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Effect of nedocromil sodium and sodium cromoglycate against bronchoconstriction induced by inhaled adenosine 5'-monophosphate

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ABSTRACT: In this randomized, double-blind, placebo controlled study, the effect of prior inhalation of nebulized sodium cromoglycate (SCG) (7.3±0.6 mg) and nedocromil sodium (NED) (7.5±0.6 mg) was observed on adenosine 5'-monophosphate (AMP)-induced bronchoconstriction in 11 non-atopic asthmatic subjects. The geometric mean provocation doses of methacholine and AMP required to produce a 20% decrease in forced expiratory volume in one second (FEV_1) ($PD_{20}FEV_1$) were 0.6 (0.1–18.8) and 5.1 (0.8–130.7) μmole respectively. The repeatability of the AMP challenge procedure for $PD_{20}FEV_1$ was within one doubling dose difference. SCG and NED, administered 30 min prior to bronchoprovocation with AMP, displaced the AMP dose-response curve to the right by 9.6 (1.5–41.6) ($p<0.01$) and 22.2 (3.7–89.1) ($p<0.01$)-fold, respectively, the difference between the two drugs being significant ($p<0.05$). There was a significant correlation ($r=0.7$, $p=0.02$) between the log dose ratios for $PD_{20}FEV_1$ for SCG and NED. We conclude that both SCG and NED protect against AMP-induced bronchoconstriction, NED being at least 2.3 (0.7–11.5)-fold more potent than SCG, and that they achieve this effect by a similar mechanism(s).

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Adenosine 5'-monophosphate (AMP) causes bronchoconstriction when inhaled by atopic [1, 2] and non-atopic [1, 3] asthmatics and atopic normal subjects [4], probably after *in vivo* conversion to adenosine by the exo-enzyme 5'-nucleotidase [5]. Adenosine affects physiological processes by interacting with cell surface purinoceptors to decrease or increase intracellular levels of cyclic 3',5'-AMP [6]. The mode of action of adenosine in causing bronchoconstriction remains to be determined, but potentiation of ongoing mediator release, principally histamine, from pre-activated bronchial mast cells [2, 3], an interaction with neurological mechanisms [7] or a combination of these two actions [8] have been proposed.

Nedocromil sodium (NED) is a new anti-inflammatory drug recently introduced for the treatment of asthma. It has been shown to be 200 times more potent than sodium cromoglycate (SCG) in inhibiting preformed and newly generated mediator release from mast cells lavaged from the bronchoalveolar lumen of Ascaris-sensitized primates [9], and produces a 50–60% inhibition of histamine release from mast cells similarly obtained from normal human subjects [10]. In addition, NED has potent inhibitory activities on mediator release from, and cytotoxic functions of eosinophils [11], neutrophils [11], macrophages [12] and platelets [13]. In bronchoprovocation studies, NED protects against bronchoconstriction provoked by inhaled hypotonic solutions [14], sulphur dioxide [15], cold dry air [16] and exercise [17], and inhibits the immediate and late bronchoconstrictor responses following inhalation of allergen [18]. In four previous reports, NED has been shown to protect against bronchoconstriction provoked by inhaled adenosine and AMP [19–22]. In two of these, NED was suggested to be more potent in this respect than SCG [20, 21]. However, interpretation of studies employing adenosine as the agonist [19, 20, 22] is limited by the amount of the nucleoside that could be administered on account of its poor solubility, and the only study employing the more soluble AMP as agonist was performed on atopic non-asthmatic subjects [21]. Moreover, there have been no studies which have specifically examined the ability of NED or SCG to protect against the airways response to inhaled AMP in non-atopic asthmatic subjects. In the present study, we have investigated the comparative abilities of SCG and NED to protect against bronchoconstriction provoked by AMP in non-atopic asthmatic subjects, and have

determined the repeatability of the AMP-bronchoprovocation procedure.

