

Protective Effect of a New Anti-Asthmatic Agent (Minocromil) in Bronchial Allergen Challenge Tests

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Ten patients were included in a double-blind crossover trial, designed to compare the effects of a new anti-asthmatic agent Minocromil, an organic decarboxylic acid, and placebo on bronchial allergen challenge. The challenges were performed at weekly intervals. Significant differences in favour of Minocromil were found in the concentration of antigen reached at which FEV₁ fell below 20 % of baseline. This was confirmed by analysis of the decrease in FEV₁ recorded at the highest concentrations of antigens, which showed statistically significant differences in favour of Minocromil.

Key words: allergic bronchial asthma; bronchial allergen challenge; cromoglycate-like; placebo.

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The efficacy and low toxicity of topically applied sodium cromoglycate in protecting atopic asthmatic subjects from allergen-induced bronchoconstriction is well known (1). New topically active compounds have for some time been investigated in different centres aiming at developing more potent pharmacologically related drugs. Minocromil is such a compound, recently developed by Fisons laboratories for topical use in the treatment of asthma (2). Inhalation of Minocromil both as an aqueous aerosol, or from a pressurized aerosol at various dose levels, has shown the compound to be well tolerated and free from significant drug-related adverse effects (2). The purpose of the present study was to compare the protective effect of Minocromil and placebo administered by pressurized aerosols in bronchial antigen challenge tests in extrinsic asthmatic subjects. The trial was a double-blind crossover study and the patients were randomly assigned to treatment sequences.

MATERIAL AND METHODS

Patients. Six males and four females with a history of allergic asthma with a relevant positive skin test or RAST. Five patients were allergic

to cat allergens, two to dog and three to *Dermatophagoides pteronyssinus*, and the patients in question were subsequently challenged with these allergens. Allergy to seasonal antigens was tested for and, if demonstrated, the trial was performed out of the season.

Lung function was to be no less than 75 % of the predicted normal value. Mean age was 29.2 years (range: 18-46), mean weight 69.5 kg (range: 53-92 kg) and the mean height was 174 cm (range: 166-184 cm). A histamine bronchial challenge was performed on all patients as described previously (3). Mean PC₂₀-histamine was 0.231 mg/ml, range 0.028-0.700 mg/ml.

Nine of the 10 patients were currently treated with inhaled bronchodilators, two with theophylline, one with a steroid pulmonary spray and four with nasal steroids. Two patients received nasal sodium cromoglycate. None of the patients had any disease of significance other than allergy, and no abnormalities were found in haematological or clinical biochemistry data. No patient had been treated with oral corticosteroids within the previous 3 months.

Bronchial challenge. The patients attended for an initial screening session followed by 2 study

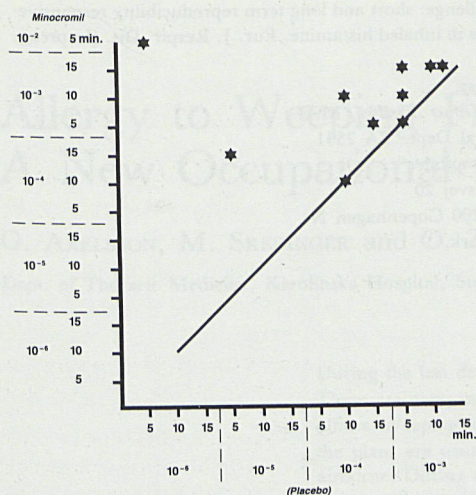


Fig. 1. Scattergram of stage of challenge reached before withdrawal.

days at weekly intervals - at the same time of the day and on the same day of the week. On each occasion they were to have abstained from the use of medication as previously described (3). On each study day, two baseline measurements of lung function were made at a 5-min interval. After an additional 5 min one of the trial treatments was administered and lung function tests were repeated 5, 10, 20 and 25 min after. The challenge consisted of increasing concentrations of antigen given at 15-min intervals between doses beginning with saline and followed by antigen at dilutions of 10^{-6} , 10^{-5} , 10^{-4} , 10^{-3} and 10^{-2} . Lung function measurements were taken 5, 10 and 15 min after each dose. If the FEV_1 reading decreased by more than 20% from the pre-challenge levels the challenge was discontinued and a bronchodilator administered. Any adverse effects were recorded.

Trial treatments

Minocromil (2 mg/actuation) and placebo were administered by two inhalations from identical-looking pressurized aerosols. The two inhalations were given in successive breaths, or as close as convenient.

Statistical significance has been assessed using two-tailed tests at the 5% level.

RESULTS AND CONCLUSIONS

Treatment effects were assessed on changes in lung function during the trial as measured by the forced expiratory volume in the 1st sec (FEV_1). No differences were observed between the average of the pre-treatment values and the average value of the three readings taken after the inhalation of saline and, therefore, the latter was used as a baseline for further comparisons.

Fig. 1 is a scattergram showing at which stage of the challenge with placebo and Minocromil the FEV_1 fell by more than 20%. In two patients this occurred at the same antigen concentration on both Minocromil and placebo treatment days. But in the remaining eight patients a higher antigen concentration was required after Minocromil than after placebo. This outcome, in favour of Minocromil over placebo, is statistically significant ($P < 0.01$, binomial test).

This finding was confirmed by also comparing the effect of the treatments on the decrease in lung function at the last antigen concentration time-point at which readings were available with both treatments. Eight of 10 patients had smaller absolute decreases in FEV_1 after pre-treatment with Minocromil compared with placebo, and 10 patients had smaller percentage decreases in FEV_1 with Minocromil. The latter result was statistically significant at the 1% level using Student's *t* test. No unusual symptoms or adverse reactions were reported.

We conclude that Minocromil, this new anti-asthmatic agent, confers an effective protection against antigen-induced bronchoconstriction in extrinsic allergic patients and that the agent deserves further evaluation of its therapeutic potential by investigating its efficacy in controlled clinical trials.

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