The effect of respiratory manoeuvres and pharmacological agents on the pharmacokinetics of nedocromil sodium after inhalation

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- 1 Eight healthy subjects inhaled nedocromil sodium from a metered-dose inhaler using a standardised inspiratory technique. Blood samples were taken for up to 270 min after inhalation for radioimmunoassay of plasma nedocromil sodium concentrations.
- 2 To investigate the possibility that respiratory manoeuvres can alter the absorption of the drug from the lungs, on the first (control) study day at 70 min after dosing, subjects performed nine forced expiratory manoeuvres over a 3 min period. At 110 min after dosing, subjects took a slow, full inspiration with a 30 s breath-hold, and at 150 min after dosing the subjects performed one single forced expiration.
- 3 On the second study day, subjects inhaled methoxamine, 0.15 mg kg⁻¹ of a 20 mg ml⁻¹ solution at 60 min after dosing, and the study continued as above. On the third day, subjects repeated the sequence of respiratory manoeuvres, after having taken phenoxymethyl penicillin and probenecid by mouth for 48 h.
- 4 Both multiple forced expirations and the deep inspiration with breath-hold produced significant increases in the absorption of nedocromil sodium. Inhaled methoxamine did not alter airway calibre or the response to the respiratory manoeuvres. Probenecid, but not penicillin, was detected in the subjects' plasma, and had the effect of increasing the rise in plasma nedocromil sodium concentrations after the multiple forced expirations when compared with the control day.
- 5 These data suggest that disruption of epithelial tight junctions induced by the respiratory manoeuvres leads to enhanced paracellular transport of nedocromil sodium into the draining circulation of the airways and alveoli. The effects of probenecid are consistent with the presence of a facilitated-transport mechanism for the absorption of a proportion of nedocromil sodium.

Keywords nedocromil sodium respiratory manoeuvres probenecid

Introduction

Nedocromil sodium (Tilade) is the disodium salt of a pyranoquinolone dicarboxylic acid which has been developed as an inhaled prophylactic treatment for asthma. Like sodium cromoglycate, it has a range of actions against many of the inflammatory cells implicated in the pathogenesis of airways inflammation. It inhibits the activation of mucosal-type mast cells (Leung *et al.*, 1988), eosinophils (Moqbel *et al.*, 1989), macrophages (Damon *et al.*, 1989), platelets (Thorel *et al.*, 1988) and neutrophils (Moqbel *et al.*, 1988) by preventing mediator release initiated by a range of stimuli. It also inhibits neutrophil and eosinophil chemotaxis (Bruijnzeel *et al.*, 1989). When administered by inhalation to asthmatic subjects, nedocromil

protects the airways from bronchoconstriction provoked by exercise (Shaw & Kay, 1985), allergen (Nair *et al.*, 1989), adenosine (Crimi *et al.*, 1987) and its 5'-monophosphate (AMP) (Phillips *et al.*, 1989), cold dry air (Juniper *et al.*, 1987), sulphur dioxide (Altounyan *et al.*, 1986), bradykinin (Dixon & Barnes, 1989), substance P (Crimi *et al.*, 1988) and neurokinin A (Joos *et al.*, 1988). In clinical trials, it has been found to be effective in the treatment of asthma when compared with placebo (Dorow, 1986; Fyans *et al.*, 1986) or when used as additional therapy (Bone *et al.*, 1989; Fyans *et al.*, 1989). In many of these situations, nedocromil has been compared with sodium cromoglycate and in general it exhibits greater potency.

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The pharmacokinetics of nedocromil have been studied in humans (Neale *et al.*, 1987), and are similar to those of sodium cromoglycate (Neale *et al.*, 1986). When administered by inhalation from a metered-dose inhaler or nebuliser, the plasma drug concentrations measured by radioimmunoassay (Gardner *et al.*, 1988) rise rapidly to a peak, and then decline with a half-life that is longer than the terminal elimination phase observed after steady-state intravenous infusion. Thus, when delivered to the airways the terminal half-life of nedocromil represents the absorption half-life, signifying that the quantity of drug deposited in the lungs is the major determinant of the plasma drug concentration.

