Eur Respir J
1988, 1, 896–901

Inhalation rate of sodium cromoglycate determines plasma pharmacokinetics and protection against AMP-induced bronchoconstriction in asthma

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Inhalation rate of sodium cromoglycate determines plasma pharmacokinetics and protection against AMP-induced bronchoconstriction in asthma. R. Richards, S.F. Simpson, A.G. Renwick, S.T. Holgate.

ABSTRACT: We have investigated whether the inspiratory flow at which sodium cromoglycate (SCG) is inhaled influences the efficacy of SCG. Seven atopic asthmatic subjects (age 25±2 yrs) inhaled dry powder SCG from a Spinhaler on separate occasions at three flow rates, maximum ($\dot{V}_1$), 100 l·min^{-1} ($\dot{V}_2$), and 50 l·min^{-1} ($\dot{V}_3$), or placebo, according to a double-blind structured study. Thirty minutes after administration a bronchial provocation test was performed with adenosine 5'-monophosphate (AMP). Blood samples for measurement of plasma SCG concentration were taken and the area under the plasma concentration-time curve (AUC) calculated for each flow rate. Both inspiratory flow rate and AUC correlated significantly with the degree of protection afforded against AMP-induced bronchoconstriction ($r=0.73$, $p<0.001$; $r=0.66$, $p<0.001$). These findings indicate that the flow rate used to inhale powdered SCG is a major factor in determining the protective efficacy of this drug against bronchial challenge and therefore has important clinical implications.

Eur Respir J., 1988, 2, 896–901.

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Keywords:AMP-induced bronchoconstriction; bronchial asthma; pharmacokinetics; sodium cromoglycate.

Accepted after revision August 1, 1988.

Sodium cromoglycate (SCG) has found wide use in the treatment of asthma, especially in children. Conventionally the drug is administered to the airways as a dry powder dispersed into the inspirate using the Spinhaler propeller device, the unit dose being 20 mg. SCG has multiple pharmacological activities pertinent to its therapeutic effects in asthma which include inhibition of mediator release from activated mast cells [1, 2] and other mediator secreting cells [3, 4] and inhibition of neural reflexes [5, 6]. These activities of SCG are reflected in its ability to attenuate bronchoconstriction provoked by inhaled allergens [7, 8], sulphur dioxide [9], adenosine [10], exercise and isocapnic hyperventilation [11, 12].

Following inhalation, SCG is absorbed into the systemic circulation almost entirely from sites of deposition within the lung, with <1% absorption from the buccal mucosa and gastrointestinal tract [13–16]. When delivered to the airways as a dry powder, an aerosolized solution, an aerosol from a pressurized metered-dose inhaler, or when deposited directly into a second order bronchus *via* a bronchoscope, SCG exhibits absorption rate-limited plasma pharmacokinetics [14–17]. Following absorption, the drug is rapidly excreted unchanged in the urine and bile in approximately equal proportions [13].

In a recent study we have shown that the peak plasma concentration and area under the plasma concentration-time curve (AUC) of inhaled dry powder SCG are directly influenced by the inspiratory flow rate used to disperse the drug into the inspirate [15]. Thus the total dose of the drug delivered to the airways and available to produce a local pharmacological effect is proportional to the inspiratory flow rate.

Since the introduction of SCG in the treatment of asthma in the late 1960's there has been little information available concerning the relationship between the dose administered, the amount of drug reaching the airways, and its subsequent protective effect. Patel and co-workers [18] have reported that increasing doses of SCG administered by metered-dose aerosol produce an increase in protection against asthma provoked by exercise and an increase in the total drug absorbed into the circulation. In the present study we have extended this observation by determining the effect of inspiratory flow rate on the plasma pharmacokinetics of a single inhaled dose of dry powder SCG in relation to its ability to protect the airways against bronchoconstriction provoked by inhaled adenosine 5'-monophosphate (AMP). This stimulus is believed to augment histamine release from preactivated mast cells in asthmatic airways and consequently is sensitive to inhibition by SCG and related drugs [19, 20].

