

Effect of nedocromil sodium on sulphur dioxide induced bronchoconstriction

CAROLINE M S DIXON, RICHARD W FULLER, PETER J BARNES

From the Department of Clinical Pharmacology, Cardiothoracic Institute, London; and the Department of Clinical Pharmacology, Royal Postgraduate Medical School, London

ABSTRACT Nedocromil sodium is a pyranoquinoline derivative that has been developed for the treatment of asthma. We report the results of a double blind randomised study of the effect of two doses of nedocromil sodium (2 and 4 mg) and matched placebo, delivered by metered dose pressurised aerosol, on bronchoconstriction induced by sulphur dioxide in six asthmatic subjects. Nedocromil sodium had no effect on baseline lung function. The magnitude of sulphur dioxide induced bronchoconstriction monitored by partial forced expiratory flow at 30% of reference vital capacity was significantly inhibited by nedocromil sodium 4 mg ($p < 0.05$) but not by 2 mg. The maximum changes after placebo and after nedocromil 2 mg and 4 mg were -44.7 , -32.7 , and -11.8 l min⁻¹. The area under the curve monitoring the effect over 6 minutes was significantly inhibited by both doses to the same extent, the mean changes after placebo and after nedocromil 2 mg and 4 mg being -349.3 , -31.2 , and 44.6 l. Dyspnoea was monitored by visual analogue scale and showed a significant reduction over 6 minutes with both doses of nedocromil. After placebo and after nedocromil 2 mg and 4 mg the mean maximum changes were 31.5, 13.7, and 15.7 mm, and the mean changes in area under the visual analogue scale-time curve were 289, 194, and 151 mm.min respectively.

Nedocromil sodium, the disodium salt of a para-quinoline dicarboxylic acid, has been developed for the treatment of asthma. Nedocromil sodium protects against exercise induced asthma,¹ antigen induced bronchoconstriction,² antigen induced nasal obstruction,³ and bronchoconstriction caused by non-specific stimuli.⁴ When administered four times daily for one month, it improves the control of bronchial asthma.⁵

The profile of action of nedocromil sodium is similar to that of sodium cromoglycate. Since sodium cromoglycate protects against bronchoconstrictor responses to sulphur dioxide⁶ we have investigated whether nedocromil sodium 2 or 4 mg confers similar protection against sulphur dioxide induced bronchoconstriction when compared with matched placebo. It seems likely that part at least of sulphur dioxide induced bronchoconstriction depends on neural mechanisms since it is reduced by cholinergic

antagonists,⁷ and in animals sulphur dioxide stimulates afferent fibres in the airways.⁸⁻¹⁰

Methods

SUBJECTS

We studied six subjects (three of them men) with mild asthma, aged 25-58 years. Three were ex-smokers and three non-smokers. All subjects were atopic and currently receiving β_2 agonists as necessary. FEV₁ ranged from 2.8 to 4.1 litres and asthma duration from 10 to 42 years. Subjects gave informed, written consent to take part in this study, which had the approval of the hospital ethics committee.

Airway function

Measurements of airflow and volume were made with a rolling seal spirometer (PK Morgan) linked to microcomputer (Hewlett Packard) (Flow analysis, Collingwood Measurements, Leicester). The best of three vital capacity manoeuvres was used as the reference volume for subsequent measurements. The subject performed a forced partial expiratory manoeuvre first inhaling to end tidal inspiration and then forcibly

Address for reprint requests: Ms CMS Dixon, Department of Medicine (Respiratory), Royal Postgraduate Medical School, London W12 0HS.

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exhaling into the spirometer to residual volume before immediately inhaling to total lung capacity and finally exhaling to residual volume, as previously described.¹¹ Flow ($l\text{ min}^{-1}$) at 30% of the reference vital capacity was then computed ($\dot{V}_{P_{30}}$).

DYSPNOEA SCORE

To quantify the subjective feeling of breathlessness a visual analogue scale was used. The subject marked an appropriate point on a 10 cm line labelled at one end "very breathless" and at the other end "not breathless." It was explained that the feeling of breathlessness was to include any feeling of retro-sternal discomfort. The position of the subject's mark on this line was later measured in millimetres from the end of the line labelled "not breathless" and the measurement was used as the dyspnoea score in subsequent analysis. After being marked the line was obscured to prevent comparison when subsequent lines were marked.