Methods

Subjects

Eleven subjects, 6 male, 5 female, mean±SEM (standard error of the mean) age 56.8±4.1 yrs, participated in this study (table 1). All subjects were nonsmokers with non-atopic (intrinsic) asthma as defined by negative prick skin tests (<2 mm weal response) to ten common aeroallergens (house dust, *Dermatophagoides pteronyssinus, Dermatophagoides farinae,* mixed grass pollen, tree pollen, cat fur, dog hair, feathers, *Candida albicans* and *Aspergillus fumigatus,* all obtained from Bencard, Brentford, Middlesex, UK), a negative history of diseases associated with atopy, such as allergic rhinitis and atopic dermatitis, no history of occupational asthma and serum immunoglobulin E (IgE) levels falling within the accepted normal range (<81 IU·ml^{-1}). All patients had baseline forced expiratory volume in one second (FEV_1) >60% of their predicted maximum or >1.5 *l*, and none was receiving oral corticosteroids or theophylline for regular treatment (table 1). All inhaled medication was continued throughout the period of the study, but was omitted for 8 h prior to each visit to the laboratory, and patients were not studied within a four week period following an upper respiratory tract infection or an exacerbation of their asthma. Subjects gave their written informed consent and the study was approved by the Southampton University and Hospitals Ethical Committee.

Bronchial provocation and measurements of pulmonary function

Pulmonary function was recorded both as the forced expiratory volume in one second (FEV_1) and maximum flow at 70% of vital capacity (VC) below total lung capacity (TLC) during a forced partial expiratory manoeuvre ($\dot{V}p_{30}$). Both measurements were derived from flow-volume curves produced on a rolling seal, flow rate-dependent spirometer (Morgan Spiroflow, P.K. Morgan Ltd, Kent, UK) connected to an 85B desk top computer *via* an 8294A GP-10 interface (Hewlett Packard, Wokingham, Berkshire, UK). The flow-volume curves for the partial expiratory manoeuvre were obtained after a period of normal tidal breathing by asking the subject to expire maximally into a mouthpiece connected to the spirometer from end tidal inspiratory capacity to residual volume (RV). On reaching RV, the subject was asked to inspire to TLC and expire maximally back to RV, allowing a measurement of FEV_1 to be recorded.

On each study day, methacholine (Sigma Chemical Co., Poole, Dorset, UK) and AMP (Sigma Chemical Co., St. Louis, USA) were made up freshly in 0.9% sodium chloride to produce a range of doubling concentrations of 0.03–64 mg·ml^{-1} (0.2–327 mmol·l^{-1}) and 0.04–400 mg·ml^{-1} (1.1–1151.4 mmol·l^{-1}), respectively. The solutions were administered as aerosols generated from a starting volume of 3 ml in a disposable Inspiron Mini-nebulizer (C.R. Bard International, Sunderland, UK) connected to a Rosenthal-French dosimeter (Bethesda Hospital, Rochester, New York, USA) driven by compressed air at a pressure of 20 lb·in^{-2}. Under these conditions, the nebulizer generates an aerosol with a mass median particle diameter of 4.7 μm [23]. Subjects, wearing a nose-clip, were instructed to take 5 consecutive breaths from functional residual capacity (FRC) to TLC *via* a mouthpiece [24], the dosimeter being adjusted so that this procedure delivered 60 μl of aerosol into the inspirate.

Study design

The study was divided into three phases. In the first phase, a dose-response study with inhaled methacholine was performed. After 15 min rest, three baseline measurements of FEV_1 and Vp_{30} were recorded at 5 min

Table 1. – Details of patient characteristics

Subject	Sex	Age yrs	Baseline FEV_1 % predicted	PC_{20} Methacholine mg·ml^{-1}	Treatment
1	F	20	81	0.4	S, C
2	M	58	78	1.2	S, Bf
3	M	67	76	0.8	S
4	F	52	80	2.4	S, B
5	F	57	85	21.4	S
6	F	62	103	0.7	S, B
7	M	68	98	60.3	S, B
8	M	60	89	1.3	S
9	M	51	53	0.8	S, B
10	M	67	102	1.9	S, B
11	F	63	58	0.5	S
Mean±SEM	6M, 5F	57±4	82±5	1.8*	

*: Geometric mean; S: salbutamol; B: beclomethasone dipropionate, 50 μg per actuation; Bf: beclomethasone dipropionate, 250 μg per actuation; C: disodium cromoglycate. FEV_1: forced expiratory volume in one second; PC_{20} Methacholine: provocation concentration of methacholine producing a 20% fall in FEV_1.