Methods

The study consisted of four treatment days each separated by at least one week. All subjects gave their

informed consent and the project was approved by Southampton University and the Hospital's Ethical Committee.

Seven mild atopic asthmatics aged 21–33 yrs (6M, 1F) who were all non-smokers took part in the study (table 1). Prior to the study their mean (±SEM) forced expiratory volume in one second (FEV_1) was 4.3±0.4 *l* and their regular treatment consisted of inhaled β_2-adrenoceptor agonists supplemented by inhaled corticosteroids in two subjects. All drugs were stopped 12 h before each study day. At each visit, the baseline FEV_1 was measured on three occasions 5 min apart to ensure that this did not

Table 1. – Subject details

Subject	Age yrs	Treatment	FEV_1 *l*	PC_{20} Meth mg·ml^{-1}
1	22	BA	4.2	1
2	23	BA	4.4	0.7
3	22	BA	4.3	0.3
4	32	BA	5.7	8
5	25	BA Ist	2.9	0.8
6	21	BA Ist	3	1.7
7	34	BA Ist	5.1	2.3

BA: beta agonist; Ist: inhaled steroids; FEV_1: forced expiratory volume in one second; PC_{20} Methacholine

differ by more than 10% from original baseline values. An indwelling teflon cannula (Venflon® 18 gauge) was inserted into an antecubital vein for blood sampling. According to the double-blind design each subject inhaled either lactose placebo or 20 mg of pelletized SCG from a Spinhaler (Intal Spincaps). Three different inspiratory flow rates were used by the subject sucking through the Spinhaler attached to an adjustable iris resistor. The three inspiratory flow rates used were adjusted to achieve the maximum possible ($\dot{V}_1$), 100 *l*·min^{-1} ($\dot{V}_2$), and 50 *l*·min^{-1} ($\dot{V}_3$) with subjects inspiring from residual volume (RV) to total lung capacity (TLC). The Spinhaler was attached to a P.K. Morgan rolling seal spirometer interfaced to a microcomputer (Collingwood Instruments Ltd, Leicester, UK) to enable direct measurement of the inspiratory flow rate. On each occasion the Spinhaler was weighed before and after completion of the inhalation.

Before and at regular intervals up to 4 h after inhalation of SCG or placebo, 5 ml of blood was removed, anticoagulated with heparin and centrifuged at 500 g for 10 min at room temperature. The plasma was separated and stored at -40°C until analysis. Plasma concentrations of SCG were measured by a double antibody radioimmunoassay which had a limit of detection of 0.7 ng·ml^{-1} and coefficients of variation for reference spiked samples of 6% at 3 ng·ml^{-1} and 11% at 5 ng·ml^{-1} [15, 21].

Thirty minutes after each inhalation of SCG or placebo a bronchial provocation test with AMP (Sigma, Chemical Co. Ltd, Dorset, England) was carried out. After recording three measurements of baseline FEV_1, subjects inhaled normal saline followed by increasing doubling concentrations of aerosolized AMP (0.195–800 mg·ml^{-1}). The aerosols were generated from an Inspiron Mini-Neb nebulizer (Bard International, Sunderland, UK) operated at an air flow of 8 *l*·min^{-1} and inhaled as five deep breaths from functional residual capacity to TLC over 1 min. Under these conditions the mass median particle diameter was 4.2 microns and the nebulizer output 0.9 ml·min^{-1}. One measurement of FEV_1 was made at 3 min and 4 min after each inhalation and the highest value recorded.

The concentration of AMP inhaled was increased progressively until the FEV_1 had fallen by >20% of the starting post-saline value. Plots of AMP concentrations, (logarithmically transformed), against percentage fall in FEV_1 from the post-saline value were constructed for each subject following each of the four treatments. The concentration of agonist producing a 20% fall in FEV_1 (PC_{20}) was then derived by interpolation of the linear portion of the concentration response curve.

