

Protective Effect of Disodium Cromoglycate on Propranolol Challenge

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The protective activity of cromoglycate in histamine and propranolol bronchial provocation tests was studied in seven asthmatic patients by inhalation of increasing doses of histamine and propranolol in the absence and presence of inhaled cromoglycate. Cromoglycate showed a significant protective effect on the propranolol challenge, whereas no protection against histamine challenge could be observed.

Key words: airway reactivity; cromoglycate; histamine; propranolol.

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An increased airway reactivity is a common phenomenon in bronchial asthma. The degree of this airway reactivity can be assessed by provocation tests with increasing doses of inhaled histamine, using standard techniques (14). This agent induces a bronchial obstruction by an interaction with H₁-receptors on the bronchial smooth muscle and by a stimulation of irritant receptors of the vagal nerve (9). Apart from histamine also other agents can be used to assess airway reactivity, including propranolol (8). In earlier studies we found that positive inhalation provocation tests with this non-selective beta-blocker are predominantly found in young allergic asthmatics (16). The mechanism of the bronchial obstructive activity of propranolol has not been solved. It may be assumed that this is caused by blocking the effects of circulating catecholamines on the beta-adrenergic receptors which are present on the bronchial smooth muscle and on the mast cells. This would imply that inhaled propranolol may induce a bronchial obstruction by a direct effect on the bronchial smooth muscle and by mediator release from the mast cell.

To investigate the latter possibility, protection tests with cromoglycate on propranolol challenges were carried out and compared with the effects of this "anti-allergic" drug on histamine challenges.

PATIENTS AND METHODS

Seven patients with a history of episodic wheezing gave their informed consent to participate in this study. The patients (5 males and 2 females) aged between 19 and 27 years (mean 21.4), were selected on the basis of positive skin tests for at least two common allergens and an increased airway reactivity to inhaled histamine. The patients had had no acute asthmatic attacks for at least 2 months, and there was no history of respiratory tract infections during this period. Bronchodilators and cromoglycate were withheld 48 h before each test. No one used corticosteroids regularly.

The FEV₁ of these asthmatic patients was higher than 65% of their predicted values.

Inhalation tests

Histamine diphosphate and propranolol solutions were nebulized with a Wiesbadener doppel spray with an airflow of 8 l/min (6). The aerosols were inhaled during quiet tidal breathing with the nose clipped. The FEV₁ was measured with a Lode water spirometer. After a control measurement histamine solutions were inhaled during 30 s in concentrations of 0.5, 1, 2, 4, 8, 16 and 32 mg/ml, respectively. After each inhalation the FEV₁ was measured at once and after 3 min. The lowest concentration inducing a fall in FEV₁ of 15% or more was called the threshold value (14).

Propranolol was inhaled during 2 min starting with a 0.5% solution, increasing the concentration by steps of 0.25% until a solution of 1.5% was reached. The FEV₁ was measured 5 min after each step (16). Only patients with a histamine and propranolol threshold were admitted to this study.

Study design

The inhalation tests were carried out on 2 separate days with an interval of 2 days or more within 1 week. Just before the challenges a placebo or a watery solution of 20 mg disodium cromoglycate was nebulized with a Wiesbadener doppel spray. The active drug and the placebo

were administered in a randomized manner. The histamine threshold was then measured, followed 1 h later by the propranolol threshold measurement.

Statistical analysis

For statistical analysis the histamine thresholds were expressed as exponents of 2. When no bronchial response followed after inhalation of a 1.5% propranolol solution, a threshold value of 1.75% was used for calculations. Paired *t*-tests were used to examine the differences between the thresholds in the absence and in the presence of cromoglycate.

RESULTS

The mean histamine threshold was 8.0 mg/ml after placebo and 7.3 mg/ml after pre-treatment with cromoglycate (n.s. Fig. 1, Table 1). The mean propranolol threshold in these patients was 1.04% and changed by cromoglycate pre-treatment to 1.64% ($P < 0.001$). After inhalation of cromoglycate four of the seven patients showed no bronchial response to the highest concentration (1.5%) of propranolol (Fig. 1, Table 1). The initial pulmonary function given as percentage of FEV₁ predicted did not significantly differ before each challenge (Table 1).