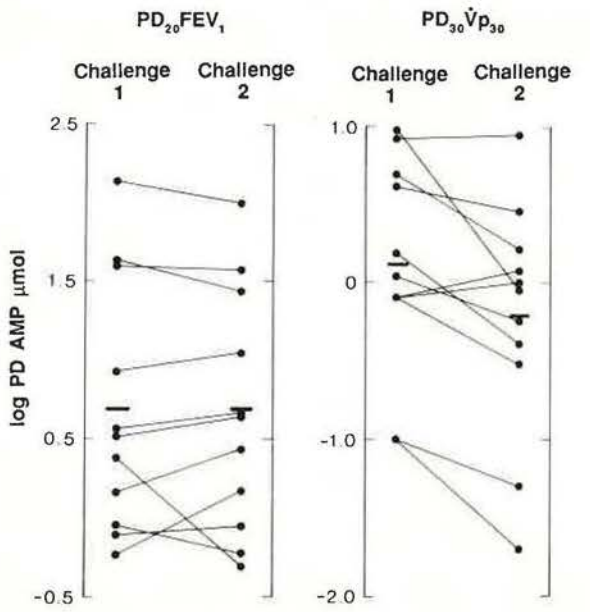

Fig. 1. – Values of $PD_{20}FEV_1$ and $PD_{30}\dot{V}p_{30}$ for AMP obtained in two consecutive challenges. $PD_{20}FEV_1$: provocation dose of adenosine 5'-monophosphate (AMP) required to produce a 20% decrease in forced expiratory volume in one second (FEV_1); $PD_{30}\dot{V}p_{30}$: provocation dose of AMP required to produce a 30% fall in maximal flow at 70% vital capacity below total lung capacity during a forced partial expiratory manoeuvre ($\dot{V}p_{30}$).

intervals, followed by inhalation of 0.9% sodium chloride and repeat measurements at 1 and 3 min post-inhalation. Provided FEV_1 and $\dot{V}p_{30}$ did not change by >5% and >15% of baseline values respectively, a dose-response study with inhaled methacholine was carried out. Increasing doubling doses of methacholine, 0.01–20 µmole, were inhaled at 5 min intervals until FEV_1 and $\dot{V}p_{30}$ had fallen by >20% and >30% of the post-saline values respectively, or the highest dose of methacholine had been administered.

In the second phase of the study, the repeatability of the AMP challenge procedure was determined. Subjects attended the laboratory on two separate occasions, at least 48 h apart, within the same week and at the same time of day, to perform dose-response studies with inhaled AMP, in a manner similar to that described for methacholine. Increasing doubling doses of AMP, 0.01–70.4 µmole, were inhaled at 5 min intervals until FEV_1 and $\dot{V}p_{30}$ had fallen by >20% and >30% of post-saline baseline values respectively. If these decreases in airway calibre were not achieved after 5 breaths of the highest concentration of AMP (cumulative dose, 140.8 µmole), two further doses of AMP were administered by inhaling 10 breaths (281.6 µmole) and 20 breaths (563.2 µmole) of the highest concentration, respectively, until either the target decreases in airway calibre had been achieved, or the highest AMP dose had been administered.

In the third phase of the study, subjects attended on three further occasions, at least 72 h apart and at the same time of day, to perform dose-response studies with inhaled AMP. On each occasion, after 15 min rest, three baseline measurements of FEV_1 and $\dot{V}p_{30}$ were recorded at 5 min intervals, followed by inhalation of nedocromil sodium, sodium cromoglycate or matched placebo (Fisons Pharmaceuticals, Loughborough, UK). The drugs were administered, in randomized order and double-blind fashion, as aerosols generated from 4 ml of solution containing 1% w/v in a disposable Inspiron Mini-nebulizer connected to a Rosenthal-French dosimeter driven by compressed air at a pressure of 20 lb·in². Subjects, wearing a nose-clip, inhaled the aerosols in 60 consecutive deep tidal breaths over a 6 min period, the mean volumes of solution delivered being 774±60 µl (7.7 mg) for SCG and 752±60 µl (7.5 mg)