Analysis of data

Baseline values of FEV_1, inspiratory flow rates and amount of SCG lost from the capsule on the different study days were compared by analysis of variance for two variables.

After inhalation of SCG the time-course of plasma SCG concentrations were analysed using a non-linear least squares regression analysis (NON-LIN). The data were fitted to a one-compartment open model with first order absorption kinetics [15]. From this programme we derived the half-life for the initial increase in plasma SCG concentration ($t\frac{1}{2}_i$), the terminal half-life ($t\frac{1}{2}_t$) and the area under the plasma concentration-time curve (AUC) extrapolated to infinity. The maximum plasma concentration of SCG (C_{max}) and the time taken to achieve this (t_{max}) are presented as the observed values.

Table 2. – The influence of inspiratory flow rate on the plasma pharmacokinetics of sodium cromoglycate

	$\dot{V}_1$	$\dot{V}_2$	$\dot{V}_3$
Inspiratory flow rate *l*·min^{-1}	211±87[a]	108±3[b]	59±3[c]
C_{max} ng·ml^{-1}	32±9[a]	15±3[b]	9±3[b]
AUC ng·min·ml^{-1}	3318±925[a]	1702±378[b]	1073±218[b]
tmax min	36±11[a]	27±10[a]	23±4[a]
$t\frac{1}{2}_i$ min	3.0±1.3[a]	4.4±1.8[a]	3.5±2.0[a]
$t\frac{1}{2}_t$ min	92±18[a]	80±11[a]	90±15[a]

Values not sharing the same superscript (a, b, or c) were significantly different from each other ($p<0.05$). The data are given as mean±SEM. C_{max}: maximum plasma concentration of sodium cromoglycate; AUC: area under plasma concentration-time curve; t_{max}: time to C_{max}; $t\frac{1}{2}_i$, $t\frac{1}{2}_t$: half-life of initial increase and maximum increase in plasma sodium cromoglycate concentration, respectively.

