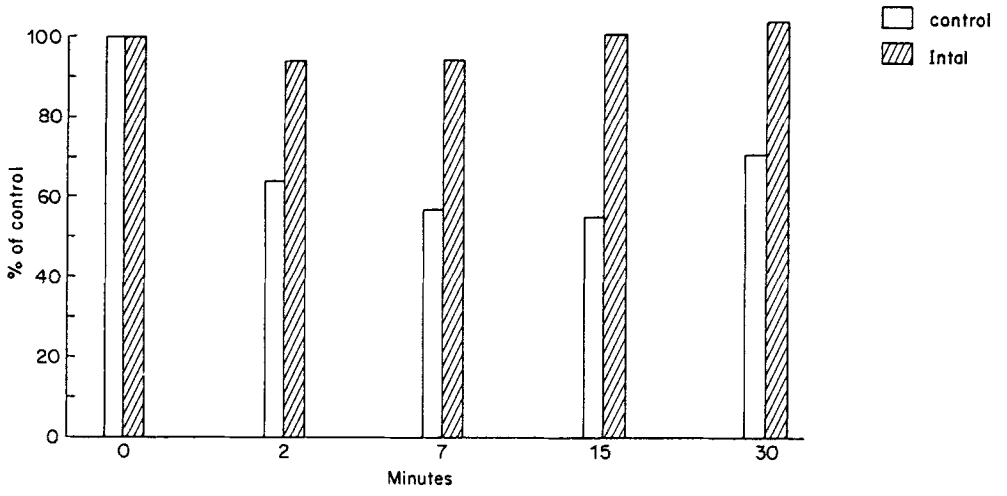

Fig. 4. Comparison of MMFR values after polymyxin B inhalation at the threshold concentration before and after disodium cromoglycate (Intal®) therapy in 13 out of 18 patients.

The polymyxin B threshold increased significantly in 13 out of 18 patients in whom the polymyxin B tests were repeated following therapy with sodium cromoglycate (Fig. 4). This constitutes one more piece of evidence that mast cells are the place of action of these two opposing agents.

Discussion

The mechanism of reversible bronchial obstruction after therapeutic inhalation of polymyxin B in bronchopulmonary infections may be explained by the action of this antibiotic on mast cells which are sensitive to histamine-releasing agents [1, 2, 7, 8]. Immunological polymyxin B-induced responses which may lead to airway obstruction have been described previously [5, 6]. However, it is difficult to explain the response in our study by allergy to polymyxin B because it is unlikely that such an allergy occurred in 45 out of 49 (92%) of the patients with asthma whom we examined. There is also little or no evidence that polymyxin B acts directly on peripheral nervous mechanisms. Although such mechanisms cannot be excluded, the different time course of the responses to polymyxin B and to histamine suggests that the two agents act via different mechanisms.

Since it is known from experiments that polymyxin B is a histamine-releasing agent, the most logical assumption is that polymyxin B induces airway obstruction via degranulation of mast cells and subsequent release of chemical mediators. The prolonged duration of the polymyxin-induced bronchoconstriction may be attributed to gradual penetration of the drug into the tissues and to the time required for the histamine release response.

The airways constriction may be sustained by mediators such as SRS-A, which act later and longer than histamine. The considerable increase in the polymyxin B threshold after administration of disodium cromoglycate (Intal®) is indirect evidence that mast cells are involved in the action of polymyxin B on the bronchi.

The varying polymyxin threshold and lack of response to the highest dose of polymyxin B in some cases indicate that the sensitivity of mast cells to this agent varies among individuals. However, the present results do not allow any evaluation of these individual differences in the threshold dose of polymyxin, nor of those in other bronchial provocation tests.

Conclusions

1. Most patients with asthma (45 out of 49; 92%) in our study reacted with bronchospasm to inhalation of small doses (0.5-5.0 mg/ml) of polymyxin B in saline solution.
2. Bronchospasm induced by inhaled polymyxin B lasts up to about 3 hrs. It develops more slowly than histamine-induced bronchospasm. In this respect it is similar to exercise-induced bronchospasm.
3. Treatment with disodium cromoglycate increases the polymyxin B threshold dose in most (13/18) patients. Hence, it is likely that polymyxin B acts on the mast cells.
4. Inhalation of polymyxin B may be used as a bronchial provocation test and may provide a model for short-lasting bronchospasm in asthma.

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