Richards *et al.* (1989) showed that, during the terminal absorption rate-limited phase of sodium cromoglycate kinetics, plasma concentrations of the drug rapidly increased immediately following a forced expiratory manoeuvre, and then declined rapidly to reach the baseline value from which they departed. The inspiratory limb of its manoeuvre was shown to be responsible for this increase in drug absorption. After inhalation of nedocromil, a period of vigorous exercise performed by normal and asthmatic subjects has also been shown to increase plasma concentrations of nedocromil (Neale *et al.*, 1988). On the basis that circulating drug concentrations also increase after both exercise and forced expirations, but not after Valsalva manoeuvres, Ghosh *et al.* (1989) have suggested that the rapid absorption of nedocromil may be due to lung inflation and/or deflation rather than any change in the bronchial or pulmonary circulations.

Both sodium cromoglycate and nedocromil are hydrophilic anions with molecular weights of 512 and 415 daltons respectively. The absorption of sodium cromoglycate across rat tracheal epithelium has been shown to occur in part by a saturable carrier-mediated transport, and can be inhibited by other anionic compounds such as probenecid and penicillin, indicating some specificity for the transport process (Gardiner & Schanker, 1974). On the basis of the similar pharmacokinetics of sodium cromoglycate and nedocromil, it is possible that a similar carrier-mediated transport system also exists in the human lung for nedocromil.

To investigate these phenomena, we have studied the effects of respiratory manoeuvres on the absorption of nedocromil from the airways. Since changes in lung volume and intrathoracic pressure may change bronchial blood flow, we have also investigated the effect on the absorption of the drug of reducing bronchial mucosal blood flow using the vasoconstrictor agent, methoxamine (Modell *et al.*, 1981; Wagner *et al.*, 1987a). Finally, to investigate the possibility of competition for the transport of nedocromil across the bronchial epithelium, we have observed the effect of oral probenecid and phenoxymethyl penicillin on plasma concentrations of nedocromil.

Methods

Subjects

Eight healthy non-smoking volunteers (six male, two female) aged 18–25 years took part in the study. No

subject had a past history of respiratory disease or an upper respiratory tract infection within 4 weeks prior to the study, and none was taking any medication. All the subjects had normal baseline pulmonary function and were able to inhale nedocromil from a metered-dose inhaler correctly. The study was approved by the Southampton University and Hospitals Ethics Committee and all subjects gave their written informed consent.

Drug administration

Nedocromil sodium was supplied by Fisons plc, Pharmaceuticals Division (Loughborough, UK) as the standard commercially available preparation (Tilade). It was administered from a pressurised metered-dose inhaler (MDI) which delivered a nominal dose of 2 mg nedocromil sodium per actuation.

Subjects were taught a standardised inhalation technique to maximise the dose deposited in the lungs and to eliminate variables that may influence intrapulmonary drug deposition. It was intended to deliver the inhaled aerosol at approximately 20% of the inspired volume. This was achieved using an electronic spirometer (Vitalograph Compact, Vitalograph, Bucks, UK) modified so as to display inspiratory flow rate on-screen during inhalation, coupled with a solenoid-actuated piston which, when activated remotely, depressed the MDI canister to deliver the aerosol to the subject. The pneumotachygraph of the Vitalograph was connected to the housing within which the MDI was contained, so that inspiration through the MDI mouthpiece produced a signal on the Vitalograph screen (Figure 1). A cross

Figure 1 A diagram of the apparatus used for inhalation. The Vitalograph Compact displays inspiratory flow rate on-screen during inhalation, and is coupled with a solenoid-actuated piston which, when activated remotely, depresses the metered dose inhaler canister to deliver the aerosol to the subject. The pneumotachygraph of the Vitalograph is connected to the housing within which the metered dose inhaler is contained, so that inspiration through the metered dose inhaler mouthpiece produces a signal on the Vitalograph screen.