SULPHUR DIOXIDE CHALLENGE

The sulphur dioxide challenges were performed with the subject wearing a noseclip, breathing through a mouthpiece attached to a non-rebreathing valve in a circuit designed to deliver sulphur dioxide at various concentrations at a fixed flow rate. Sulphur dioxide at 400 ppm from a special gas mixture (British Oxygen Co, Brentford, Middlesex) was passed through a rotameter (range 0.1–1.0 $l\text{ min}^{-1}$, Fisher Controls, Croydon, Surrey) and then mixed with air from a compressor also passing through a rotameter (range 15–150 $l\text{ min}^{-1}$). The gases were mixed in a 25 litre chamber before inhalation via the two way valve. The exhaust gases were dispersed under water. Sulphur dioxide concentrations in the mixture were sampled proximal to the two way valve by a sulphur dioxide analyser (pulsed fluorescent sulphur dioxide analyser, Thermo Electron Corporation, Waltham, Massachusetts) connected to the sampling port by Teflon tubing. By varying the flow of sulphur dioxide from 0.125 to 0.2 $l\text{ min}^{-1}$ and maintaining the air flow at 15 $l\text{ min}^{-1}$ different concentrations of sulphur dioxide were produced. The volume of sulphur dioxide and air inhaled was measured by a respirometer (Wright) on the input side of the mouthpiece.

STUDY DESIGN

Each subject was asked to attend the laboratory at the same time of day on five occasions, with intervals of at least five days between each visit. The subjects did not take β adrenoceptor agonists for 12 hours and refrained from having drinks containing caffeine for four hours before each study. In preliminary studies the construction of a dose-response curve for sulphur dioxide proved not to be possible because of the

development of tachyphylaxis. We therefore decided to study a single concentration of sulphur dioxide that would give a greater than 40% fall in $\dot{V}_{P_{30}}$. On the first attendance a partial dose-response curve for sulphur dioxide was constructed to determine the dose required to cause the desired degree of bronchoconstriction. This concentration and volume were then used on the three subsequent study days.

On the next three visits, after measurement of baseline $\dot{V}_{P_{30}}$, placebo or 2 or 4 mg of nedocromil sodium was administered from matching pressurised aerosols in a double blind manner in random order. $\dot{V}_{P_{30}}$ was measured 10, 20, and 30 minutes after treatment. The visual analogue scale was recorded 30 min after drug inhalation. The dose of sulphur dioxide was then inhaled and $\dot{V}_{P_{30}}$ and the visual analogue scale were monitored for 20 minutes or until the values returned to within 10% of baseline values. On the final day the dose of sulphur dioxide used on the drug study days was repeated to ensure that the subject's bronchial responsiveness to sulphur dioxide had not altered during the period of study.

DATA ANALYSIS

The duration of bronchoconstriction measured by $\dot{V}_{P_{30}}$ and the duration of breathlessness measured by visual analogue scale scores were calculated by measurement of the area under the $\dot{V}_{P_{30}}$ -time (l) and visual analogue scale time (mm.min) curves (AUC) by the trapezoidal rule. The AUC was measured up to six minutes after sulphur dioxide inhalation, a time at which all subjects had readings on all study days. The values for $\dot{V}_{P_{30}}$ ($l\text{ min}^{-1}$) were analysed by analysis of variance and the differences tested by the application of the Bonferroni modification for multiple comparisons of Student's *t* test.¹² The Mann-Whitney U test was used to analyse the values for visual analogue scale. All results are expressed as mean (SD) values.

Results

No significant difference was found between baseline values of lung function on any of the five study days. Neither 2 nor 4 mg nedocromil sodium produced any significant change in $\dot{V}_{P_{30}}$ up to 30 minutes after administration from the values obtained before drug inhalation or after placebo.

BRONCHOCONSTRICTOR RESPONSES

The mean maximum changes in $\dot{V}_{P_{30}}$ after inhalation of sulphur dioxide are shown in table 1. There was no significant difference in the changes after exposure to sulphur dioxide on control days and after placebo. The maximum bronchoconstrictor response to sulphur dioxide was significantly attenuated ($p < 0.05$) by nedocromil sodium 4 mg, but not by the 2 mg

Table 1 Mean (SD) maximum change in $\dot{V}_{P_{30}}$ and mean change in area under the $\dot{V}_{P_{30}}$ -time curve after administration of placebo and nedocromil sodium 2 and 4 mg compared with control values following exposure to sulphur dioxide in six asthmatic patients

	Maximum change ($l\ min^{-1}$)	AUC (l)
1st control	-51.6 (26.4)	-553.6 (399)
2nd control	-34.0 (15.9)	-383.1 (302)
Placebo	-44.7 (30.4)	-349.3 (299)
Nedocromil sodium 2 mg	-32.7 (14.0)	-31.2 (58)*
Nedocromil sodium 4 mg	-11.8 (12.6)*	+44.6 (139)*

* $p < 0.05$.