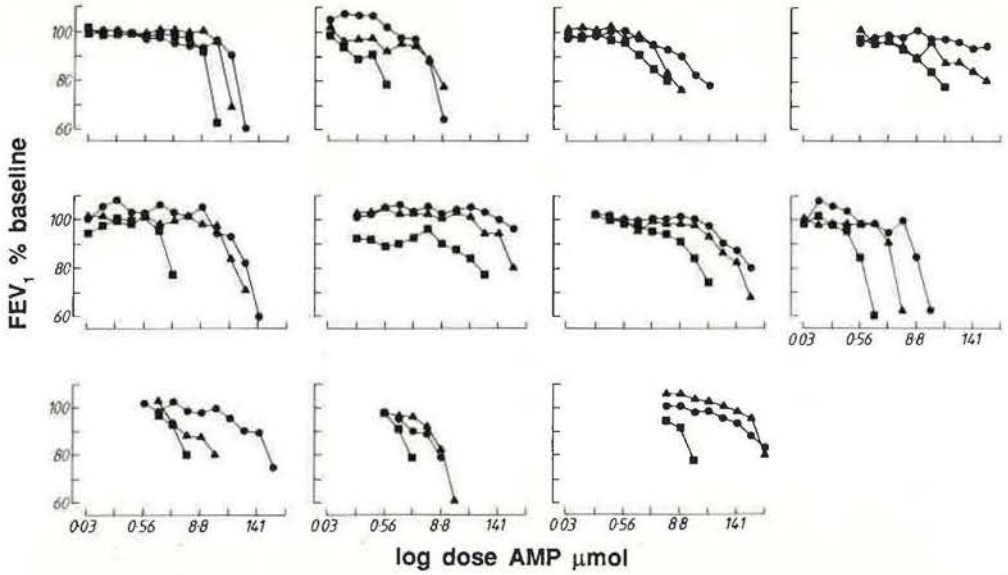

Fig. 2. – Effect of placebo (■), sodium cromoglycate (▲) and nedocromil sodium (●) on AMP-induced falls in FEV_1 in 11 non-atopic asthmatic subjects. See figure 1 for abbreviations.

for NED. Measurements of FEV_1 and $\dot{V}p_{30}$ were repeated at 5 min intervals for 30 min post-inhalation and subsequently followed by a dose-response study with inhaled AMP, in the manner described previously.

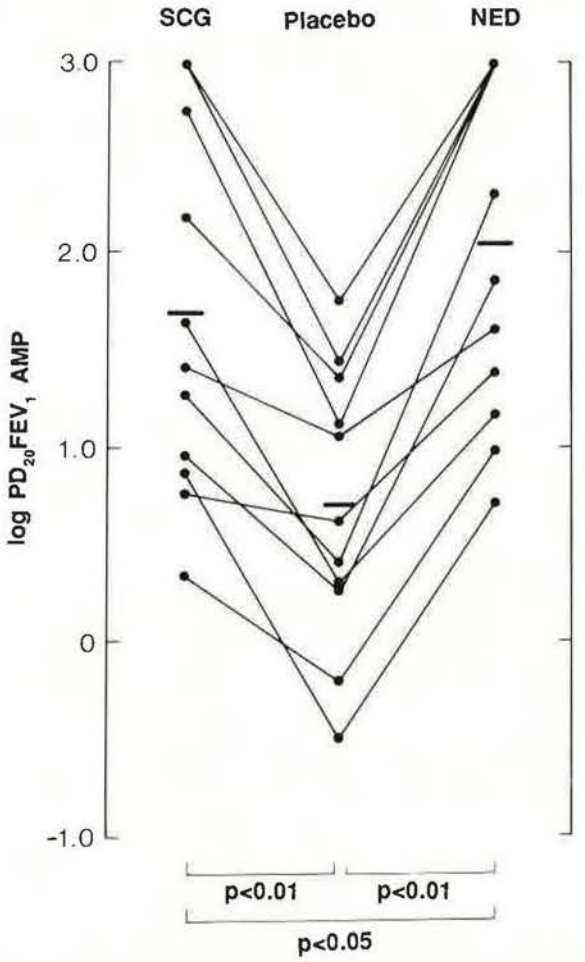

Fig. 3. – Changes in provocation doses of AMP required to produce a 20% decrease in FEV_1 ($PD_{20}FEV_1$) after sodium cromoglycate (SCG) and nedocromil sodium (NED) in 11 non-atopic asthmatic subjects. The horizontal bars refer to the geometric mean values. For abbreviations see figure 1.

