

Effect of nedocromil sodium on the airway response to inhaled capsaicin in normal subjects

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ABSTRACT In six normal subjects treatment with 4 mg nedocromil sodium failed to alter the cough and bronchoconstriction induced by inhaled capsaicin. Because nedocromil has previously been shown to inhibit reflex bronchoconstriction provoked by inhaled sulphur dioxide and inhaled bradykinin, the results suggest that inhaled capsaicin acts on different nerve fibres.

Nedocromil sodium is a potent inhibitor of mucosal and connective tissue mast cells in primates and it inhibits antigen induced bronchoconstriction in man.¹ It is also a potent inhibitor of reflex bronchoconstriction induced by inhaled sulphur dioxide² and bradykinin,³ both of which may act by stimulating airway C fibres. Capsaicin, the active ingredient of red pepper, in animals has been shown to stimulate C fibres accessible to both pulmonary and bronchial artery circulation. Inhaled capsaicin in man causes reproducible cough⁴ and bronchoconstriction.⁵ These effects are inhibited by lignocaine⁴ and muscarinic antagonists,³ suggesting that they are due to stimulation of a reflex mechanism. We have therefore examined whether inhaled nedocromil sodium (4 mg) alters the cough and reflex bronchoconstriction induced by inhaling capsaicin.

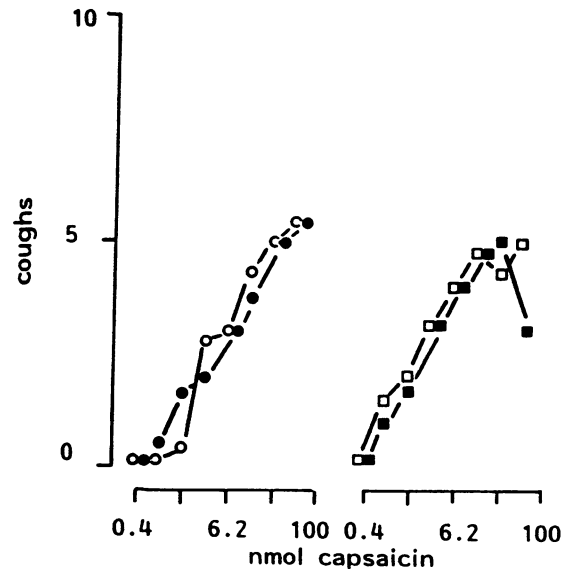
Methods

Six healthy subjects (three female) aged 23-34 years took part in the study, which had the permission of the local medical school ethics committee. For the construction of capsaicin cough dose-response (CDR) curves the subjects took single breaths at one minute intervals of either 0.9% w/v sodium chloride or a range of doses of capsaicin (0.4-50 nmol) dissolved in 0.9% NaCl with 1% w/v ethanol in random order from a nebuliser controlled by a breath activated dosimeter (P K Morgan) with an output 0.02 ml per breath. The number of coughs was recorded by a microphone connected to a pen recorder running at 50 mm/s (Mingograph). Total respiratory resistance (R_{rs}) was measured by a forced oscillation technique that averaged resistance over 16 second periods of tidal breathing.⁶ Three

baseline measurements of R_{rs} were performed with the subjects supporting the floor of the mouth and cheeks while breathing quietly on to a mouthpiece attached to the oscillation apparatus. The R_{rs} at 6 Hz was then recorded. Subjects then inhaled a single breath of the highest dose of capsaicin that caused less than two coughs during the preliminary CDR manoeuvre and R_{rs} at 6 Hz was recorded over the following 16 seconds. The percentage increase in R_{rs} was then calculated from the mean of the previous baseline measurements. Subjects attended the laboratory on two occasions and had capsaicin CDR and R_{rs} responses recorded before inhaling two puffs of either nedocromil sodium (2 mg/puff) or matched placebo in a randomised double blind fashion. Fifteen minutes later the capsaicin responses were repeated. Statistical analysis was by multiple analysis of variance.

Results

The effect of nedocromil on the capsaicin cough dose-response relationship is shown in the figure. The dose of



Median number of coughs at each dose of capsaicin before (open symbols) and after (closed symbols) nedocromil (squares) and placebo (circles).

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capsaicin causing two or more coughs (D_2) was not altered by treatment with placebo or nedocromil sodium (4 mg). The geometric mean (95% confidence intervals) (nmol) was 3.2 (3.2–3.2) before and 1.8 (1.2–2.8) after placebo and 1.6 (0.8–3.2) before and 1.6 (1.2–2.1) after nedocromil. The dose causing five or more coughs (D_3) was also unaffected by either treatment, being 17.7 (7.0–44.7) before and 28.1 (22.3–35.4) after placebo and 9.9 (4.6–21.4) before and 9.9 (4.6–21.4) after nedocromil.

The percentage increase in R_{rs} after a single breath of capsaicin was also unaffected by either treatment, the mean (95% confidence interval) percentage increase being 20 (8.6–31.4) before and 17.7 (7.9–27.5) after placebo and 18.0 (12.3–24.6) before and 22.5 (4.9–40.1) after nedocromil. The probability of a type 2 error (β) causing a change of one dilution of capsaicin for either D_2 or D_3 to be missed after nedocromil was <0.005 (calculated from the between group variance of the data from the placebo day). The probability of a type 2 error (β) causing a 29% difference in R_{rs} to be missed was <0.5 (calculated from data on the placebo day).

Discussion

In this study a single dose of 4 mg inhaled nedocromil sodium did not alter either cough or reflex bronchoconstriction caused by inhaling capsaicin. The results are therefore the same as those observed with sodium cromoglycate,^{4,5} which, like nedocromil sodium, inhibits the reflex bronchoconstriction caused by sulphur dioxide⁷ and bradykinin.⁸ Capsaicin cough and bronchoconstriction challenges can be repeated on the same day as there is no tachyphylaxis to this response.^{4,5} The probability therefore of a false negative result is low. The study implies that capsaicin stimulates sensory nerves different from those stimulated by inhaled sulphur dioxide and bradykinin in man. Although all three substances have been shown to stimulate C fibres⁹ in

animals it is possible that capsaicin stimulates C fibres in the larynx and the other substances fibres elsewhere in the airways. Alternatively, the substances may stimulate fibres of different anatomical types in man.

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