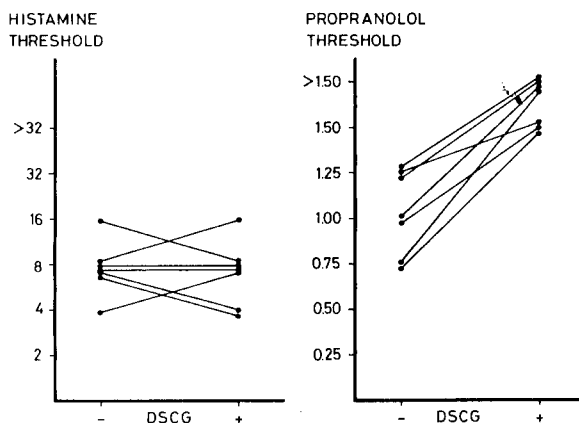


Fig. 1. The effect of disodium cromoglycate on histamine and propranolol thresholds in seven asthmatic patients.

Table 1

Protection test with disodium cromoglycate (DSCG) on histamine and propranolol thresholds

Pat.	FEV ₁ /FEV ₁ pred	Histamine + placebo	FEV ₁ /FEV ₁ pred	Histamine + DSCG	FEV ₁ /FEV ₁ pred	Propranolol + placebo	FEV ₁ /FEV ₁ pred	Propranolol + DSCG
1	124.7	8	129.5	16	119.9	1.0	130.7	> 1.5
2	65.1	8	82.4	8	74.2	1.25	87.9	> 1.5
3	68.5	8	67.8	4	71.1	0.75	68.5	> 1.5
4	85.8	8	83.5	8	82.4	1.25	83.5	> 1.5
5	70.3	8	67.6	4	75.7	0.75	70.3	1.5
6	108.0	16	88.9	8	108.0	1.25	96.9	1.5
7	75.6	4	74.7	8	81.1	1.0	84.9	1.5
Mean	85.4	8.0	84.9	7.3	87.5	1.04	80.4	1.64
SD	22.7		21.3		18.8		28.1	

DISCUSSION

Shortly after the introduction of propranolol as a beta-blocker, it was reported that this drug could induce a bronchial obstruction in asthmatic patients (12). This response could be markedly reduced by pre-treatment with atropine, indicating that a propranolol effect in asthmatics partially depends on an increased vagal activity (7, 11). In a previous study we found that propranolol threshold measurements are often positive in young allergic asthmatics. This is in contrast to measurements carried out in bronchitics (8, 16). The question thus is whether the mast cell is involved in the bronchial obstruction induced by propranolol inhalation. To examine this possibility protection tests with cromoglycate on the inhalation of propranolol were performed.

In this study cromoglycate was found to have a significant protective effect on the propranolol challenge, whereas no protection could be observed on histamine challenge. This result suggests the involvement of the mast cell. In allergic asthmatics the mediator releasability of these cells seems to be controlled by circulating catecholamines. Evidence for the inhibition of mediator release by circulating adrenalin was given by Barnes et al. (2) who showed that a decrease in adrenalin resulted in an increase in circulating histamine. The obstructive activity of propranolol may be explained by the interaction with beta-adrenergic receptors on the mast cell

together with an interaction with beta-receptors on the bronchial smooth muscle.

It is known that cromoglycate prevents the release of mediators after the antigen has reacted with a specific antibody on the mast cell surface. This mode of action of cromoglycate has been found *in vitro* as well as *in vivo* (13). The drug has been shown to be effective in reducing the asthmatic response to inhaled allergen (4).

However, also the effects of non-allergic bronchial obstructive stimuli can be prevented by cromoglycate. Pre-treatment with cromoglycate was found to produce an inhibition of the post-exercise fall in FEV₁ (5). Furthermore, it inhibits the effects of cold air (3) and SO₂ challenge (15). Nevertheless, that cromoglycate prevents the effects of non-allergic stimuli does not prove that this drug has other effects than mast cell stabilization.

The possibility must be considered that cromoglycate also inhibits mediator release from mast cells by a non-allergic mechanism. In dogs, however, there is evidence that cromoglycate inhibits the vagally mediated bronchial obstruction produced by histamine (10). But it is still under discussion whether this mode of action is operative in man (1).

In accordance with other reports with similar clinical experiments (17) we found no protective effect of cromoglycate on the histamine challenges, indicating that this drug does not inhibit the degree of airway reactivity.

Our results support the view that in bronchial hyperreactivity, apart from the reflex mechanism, the involvement of the mast cell and the beta-adrenergic system has to be considered.

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