Data analysis

In all statistical analyses, the $p<0.05$ level of significance was accepted, and figures refer to the mean±SEM unless otherwise stated. Baseline values of FEV_1 and $\dot{V}p_{30}$ were compared between study days using two-factor analysis of variance followed by the Newman Keuls procedure. Pre- and post-drug measurements of FEV_1 and $\dot{V}p_{30}$ were compared using Student's t-test for paired data. Following administration of each dose of agonist, the decreases in FEV_1 and $\dot{V}p_{30}$ were expressed as a percentage of the post-saline baseline values, and plotted against the cumulative doses of agonist administered on a logarithmic scale. The provocation doses of agonist required to produce a 20% fall in FEV_1 ($PD_{20}FEV_1$) and a 30% fall in $\dot{V}p_{30}$ ($PD_{30}\dot{V}p_{30}$) from post-saline baseline values, were derived by linear interpolation. If the percentage fall in airway calibre with the highest cumulative dose of AMP (561.9 µmole) failed to achieve a value of 20% for FEV_1 or 30% for $\dot{V}p_{30}$, then the provocation dose was estimated as being one doubling dose above the highest cumulative dose administered (1123.8 µmole) [25].

The bronchoconstrictor potency of AMP on the airways relative to methacholine, was determined using the mean results for each subject obtained from the two AMP dose-response studies performed in the second phase of the study. The repeatability of the AMP challenge procedure was examined using the method described by ALTMAN and BLAND [26], of plotting the difference against the mean using logarithmically transformed data obtained from two consecutive AMP dose-response studies. The standard deviation of the differences between the results for the two challenges was calculated, and from this the 95% confidence interval for the difference in results derived.

The slopes of the AMP dose-response curves after placebo and each of the two active drugs were determined by linear regression analysis and compared using two-factor analysis of variance and the Newman Keuls procedure.

In the third phase of the study, drug-induced changes in the $PD_{20}FEV_1$ and $PD_{30}\dot{V}p_{30}$ values for AMP were logarithmically transformed and compared by two-factor analysis of variance. Paired comparisons between nedocromil sodium, sodium cromoglycate and placebo were then made using the Newman Keuls procedure. Dose ratios for the effect of each of the two drugs in protecting against AMP-induced bronchoconstriction were calculated by dividing the $PD_{20}FEV_1$ and $PD_{30}\dot{V}p_{30}$ values obtained after administration of active drug, by those obtained after placebo. Least squares linear regression analysis of the logarithmically transformed data was used to examine the relationships between the dose ratios for nedocromil sodium and sodium cromoglycate, and the $PD_{20}FEV_1$ and $PD_{30}\dot{V}p_{30}$ values for methacholine and the first of the two control AMP challenges.

Results

There were no significant differences in baseline values of FEV_1 and $\dot{V}p_{30}$ between any of the study days. The geometric mean (range) of $PD_{20}FEV_1$ and $PD_{30}\dot{V}p_{30}$ values for methacholine were 0.6 (0.1–18.8) and 0.1 (0.02–0.7), and for AMP 5.1 (0.8–130.7) and 1.0 (0.1–8.7) µmole, respectively. Thus, on a molar basis, AMP was 9–15 times less potent than methacholine in causing bronchoconstriction in this group of non-atopic asthmatic subjects. A significant correlation was found between $PD_{20}FEV_1$ values for methacholine and AMP ($r=0.75$, $p=0.01$) but not between the $PD_{30}\dot{V}p_{30}$ values. The AMP challenge procedure was more highly repeatable when pulmonary function was followed as FEV_1 than as $\dot{V}p_{30}$, there being a variation of 0.4–2.3-fold between the results for the two challenges for $PD_{20}FEV_1$, and 0.2–4.4-fold for $PD_{30}\dot{V}p_{30}$ (95% confidence intervals) (fig. 1).