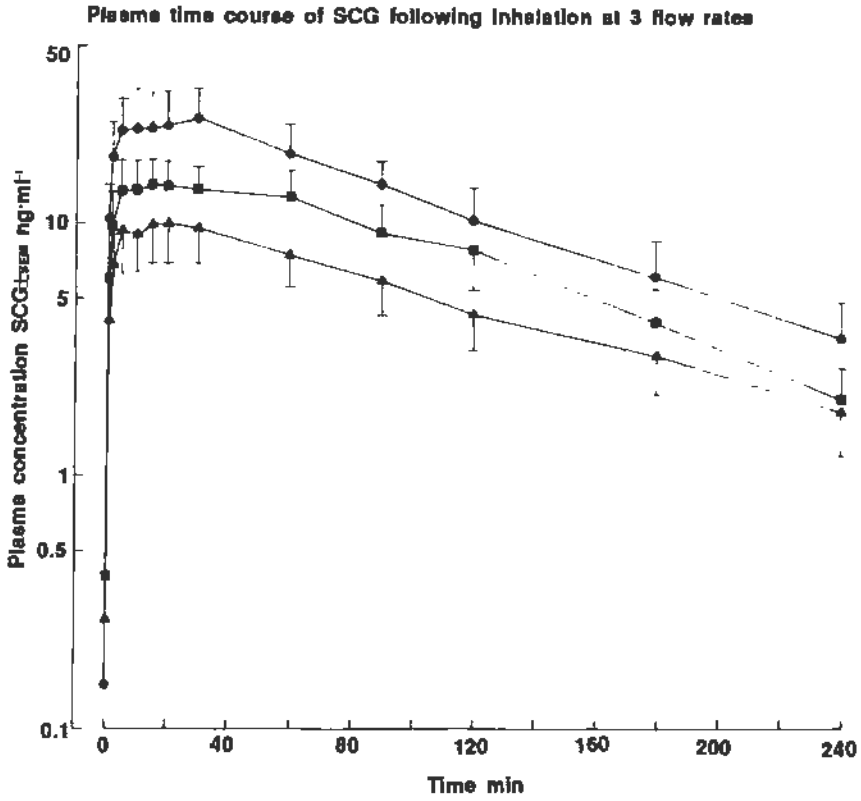

Fig. 1. – Plasma pharmacokinetic profile of sodium cromoglycate inhaled as a dry powder at three inspiratory flow rates: $\dot{V}_1$: maximum possible (●); $\dot{V}_2$: 100 *l*·min^{-1} (■); $\dot{V}_3$: 50 *l*·min^{-1} (▲). Each point represents the mean±SEM of dry concentration plotted on a logarithmic scale for seven subjects.

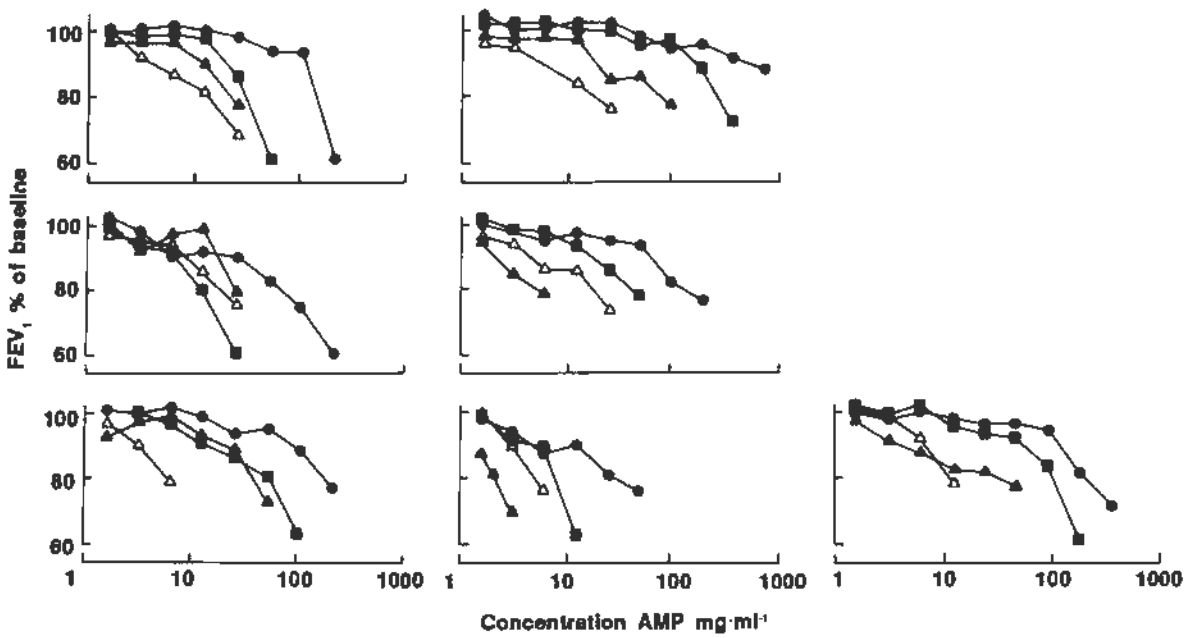

Fig. 2. – The effect of inhaled lactose placebo (Δ) and sodium cromoglycate at three inspiratory flow rates: (●): $\dot{V}_1$; (■): $\dot{V}_2$; (▲): $\dot{V}_3$, on bronchoconstriction provoked by increasing concentrations of inhaled adenosine 5'-monophosphate. The graphs represent the data obtained from each of the seven subjects studied.

Two-way analysis of variance was used to investigate the relationship between inspiratory flow rates and indices of SCG pharmacokinetics, with significance being evaluated by the Newman-Keuls procedure. The protective effect of SCG against AMP-induced bronchoconstriction was derived both as changes in the PC_{20} values and as the ratio of the PC_{20} after SCG inhalation divided by that after placebo. After logarithmic transformation the PC_{20} values and concentration ratios were compared by a 2-way analysis of variance. One subject (no. 4) failed to constrict by 20% and so a maximum value of 800 mg·ml^{-1} was used as an estimate of the PC_{20} AMP.