$\dot{V}_{P_{30}}$, flow at 30% above reference residual volume; AUC, area under the curve.

Table 2 Mean (SD) maximum change in visual analogue scale score and mean change in area under the visual analogue score time curve after treatment with placebo and nedocromil sodium 2 and 4 mg compared with control values following exposure to sulphur dioxide in six asthmatic patients

	Maximum change (mm)	AUC (mm.min)
1st control	36.8 (21.1)	436.6 (457)
2nd control	24.7 (10.7)	352.0 (390)
Placebo	31.5 (11.6)	289.0 (287)
Nedocromil sodium 2 mg	13.7 (11.3)*	194.6 (278)*
Nedocromil sodium 4 mg	15.7 (11.8)	151.6 (177)*

* $p < 0.05$.

AUC—area under the curve.

dose, by comparison with placebo.

The duration of bronchoconstriction, measured by calculation of the area under the $\dot{V}_{P_{30}}$ -time curve after sulphur dioxide inhalation, did not differ significantly between control days or after placebo (table 1). Both 2 and 4 mg of nedocromil sodium significantly reduced the $\dot{V}_{P_{30}}$ AUC after inhalation of sulphur dioxide ($p < 0.05$).

DYSPNOEA SCORE

The mean maximum changes on the visual analogue scale after inhalation of sulphur dioxide are shown in table 2. No significant differences were observed following sulphur dioxide between control days or after placebo. A significant reduction ($p < 0.05$) was observed with 2 mg nedocromil sodium after inhalation of sulphur dioxide. The maximum visual analogue scale score after the 4 mg dose did not differ significantly from that after placebo as a result of one subject, in whom only the duration of response and not the maximum response was altered by the drug.

The duration of dyspnoeic symptoms, measured by calculating the area under the visual analogue scale score-time curve after sulphur dioxide inhalation did

not differ significantly between control days or after placebo (table 2) but was significantly reduced with both 2 mg and 4 mg nedocromil sodium ($p < 0.05$).

Discussion

Inhaled nedocromil sodium significantly inhibited the magnitude and duration of bronchoconstriction and breathlessness after inhalation of sulphur dioxide. The 4 mg dose had a greater protective effect than the 2 mg dose against the maximum change in $\dot{V}_{P_{30}}$; but the two doses were equally effective in limiting the duration of change in $\dot{V}_{P_{30}}$ and dyspnoea score.

Although some workers have been able to construct a three point dose-response curve for sulphur dioxide,¹³ like others¹⁴ we were unable to do this with our system owing to development of tachyphylaxis to sulphur dioxide. We therefore observed the effect of nedocromil sodium on the bronchoconstrictor response to a single concentration of sulphur dioxide. This protocol also allowed us to examine the effect of nedocromil sodium on the duration of bronchoconstriction. To detect any change in the subject's sensitivity to sulphur dioxide during the course of the study a final control day as well as a placebo day was incorporated. This showed that bronchoconstrictor responses to fixed concentrations of sulphur dioxide were consistent for each subject.

A dyspnoea score was incorporated because sulphur dioxide inhalation provoked a retrosternal discomfort and feeling of breathlessness that appeared to be out of proportion to the degree of bronchoconstriction when compared with other non-specific bronchial challenges such as histamine and methacholine. We therefore considered it important to monitor the subjective assessment of dyspnoea using a visual analogue scale.¹⁵ The mechanism by which nedocromil inhibits sulphur dioxide induced bronchoconstriction is uncertain. Nedocromil sodium inhibits the change in lung mechanics produced by antigen challenge in *Ascaris* sensitive monkey in vivo and inhibits histamine release from mucosal mast cells in vitro with a much greater potency than sodium cromoglycate.¹⁶ Sodium cromoglycate, however, which has a profile of action similar to that of nedocromil sodium, also inhibits afferent nerve activity in animals,¹⁷ so possibly nedocromil sodium acting by blocking the effect of sulphur dioxide on afferent discharge. The reduction of dyspnoea score by nedocromil sodium provides some support for an effect on afferent nerve endings.

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