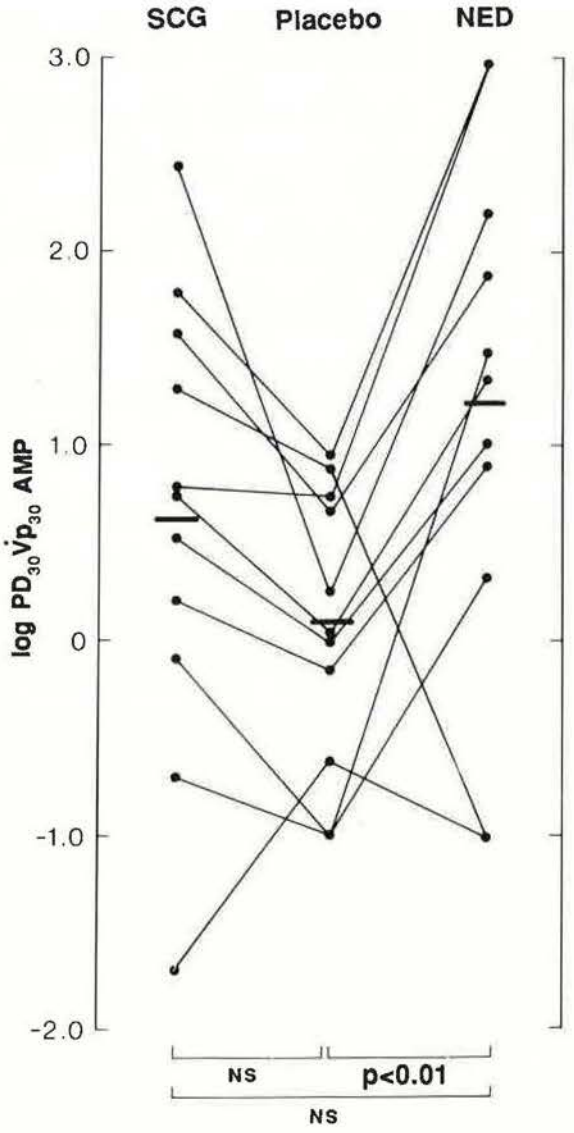

Fig. 4. – Changes in provocation doses of AMP required to produce a 30% decrease in $\dot{V}p_{30}$ ($PD_{30}\dot{V}p_{30}$) after sodium cromoglycate (SCG) and nedocromil sodium (NED) in 11 non-atopic asthmatic subjects. The horizontal bars refer to the geometric mean values. NS: not significant. For abbreviations see figure 1.

Following inhalation of placebo or either of the two active drugs, there were no significant changes in baseline values of FEV_1 and $\dot{V}p_{30}$. When compared with placebo, SCG and NED both produced a displacement to the right of the AMP dose-response curve in all eleven subjects studied when changes in pulmonary function were followed as FEV_1 (fig. 2), but in only ten subjects when followed as $\dot{V}p_{30}$. For both FEV_1 and $\dot{V}p_{30}$, the slopes of the AMP dose-response curves before and after SCG and NED did not depart significantly from parallel ($p>0.05$). Thus for placebo, SCG and NED the geometric mean $PD_{20}FEV_1$ values were 4.9, 46.5 and 107.9 μmole, respectively, these differences being significant both for each drug when compared with placebo ($p<0.01$) and between the two drugs ($p<0.05$) (fig. 3). For $PD_{30}\dot{V}p_{30}$, the corresponding values were 1.2, 4.2 and 15.8 μmole, respectively, these differences only reaching significance for NED compared with placebo ($p<0.01$) (fig. 4). When calculated from the $PD_{20}FEV_1$ data, the geometric mean (range) dose ratios for SCG and NED compared with placebo were 9.6 (1.5–41.6) and 22.2 (3.7–89.1), respectively. Thus, NED was approximately 2.3 (0.7–11.5)-fold more potent than SCG in protecting against the airways effect of inhaled AMP. Corresponding values calculated from the $PD_{30}\dot{V}p_{30}$ data were 3.6 (0.1–144.2) and 15.5 (0.01–286)-fold respectively, indicating NED to be approximately 4.6 (0.01–193.8)-fold, more potent than SCG. There was a significant correlation between the protection afforded by SCG and NED against bronchoconstriction produced by AMP when potency ratios were calculated from $PD_{20}FEV_1$ ($r=0.7$, $p=0.02$) (fig. 5).