Results

The mean inspiratory flow rates $\dot{V}_1$, $\dot{V}_2$ and $\dot{V}_3$ achieved on the separate study days were 212±18, 108±3 and 59±3 l·min^{-1}, which were significantly different from each other (p<0.001) (table 2). The amounts of SCG leaving the Spinhaler were 16.9±0.6, 16.1±0.7 and 16.4±1.1 mg, respectively, which were not significantly different and showed no relationship to inspiratory flow rate over the range used.

At each of the three inspiratory flow rates, plasma concentrations of SCG increased rapidly during the first 10 min following inhalation with $t_{\frac{1}{2}_1}$ of less than 5 min (fig. 1, table 2). The values for C_{max} and AUC increased in proportion to the inspiratory flow rate (r=0.7, p<0.001; r=0.65, p<0.005, respectively). The values of C_{max} and AUC were significantly greater at $\dot{V}_1$ than at $\dot{V}_2$ or $\dot{V}_3$. There was no significant difference in $t_{\frac{1}{2}_1}$, t_{max} or $t_{\frac{1}{2}_1}$ for any of the manoeuvres.

Inhalation of AMP caused concentration-related falls in FEV_1 in all subjects on each study day (fig. 2). Inhaled SCG had no significant effect on either the baseline FEV_1 or on the slopes of the AMP-FEV_1 concentration-response curves (multiple linear regression analysis). However, SCG displaced the concentration-response curves in a parallel fashion to the right. The geometric mean (range) PC_{20} value for AMP after inhaled placebo was 10 (5–19) mg·ml^{-1}, but after SCG administered at increasing inspiratory flow rates the PC_{20} progressively increased to a maximum of 136 (30–800) mg·ml^{-1} at $\dot{V}_1$ (table 3). The PC_{20} AMP values were significantly higher than for placebo at the two highest flow rates (p<0.01) and significantly different from each other at all three flow rates (table 1). The degrees of protection against AMP-induced bronchoconstriction at $\dot{V}_1$, $\dot{V}_2$ and $\dot{V}_3$ when expressed as mean concentration ratios (PC_{20} AMP after placebo divided by PC_{20} AMP after SCG) were 12.8, 3.9 and 1.5, respectively, which differed significantly from each other (p<0.01) (table 1). Positive relationships were established between the inspiratory flow rate and the ability of the drug to protect the airways against AMP reflected by the log PC_{20} AMP (r=0.73, p<0.001) (fig. 3) and the concentration ratio for AMP (r=0.84, p<0.001). C_{max} and AUC, which are both indices of SCG absorbed from the lung, also correlated positively with the PC_{20} AMP (r=0.65, p<0.001; r=0.66, p<0.001, respectively) (fig. 4).

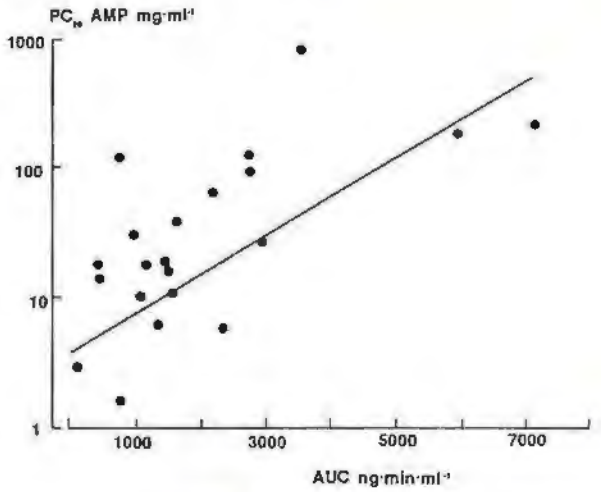

Fig. 3. – The relationship between the area under the plasma concentration-time response curve for sodium cromoglycate and the ability of the drug to protect against the bronchoconstrictor effect of inhaled adenosine 5'-monophosphate (AMP) expressed as the PC_{20}AMP (concentration of AMP required to produce a 20% fall in post-saline forced expiratory volume in one second).