was displayed on the inspiratory flow trace when the aerosol was fired. Subjects inhaled slowly from residual volume to total lung capacity at a flow rate of 30–45 l min⁻¹, followed by a 10 s breath-hold at the end of inspiration. The MDI was actuated remotely when inspiratory flow had reached the required rate. Subjects were taught to achieve this within 2 s of the start of inspiration. Inspiratory training and aerosol actuation were performed by the same researcher on every occasion. After each inhalation, the Vitalograph Compact printed out the following parameters: peak inspiratory flow during inhalation (PIF), time of firing (t_f), inspiratory flow rate at the time of aerosol firing (IF_f), total inspiratory volume (V_I), inspired volume at the time of aerosol firing (IV_f), the inspired volume at firing expressed as a percentage of total inspired volume (IV%), and breath-holding time (BHT).

Blood sampling and drug analyses

Blood samples were taken from an indwelling Teflon catheter inserted into a forearm vein before and at various times after drug administration. The cannula was kept patent by the use of 0.9% w/v sodium chloride. Blood (30 ml) was withdrawn prior to drug inhalation, and plasma from this was used to construct the nedocromil radioimmunoassay standard curve. After dosing, blood samples were taken and transferred to glass lithium-heparin tubes. The samples were centrifuged at 3000 g for 10 min and the plasma separated and stored at -20° C for subsequent drug assay. Plasma concentrations of nedocromil were assayed by a double antibody radioimmunoassay (Gardner *et al.*, 1988). All samples were analysed in quadruplicate, with a quadruplicate standard curve containing 0, 0.25, 0.5, 1.0, 1.5, 2, 3, 4, 6, and 8 ng ml⁻¹ nedocromil. All of the samples collected in one study day from an individual subject were analysed as a single batch with a standard curve prepared from the predose plasma from that subject. The 0.25 ng ml⁻¹ standard was measurable in most analyses, but for some the limit of measurement was 0.5 ng ml⁻¹. The mean intra-assay coefficient of variation for samples was $\pm 9.6\%$ at 0.8 ng ml⁻¹ or $\pm 4.9\%$ at 5.3 ng ml⁻¹.

Study design

The study involved three visits to the department. Subjects were rested throughout the study. On a preliminary visit, they were trained to inhale nedocromil from a MDI using the technique described. The first study day was conducted to investigate the effect of respiratory manoeuvres on the absorption of nedocromil, and was also a control day for comparison with subsequent visits. The sequence of manoeuvres was not randomised because the primary objective was not to define the most sensitive method of altering plasma concentrations, but to study any influence of methoxamine and penicillin on the apparent change in airways permeability produced by such manoeuvres. Nedocromil was inhaled, and blood samples were taken at 5 min intervals for 20 min, and then at 10 min intervals until 70 min after inhalation. Subjects then performed nine consecutive forced expiratory volume in one

second (FEV₁) manoeuvres over a 3 min period using a dry wedge-bellows spirometer (Vitalograph), and blood sampling continued at 73, 76, 80, 90, 100, and 110 min. At 110 min, subjects took one deep inspiration from functional residual capacity (FRC) to total lung capacity (TLC), and held their breath for 30 s with the glottis and larynx open. Blood sampling continued at 113, 116, 120, 130, 140, and 150 min. At 150 min a single FEV₁ was performed and blood samples were taken at 153, 156, 160, 165, 170, 180, 200, 220, 240 and 270 min.

On the second visit this sequence of events was repeated. However, at 60 min after drug inhalation volunteers were given methoxamine, a potent bronchial vasoconstrictor (Dinh Xuan *et al.*, 1989). A solution of methoxamine in 0.9% w/v sodium chloride at a concentration of 20 mg ml⁻¹ was nebulised using a dosimeter in order to deliver 1.46 mg methoxamine for each inspiration; the delivered dose was 0.15 mg kg⁻¹ body weight (Dinh Xuan *et al.*, 1989). The methoxamine aerosol was generated by a disposable Inspiron Mini-nebulizer (CR Bard International, Sunderland, UK) driven by compressed air at a pressure of 20 lb/in² and at a flow rate of 8 l min⁻¹. Under these conditions, the nebulizer produces an aerosol with a mass median aerodynamic diameter of 6.3 μ m and a geometric standard deviation of 1.73 (Newman *et al.*, 1986). The subjects were instructed to take the appropriate number of breaths consecutively from FRC to TLC via a mouthpiece. The study was then conducted as for the second visit. After the nine FEV₁ manoeuvres, the best value for each subject was recorded for comparison with the value recorded before methoxamine inhalation.