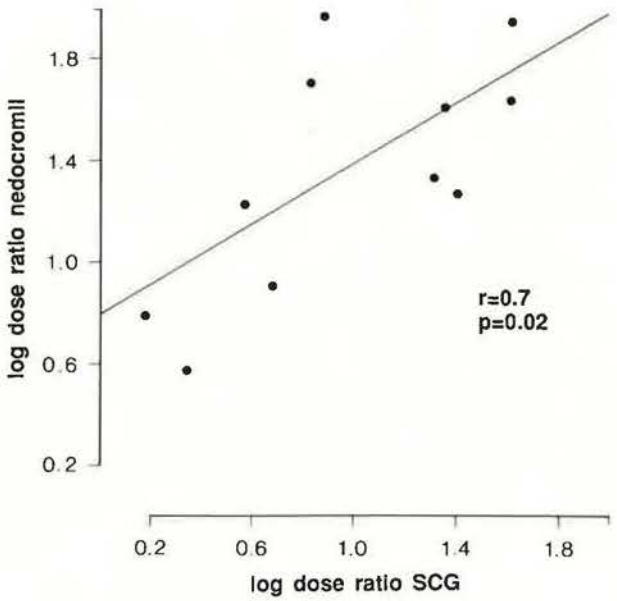

Fig. 5. – Relationship between log dose ratio $PD_{20}FEV_1$ for nedocromil sodium and sodium chromoglycate (SCG) in 11 non-atopic asthmatic subjects. For abbreviations see figure 1.

Discussion

Previously we found that SCG protected against adenosine-induced bronchoconstriction in only four out of seven atopic asthmatic subjects studied [27]. Those subjects whose airways response to adenosine was unaffected by SCG had received the drug on a regular basis until 12 h before the study, so that a persisting activity of this compound may explain these findings. However, this is unlikely to be a confounding factor in our study since only one subject was on regular treatment with SCG. The effect of inhaled corticosteroids, taken by six of our subjects, on responsiveness to AMP is at present unknown. Prolonged [28], but not acute [29] administration of these drugs inhibits allergen-induced immediate bronchoconstriction, and there is some evidence that they may reduce the number of nasal mucosal mast cells when administered over a prolonged period of time [30].

In all but one previous study [21], NED and SCG were administered by spinhaler or pressurized metered-dose inhaler. Since inter-subject variations in inhaler and spinhaler technique may cause considerable variation in the dose of drug reaching the lungs, we chose to administer the drugs in this study by nebulization using a dosimeter. This technique is more reproducible [31] and has previously been shown to achieve plasma concentrations of SCG comparable with those obtained using the 20 mg spinhaler [32]. Plasma concentrations of SCG have been shown to accurately reflect the dose of drug reaching the lungs [32]. In order to be able to compare the potency of the two drugs, we chose to deliver a similar dose of nedocromil using the same technique.

In this study, we have determined that the AMP challenge procedure is repeatable to within a single doubling dose difference when pulmonary function is followed as FEV_1. The reduced repeatability of $\dot{V}p_{30}$ may be due to both the greater variability of this measurement and the fact that older subjects with more severe airways disease were studied. However, the effect of AMP in decreasing both $\dot{V}p_{30}$ and FEV_1 in parallel suggests that its actions are not restricted to a particular level within the bronchial tree.