Table 3. – The influence of inspiratory flow rate on the protection afforded against adenosine 5'-monophosphate

	$\dot{V}_1$	$\dot{V}_2$	$\dot{V}_3$	Placebo
Inspiratory flow rate l·min^{-1}	211±8[a]	108±3[b]	59±3[c]	–
FEV_1 (baseline)	4.2±0.4[a]	4.3±0.4[a]	4.3±0.4[a]	4.3±0.4[a]
PC_{20} AMP**	136 (30–800)[a]	40 (8–296)[b]	15 (1.6–91)[c]	10 (5–19)[c]
Concentration ratio $\left\{\frac{PC_{20}\text{ after SCG}}{PC_{20}\text{ after saline}}\right\}$	12.8 (3.6–41.7)[a]	3.9 (0.7–15.4)[b]	1.5 (0.3–6)[c]	[1][c]

Values not sharing the same superscript (a, b, or c) were significantly different from each other (p<0.05). The data are given as mean±SEM or when marked ** as geometric mean (range): FEV_1: forced expiratory volume in 1 s; PC_{20} AMP: concentration of adenosine 5'-monophosphate (AMP) required to produce a 20% fall in post-saline FEV_1; SCG: sodium cromoglycate.

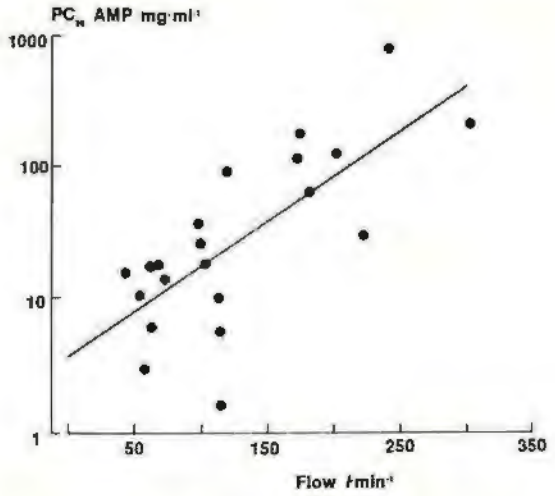

Fig. 4. – The relationship between inspiratory flow used to inhale sodium cromoglycate and the ability to protect airways against the bronchoconstrictor effect of inhaled adenosine 5'-monophosphate.

Discussion

In healthy non-asthmatic subjects we and others have shown that the plasma pharmacokinetic profile of SCG is dictated largely by its absorption from the bronchial mucosa [13–16]. The overall pharmacokinetic profile of SCG observed in mild asthmatic subjects in the present study did not differ from that reported in non-asthmatic subjects [15]. Moreover, in asthma we were able to confirm a direct relationship between inspiratory flow and total amount of drug appearing in the circulation as reflected by the area under the plasma SCG concentration-response curve (AUC). The three inspiratory flow rates used to disperse and inhale SCG differed markedly but this had no effect on the ability to empty the SCG capsule in the Spinhaler. Low inspiratory flow rates reduce the fragmentation of SCG particles on the impeller of the device and would be expected to increase the overall mass median particle diameter. Should this occur then the total quantity of drug entering the airways would decrease and there would also be more central particle deposition. In a recent study we have shown that bronchoconstriction produced more central deposition of inhaled SCG but did not affect its plasma pharmacokinetics, suggesting that the site of deposition is not important in determining the amount absorbed into the circulation [17].