Prior to the third visit, subjects were orally premedicated for 2 days with probenecid (500 mg 8 hourly) and penicillin (500 mg 6 hourly). Six hours after the last dose, nedocromil was administered. Blood samples were taken and respiratory manoeuvres were again performed at the appropriate times, as in visit 2. Prior to the beginning of this study, blood was taken for probenecid and penicillin assay (Rumble & Roberts, 1985).

Data analyses

The data are presented as the mean $\pm$ s.e. mean except where indicated. Differences between paired data were analysed using Student's *t*-test except where indicated, and the null hypothesis rejected if $P < 0.05$. To ensure that drug inhalation on the different study days was similar, the mean values for the various inspiratory parameters were compared. FEV₁ values before and after methoxamine inhalation were compared to assess the effect of this drug on airway calibre.

The time course of plasma concentrations of nedocromil after drug administration was analysed by deriving the area under the plasma concentration-time curve (AUC) for the study period (0–270 min) using the linear trapezoidal rule. The initial maximal plasma concentration ($C_{\max}$) and the time taken to achieve this ($t_{\max}$) are given as the observed values, and compared between study days.

To assess the effect of each manoeuvre the AUC for the whole plasma drug concentration-time curve was first calculated. The curve was then manipulated to

delete the three points immediately following the manoeuvre which encompassed any increase in area resulting from the rise in plasma nedocromil, and the AUC recalculated. The difference between the two AUC values was compared by Wilcoxon's matched-pairs signed rank test. The change in AUC produced by each manoeuvre was also expressed as a percentage of the total AUC. For example, to assess the effect of the nine FEV₁ manoeuvres the total AUC was calculated, the three points following the nine FEV₁s were deleted and the AUC recalculated. The same procedure was followed for the other two manoeuvres. The effect of probenecid on the pharmacokinetics of nedocromil was assessed by comparing the AUC for the whole curve with that from the control visit. The change in AUC after each manoeuvre was also compared across study days.

Results

All subjects completed the study. There were no differences when the inspiratory parameters for inhalation of nedocromil were compared between study days (Table 1). Methoxamine inhalation did not change airway calibre, the mean ($\pm$ s.e. mean) FEV₁ before and after methoxamine being 4.74 ± 0.19 and 4.78 ± 0.22 l respectively. All subjects had measurable levels of probenecid in their plasma (39, 42, 54, 39, 56, 60, 49 and 72 mg l⁻¹ respectively for subjects 1–8); however, penicillin concentrations were below the limit of detection of the assay.

Figure 2 shows the plasma drug concentration-time curves for each subject on the first (control) study day. Plasma nedocromil concentration rose rapidly to a peak in all subjects, and no differences were found between study days when $C_{\max}$ and $t_{\max}$ were compared. The peak value was always achieved within 20 min and usually within 10 min of inhalation. Thus, $C_{\max}$ was 4.12 ± 0.76 ng ml⁻¹ on the first day, 3.77 ± 0.59 ng ml⁻¹ on the methoxamine day, and 5.26 ± 1.34 ng ml⁻¹ on the probenecid day, and $t_{\max}$ was 8.75 ± 2.06 , 10.63 ± 2.20 and 8.75 ± 1.83 min, respectively. Plasma nedocromil concentrations rose rapidly after all respiratory manoeuvres in all subjects, except in one subject (no 5 at 150 min), and returned to the value from which it departed within 3 or 4 time points after the manoeuvre. It was also apparent that plasma nedocromil concentrations rose spontaneously at times not associated with a respiratory manoeuvre, and most usually toward the end of the study period (e.g. subjects 3, 4 and 6,

Figure 2). In some cases, individual plasma drug concentrations were grossly and spuriously elevated with no obvious cause at isolated time points. For example, the plasma nedocromil concentration at 165 min in subject 3 on day 1 was > 11 ng ml⁻¹, whereas the values immediately before and after this were 0.305 and 0.265. Such gross elevations were infrequent, occurring at only 11 single time points out of a total 768 samples, and could be due to contamination. Such values were deleted before analysis.