Although a similar mechanism of action for SCG and NED in protecting against AMP is suggested by the significant correlation between their abilities to displace the AMP dose-response curves, this is unlikely to be due to a non-specific effect on bronchial responsiveness [22, 33]. The present results confirm our previous observations [34] that, in atopic asthmatics, whilst there exists a relationship between responsiveness to AMP and methacholine, this is poor. This suggests that the bronchoconstrictor effect of AMP is not due to a direct action on bronchial smooth muscle or neural reflexes, and incriminates an interceding cell type. Both drugs have a number of activities pertinent to their therapeutic effect in asthma, including stabilization of mast cells [9, 10], inhibition of reflex bronchoconstriction [35] and a variety of suppressive actions on eosinophils [11, 36], neutrophils [11, 36] and monocytes [12, 36]. Although this array of activities makes speculation on the mechanism by which NED and SCG protect against bronchoprovocation with AMP difficult, one activity which may account for this effect is their capacity to inhibit mediator secretion from airway mast cells [9, 10]. Previous data suggest that AMP produces its airway effects in asthma after prior conversion to adenosine, which then stimulates mast cell purinoceptors of the A_2 subtype to enhance mediator secretion [37, 38]. The observation that, in time course studies, potent and selective H_1-histamine receptor antagonists inhibit >80% of the bronchoconstriction provoked by AMP in both atopic [2] and non-atopic [3] asthmatic subjects, indicates that histamine is the major mast cell-derived mediator of this response. The *in vitro* observation that NED is more potent than SCG in inhibiting mast cell mediator release [9] is in accord with the 2–5-fold greater potency of NED in the present study. Indeed, NED was so effective that in four subjects for FEV_1 a true PD value could not be derived and the dose ratio calculated probably underestimated the difference in potency between the two drugs.

Recent evidence suggests that AMP-induced bronchoconstriction may result from an interaction of adenosine both with airway mast cells and neurological reflex mechanisms [8]. Although cromolyn-like compounds protect against bronchoconstriction provoked by bradykinin, suggesting that their ability to inhibit non-myelinated C-fibre activation [35] may be pertinent to their protective effect against AMP, this is a less likely mode of action since antihistamines are potent inhibitors of the airway effects of AMP [2, 3], but not bradykinin [39].

In conclusion, the present study has demonstrated that both SCG and NED protect the airways against bronchoconstriction induced by AMP, and that NED is significantly more potent than SCG in this regard. One property of these drugs which may account for this action is their ability to inhibit mediator release from airway mast cells. This would support a central role of this cell type in mediating the airway effects of AMP, and by implication adenosine, although at the present time an additional action of SCG and NED in inhibiting activation of neurological reflexes by AMP cannot be excluded. The effectiveness of these two drugs in blocking AMP-provoked bronchoconstriction in asthma not associated with atopy adds some support to the view [40] that these drugs may also be active as therapeutic agents in this form of the disease.

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Effet du cromoglycate disodique et du nedocromil sur la bronchoconstriction induite par l'adénosine 5'monophosphate en inhalation. G.D. Phillips, V.L. Scott, R. Richards, S.T. Holgate.

RÉSUMÉ: Dans cette étude randomisée, en double anonymat, et contrôlée par un placebo, les effets de l'inhalation préa-

lable de cromoglycate disodique nébulisé (SCG) (7.3±0.6 mg) et de nedocromil sodium (NED) (7.5±0.6 mg) ont été étudiés sur la bronchoconstriction induite par l'AMP chez 11 sujets asthmatiques non atopiques. La moyenne géométrique des doses de provocation de métacholine et d'AMP nécessaires à produire une diminution de 20% du VEMS (PD_{20}VEMS) était respectivement de 0.6 (0.1–18.8) et 5.1 (0.8–130.7) µmole. La reproductibilité de la technique de provocation à l'AMP pour PD_{20}VEMS se situait à l'intérieur d'une différence d'un doublement de dose. SCG et NED, administrés 30 mi-nutes avant la provocation bronchique par l'AMP, ont déplacé la courbe dose-réponse de l'AMP vers la droite par 9.6 (1.5–41.6) ($p<0.01$) et par 22.2 (3.7–89.1) ($p<0.01$) fois respectivement, la différence entre les deux produits étant significative ($p<0.05$). Une corrélation significative a été observée ($r=0.7$, $p=0.02$) entre les rapports au logarithme de la dose pour PD_{20}VEMS, aussi bien pour SCG que pour NED. Nous concluons que SCG comme NED protègent contre la bronchoconstriction induite par l'AMP, mais que NED s'avère au moins 2.3 (0.7–11.5) fois plus puissant que SCG, et que tous deux obtiennent cet effet par un mécanisme similaire.
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