The protective effect of SCG was measured against bronchoconstriction provoked by inhaled adenosine 5'-monophosphate. This form of challenge was chosen for three reasons. Firstly, available evidence suggests that AMP after *in vivo* hydrolysis to adenosine produces bronchoconstriction in asthma by augmenting the IgE-dependent release of preformed mediators such as histamine from mast cells without influencing the generation of newly formed products [19, 20, 22]. However, recent evidence suggests that AMP-induced bronchoconstriction may result from an interaction of adenosine both with airway mast cells and neurological reflex mechanisms [23] so that the ability of SCG to inhibit non-myelinated C-fibre activation [6] may also be a factor. Secondly, SCG is highly effective at blocking adenosine- and AMP-induced bronchoconstriction consistent with its action on bronchial mast cells, [20]. Thirdly, AMP may be used to provoke reproducible bronchoconstriction and therefore provide dose-response data. Unlike bronchial challenge with allergens, AMP does not cause any delayed effects such as late reactions or an increase in non-specific bronchial responsiveness [24]. By defining the position of the concentration-response curve to AMP as the PC_{20} value, it was possible to quantitate the relative protective effect of SCG delivered to the airways by inhalation through a Spinhaler at three different inspiratory flow rates. Since SCG did not alter the slope of the FEV_1 concentration-response curves when compared by covariant analysis, the protection afforded could also be expressed in terms of concentration (or potency) ratio.

In this study we have demonstrated that the inspiratory flow used to disperse SCG powder was directly related to the degree of protection that this drug afforded against AMP challenge as reflected by a progressive rightward displacement of the AMP concentration-response curve. A 4-fold reduction in inspiratory flow reduced the protective effect of inhaled SCG by a factor of 8. Since the total amounts of drug leaving the capsule were almost identical at all three inspiratory flow rates, either the total dose of SCG or its site of deposition in the lung are factors likely to have influenced its protective effect. The correlation between the AUC of SCG at the three inspiratory flow rates and the change in PC_{20} suggest that the most likely explanation for the reduced protection of the drug against AMP is reduction in the total dose delivered to the airways. However, an influence arising from different patterns of drug distribution within the lung at the different flow rates cannot be entirely excluded. The plasma pharmacokinetics of SCG are not affected by the pattern of deposition [17], and thus it is possible that the reduced protection at low inspiratory flow may be due to both a decrease in total drug entering the lungs and its more central deposition. Since AMP causes bronchoconstriction through a mast cell-dependent mechanism these observations have clinical implications. The influence of inspiratory flow on the protective effect of SCG may be particularly important in those patients whose ability to generate a good inspiratory flow is limited by airways obstruction and hyperinflation.

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Le taux d'inhalation du cromoglycate sodique détermine sa pharmacocinétique plasmatique et la protection contre la bronchoconstriction induite par l'AMP dans l'asthme. R. Richards, S. Simpson, A. Renwick, S. Holgate.

RÉSUMÉ: Nous avons cherché à préciser si le débit auquel le cromoglycate sodique est inhalé influence son efficacité. Sept sujets atteints d'asthme atopique (âge 25±2 ans) ont inhalé une poudre sèche de cromolycate sodique au moyen d'un Spinhaler à différentes occasions, à trois débits différents (débit maximum, V_1; 100 $l \cdot min^{-1}$, V_2; et 50 $l \cdot min^{-1}$, V_3). Cette inhalation a été alternée avec celle d'un placebo dans un essai structuré en double aveugle. Trente minutes après l'administration, un test de provocation bronchique au moyen d'adénosine 5'-monophosphate (AMP) a été conduit. Des échantillons pour la mesure des concentrations plasmatiques de cromoglycate sodique ont été prélevés, et la surface sous la courbe concentration plasmatique-temps a été calculée pour chaque débit. A la fois le debit inspiratoire et la surface sous la courbe, étaient significativement en corrélation avec le degré de protection à l'égard de la bronchoconstriction induite par l'AMP ($r=0.73$, $p<0.001$; $r=0.66$, $p<0.001$). Ces observations indiquent que le débit utilisé pour inhaler le cromoglycate sodique en poudre est un facteur majeur déterminant l'efficacité de cette drogue pour la protection contre une provocation bronchique. Il a donc d'importantes implications cliniques.
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