The median (range) total AUC on the first study day was 365 (52–774) ng ml⁻¹ min (Table 2). The changes produced by the respiratory manoeuvres reached statistical significance for both the multiple forced expirations and the breath-hold, but not for the single forced expiration. Thus, on the control day, the median total AUC was 365 as compared to 355 ng ml⁻¹ min after deletion of the rise due to the multiple forced expirations ($P = 0.05$) and 363 ng ml⁻¹ min after deletion of the rise due to the breath-hold ($P = 0.037$).

Neither methoxamine nor probenecid significantly altered the total AUC for nedocromil. On the methoxamine day, the AUC values were 387 ng ml⁻¹ min for the total AUC, 381 after the forced expirations ($P = 0.036$) and 383 after the breath-hold ($P = 0.012$); on the probenecid day they were 388 for the total AUC, and 377 and 383 respectively ($P = 0.012$ for both).

When the change in AUC produced by each manoeuvre was expressed as a percentage of the total AUC, and compared across study days, significant differences were found (Table 2). The median change after the multiple manoeuvres on the third (probenecid) day was 2.86%, as compared with 1.74% on the first day ($P = 0.017$) and 1.50% on the methoxamine day ($P = 0.036$).

Discussion

This study has confirmed that both multiple forced expirations and a single slow deep inspiration with a breath-hold can produce significant rises in plasma nedocromil concentrations. A single forced expiration produced small changes in plasma nedocromil levels in some but not all subjects and which did not reach significance. The prior inhalation of methoxamine had no effect on the subsequent rise in plasma nedocromil after multiple forced expirations, and did not alter airway calibre. However, while premedication with oral probenecid did not alter the total AUC, $C_{\max}$ or

Table 1 Indices measured during inhalation of nedocromil sodium on the 3 study days

	No treatment	Methoxamine	Probenecid
Breath holding time (s)*	10.8 (0.3)	10.7 (0.2)	10.8 (0.2)
Inspired volume (l)	4.6 (0.2)	4.6 (0.2)	4.5 (0.2)
Peak inspiratory flow (l min ⁻¹)	50.7 (1.9)	47.7 (1.5)	49.0 (2.0)
Time of actuation (s)	1.5 (0.07)	1.5 (0.04)	1.5 (0.07)
Inspired volume at actuation (l)	0.93 (0.05)	0.92 (0.05)	0.89 (0.04)
Flow rate at actuation (l min ⁻¹)	41.1 (1.8)	37.8 (1.5)	38.3 (1.6)
Inspired volume at actuation (%)	20.3 (1.0)	20.4 (1.2)	20.1 (0.9)

* Mean (s.e. mean) for eight subjects.

Figure 2 Plasma nedocromil sodium concentrations in all subjects on the first day. The three arrows indicate the times at which the inspiratory manoeuvres were performed. The first arrow (70 min) indicates nine FEV₁ manoeuvres, the second arrow (110 min) indicates a full inspiration with a 30 s breath-hold, and the third arrow (150 min) indicates a single FEV₁.

Table 2 Plasma nedocromil sodium pharmacokinetics on the 3 study days

	<i>No treatment</i>	<i>Methoxamine</i>	<i>Probenecid</i>
AUC whole study (ng ml ⁻¹ min)	365* 52-774†	387 166-748	388 89-1889
AUC whole study minus the increase after nine FEV ₁ (ng ml ⁻¹ min)	355 50-769	381 163-753	377 86-1794
AUC whole study minus the increase after deep inspiration and breath-hold (ng ml ⁻¹ min)	363 50-764	383 166-740	383 87-1866
AUC whole study minus the increase after one FEV ₁ (ng ml ⁻¹ min)	366 51-774	386 166-748	386 90-1880
Change in AUC after nine FEV ₁ (% of total AUC)	1.74 -2.58-3.37	1.50 -0.69-3.36	2.86 0.73-5.65
Change in AUC after deep inspiration and breath-hold (% of total AUC)	1.30 -0.68-4.43	0.95 0.12-3.17	1.20 0.1-2.19
Change in AUC after 1 FEV ₁ (% of total AUC)	0.12 -0.35-1.10	0.235 -0.05-0.78	0.29 -1.22-0.98

Median* and range for eight subjects.

$t_{\max}$, a larger rise was seen in plasma nedocromil after multiple forced expirations when compared with the same manoeuvre on the other 2 study days. The failure to measure penicillin in any of the subjects' plasma is due to the time delay between dosing and blood collection. The effects of simple respiratory manoeuvres on plasma concentrations of nedocromil sodium are consistent with the fact that absorption from the airways is the rate limiting step in determining the plasma kinetics of this drug and that the facilitated transport mechanism contributes at least to some of this absorption.

These findings confirm those of Richards *et al.* (1989) for sodium cromoglycate and those of Ghosh *et al.* (1988) for nedocromil, in that both studies found significant rises in plasma drug concentrations with multiple forced expirations, although only Richards *et al.* (1989) reported the effects of a deep inspiration and breath-hold. Our current findings also indicate that it is the inspiratory limb of the manoeuvre which is responsible for the rapid increases in plasma drug concentration. We have recently shown that using the same inhalation technique applied to a radiolabelled aerosol of nedocromil and by use of single photon emission computed tomography combined with X-ray computed tomography, that 50% of the drug reaching the lungs is in the outer 3 of 10 concentric shells (Summers *et al.*, 1992). Thus any rapid changes in absorption as a consequence of respiratory manoeuvres is most likely to involve the lung periphery. This most likely produces a widening of epithelial intercellular junctions, and hence a more rapid paracellular transit of the drug into the bronchial vasculature. Other possible explanations include a thinning of the airway or alveolar lining fluid with deep inspiration facilitating more rapid absorption of drug, movement of drug to more peripheral sites with a greater surface area and/or different absorption characteristics, and changes induced in the bronchial or pulmonary circulation.

There is abundant evidence that lung stretching can give rise to increased absorption of substances across the lung. Egan (1980) showed that alveolar pore radii increased with lung inflation in dogs, and that there was a concomitant increased passage of solutes across the lung. Both Nolop *et al.* (1986) and Marks *et al.* (1985) reported that increases in lung volume accelerated the clearance of Tc^{99m} -DTPA from the lung, and Dusser *et al.* (1986) reported increased clearance of Tc^{99m} -DTPA from the upper lobes compared with the lower lobes in the upright posture, a situation in which the upper lobes are stretched because of gravity. Lorino *et al.* (1989) provided further evidence that lung stretch is the most likely cause of this phenomenon by documenting an increase in lung permeability 30 min after maximal exercise, at a time when any possible exercise-induced changes in blood flow or thickness of the airways or alveolar lining fluid would have resolved.

The finding that premedication with probenecid did not alter the plasma concentrations of nedocromil or the total absorption of the drug but did result in greater absorption with multiple forced expirations adds support to our view that the increases in absorption relate to an airway or alveolar surface phenomenon. Probenecid will inhibit only that part of sodium cromoglycate absorption that is dependent upon active

carrier-type transport (Gardiner & Schanker, 1974), and because nedocromil has almost identical pharmacokinetics it is likely that a similar mechanism exists for this drug. Both sodium cromoglycate and nedocromil are hydrophilic anions, and thus are likely to cross the respiratory mucosa through the paracellular pathway (Gumbiner, 1987), the absorptive pathway likely to be affected by stretch-induced disruption of epithelial tight junctions. The greater increase in plasma nedocromil after the multiple forced expirations following probenecid may be a consequence of that fraction of drug absorption through the transcellular route being retarded, resulting in more drug being available at the mucosal surface for paracellular transport. This is the first evidence for a probenecid-sensitive facilitated transport mechanism for a drug in the human lung.

The selective α -adrenoceptor agonist, methoxamine, when inhaled prior to the multiple forced expirations did not affect the subsequent increases in plasma nedocromil. Methoxamine was used because of its potent vasoconstrictor effect on the bronchial vasculature. The dose selected (0.15 mg kg^{-1}) was chosen because it had been shown to attenuate exercise-induced asthma, a response in asthmatic airways thought in part to be due to post-exertional airway rewarming and rebound vasodilatation (Dinh Xuan *et al.*, 1989). However, methoxamine may have a direct effect on airway calibre in asthma in causing bronchoconstriction (Snashall *et al.*, 1978), although like others (Black *et al.*, 1982; Snashall *et al.*, 1978) we have failed to find any such effect in normal subjects.

Since we have failed to show any effect of methoxamine on the absorption of nedocromil, we consider it is likely that the mucosal circulation contributes little to the absorption characteristics of nedocromil, the rate limiting step being epithelial transport. Although the dose of inhaled methoxamine was selected to produce mucosal vasoconstriction, it is not possible to exclude any effect on the bronchial circulation being at least partially responsible for the enhanced absorption resulting from respiratory manoeuvres. Wagner & Mitzner (1990) have shown that dramatic reductions in the bronchial blood flow in sheep has the effect of delaying recovery from methacholine-induced bronchoconstriction, suggesting that the bronchial circulation does play an important role in clearing the agonist from the airways, and it was anticipated that methoxamine might have produced a similar effect. However, the respiratory manoeuvres may have other effects on the bronchial circulation which would obviate the influence of methoxamine. Thus, Baile *et al.* (1984) have shown that high levels of positive end-expiratory pressure induced an increase in broncho-pulmonary anastomotic blood flow, and Wagner *et al.* (1987a) have shown that increases in airway pressure not only reduce mucosal blood flow but increase flow into the pulmonary circulation. The same group has further (Wagner *et al.*, 1987b) studied the 'paralysed' bronchial circulation in order to exclude neural- or mediator-induced changes in vessel calibre after lung inflation, and found that blood flow changes occurred irrespective of the presence of the paralysing agent. This work suggests that inflation-induced bronchovascular changes are due to mechanical factors. This may be due

to stretching of vessels, with narrowing and lengthening, or to compression of vessels, or to both, as changes in blood flow can occur both with increases in lung volume at constant transpulmonary pressure and increases in transpulmonary pressure at constant lung volume (Modell *et al.*, 1981). Thus the manoeuvres performed in this study may have diverted blood flow away from the mucosa to the pulmonary circulation, but if so it is difficult to see how this diversion of blood flow should be followed by rises in nedocromil in the peripheral circulation unless the drug was simultaneously drawn into the alveolar compartment.

In conclusion, we have shown that multiple forced expirations and deep inspiration with a prolonged breath-hold produce a rapid increase in plasma concentrations of nedocromil, a phenomenon which is

enhanced by therapeutic concentrations of probenecid. These findings can be best explained by nedocromil being rate-limited in its absorption from the lung, involving both para- and transcellular pathways. It is possible that similar environmental influences such as exercise can occur during daily life, and will therefore influence the rate of absorption of the drug. What is now clearly needed is a careful evaluation of whether such manoeuvres influence a drug's protective efficacy as indicated by at least one study (Schoeffel *et al.*, 1981).

We thank Fisons plc for financial support of Q. Summers and R. Honeywell, and for supply of the materials for the nedocromil radioimmunoassay. Mr A. Tuck and Dr R. Lowes performed the probenecid assays, and Mr Ian Shuttlewood and Mr Philip Hemes of Vitalograph Ltd kindly provided the Vitalograph Compact.

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(Received 22 March 1991,
accepted 10 December 1991)