Deep inspiration increases the absorption of inhaled sodium cromoglycate

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The plasma concentrations of sodium cromoglycate were measured for 4 h following a single dose of 20 mg given by inhalation to six normal volunteers. A series of forced expiratory manoeuvres was performed 2 h after the dose, which resulted in a rapid and marked increase in the plasma concentrations of the drug. A similar increase was found in three volunteers who undertook a single deep inspiration at 4 h. These data indicate that the absorption of cromoglycate from the airways can be affected by manoeuvres used to assess lung function.

Keywords cromoglycate deep inspiration plasma pharmacokinetics

Introduction

Inhaled sodium cromoglycate (SCG) is an effective prophylactic therapy for the treatment of asthma. When given by inhalation from a Spinhaler® plasma concentrations of the drug rise rapidly to reach a peak at 3–20 min followed by a gradual decline with a terminal half-life of 90–150 min (Richards *et al.*, 1987). When infused intravenously the terminal plasma half life of SCG is approximately 33 min indicating that the plasma pharmacokinetics following inhalation are limited by absorption from the airways (Fuller & Collier, 1983; Neale *et al.*, 1986; Richards *et al.*, 1987). Little is known about the transport of SCG across the bronchial epithelium or factors which can influence this process, although in rodents there is some evidence for a selective transport across the respiratory epithelium.

Clinical studies investigating the short and long term efficacy of SCG in asthma usually employ tests involving forced expiration to assess changes in airway calibre, such as the forced expiratory volume in one second (FEV₁) and the peak expiratory flow rate (PEFR). The permeability of the lung to highly water soluble radiolabelled ionic probes such as diethylene-triamine pentaacetate (^{99m}Tc-DTPA), which has a molecular weight of 497 daltons and an

isoelectric point of 1.4, has been shown to increase with mechanical forces (O'Brodivich & Coates, 1987). The possibility exists that mechanical contortions that occur with forced expiratory manoeuvres may also alter the permeability of the lung to inhaled SCG (molecular weight = 512 daltons, isoelectric point 2.0). To investigate this we have observed the effect of serial forced expiratory manoeuvres on the plasma pharmacokinetics of inhaled SCG.

Methods

Six healthy volunteers (five male, one female) aged 25–34 years who were all non-smokers took part in the study. No subject had an upper respiratory tract infection within 4 weeks prior to the experiment, and none was taking any medication. The study was approved by the Southampton University and Hospital Ethics Committee, and all subjects gave their informed consent.

The subjects inhaled 20 mg of dry powder sodium cromoglycate (Intal® spincaps) from a Spinhaler® (Fisons Ltd, Loughborough, Leics, U.K.). They were instructed to inspire from residual volume (RV) to total lung capacity

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(TLC) as quickly as possible so that the maximum amount of SCG was delivered to the lungs (Richards *et al.*, 1987, 1988c). Venous blood (5 ml) was taken via an indwelling antecubital teflon cannula before and at 5, 10, 15, 20, 40, 60, 80, 100 and 120 min after drug inhalation. At the 120 min time point subjects were asked to undertake three consecutive FEV₁ manoeuvres within 1 min using a dry wedge spirometer (Vitalograph®, Buckingham, UK). Each manoeuvre involved inspiration to TLC followed by forced expiration to RV; further blood samples were taken at 2 and 4 min following the last manoeuvre. The FEV₁ manoeuvres and blood sampling were repeated on three further occasions at 125, 130 and 135 min after the initial inhalation of SCG. Subsequent blood samples were taken at 140, 145, 150, 160, 180, 200, 220 and 240 min. At 240 min three of the subjects were asked to inspire slowly and fully to TLC maintaining this deep breath hold for 30 s with their glottis and larynx open, followed by a slow controlled expiration to functional residual capacity. Further blood samples were taken at 2 and 4 min after this manoeuvre.

The blood was transferred to glass lithium heparin tubes and the plasma was separated by centrifugation and stored at -40° C. Concentrations of SCG in plasma were measured using a specific radioimmunoassay (Brown *et al.*, 1983) with a detection limit of 0.7 ng ml⁻¹ as described previously (Richards *et al.*, 1987).

The area under the plasma SCG concentration-time curve (AUC) was calculated by trapezoid integration between 0 and 240 min. The increase in AUC arising from the FEV₁ manoeuvres was determined by subtracting the area calculated using the values between 0 and 120 min and at 220 and 240 min only. The terminal plasma half-life of SCG was calculated by least squares regression analysis of the log plasma concentrations values from 30–120 min and at 220 and 240 min.

The data are expressed as mean ± s.e. mean except where indicated. The linearity of the relationship between baseline FEV₁ and percentage increase in plasma SCG was analysed by least squares regression. Differences between plasma SCG concentrations were analysed by Student's *t*-test for paired data. Maximum plasma concentrations of SCG (*C*_{max}) and the time to maximum (*t*_{max}), are the observed values.

Results

Inhalation of SCG was followed by a rapid rise in plasma concentrations reaching a *C*_{max} of 42.5 ±

9.6 ng ml⁻¹ at a *t*_{max} of 11 ± 1 mins (Table 1, Figure 1). This was followed by a slow decline with a terminal *t*_{1/2} of 86 ± 5 min, which is in accordance with the absorption-limited pharmacokinetics reported previously. Plasma SCG concentrations increased within 4 min of the FEV₁ manoeuvres at 120 min in all subjects to a mean of 79 ± 25% above the 120 min value (*P* < 0.01) and was maintained throughout the remaining manoeuvres (maximum increase 99 ± 30% above the 120 min value). The plasma SCG concentrations then declined rapidly so that by about 180 min the concentrations were similar to those predicted by log-linear extrapolation of the data for 30–120 min. In subject 3 the FEV₁ manoeuvres were interrupted and had to be restarted after a 20 min rest period. Two separate increases in plasma concentrations of SCG occurred corresponding to each set of FEV₁ manoeuvres (Figure 1). For the whole group the baseline FEV₁ correlated with the percentage increase in plasma concentrations of SCG due to the forced expiratory manoeuvres when assessed by either the increase in plasma concentration (*r* = 0.931, *P* < 0.01) or the AUC as a percentage of the total AUC (*r* = 0.882, *P* < 0.02) (Table 1).

The increase in plasma SCG following the deep inspiratory manoeuvres at 240 min is also displayed in Figure 1. In the three subjects (numbers 4, 5, 6), who performed deep inspiration, the plasma concentrations increased within 4 min to an extent similar to that observed 4 min after the start of the FEV₁ manoeuvres (202 vs 152%, 41 vs 31% and 27 vs 33%, respectively).

Discussion

The initial plasma concentration-time profile of SCG administered by inhalation was similar in this study to that previously reported for both normal (Richards *et al.*, 1987) and asthmatic subjects (Richards *et al.*, 1988c) although the maximum concentrations were higher and similar to those reported by Neale *et al.* (1986). In the present study we have shown that a forced expiratory manoeuvre is sufficient to increase greatly the absorption of SCG from the airways into the systemic circulation and that deep inspiration is the major determinant of this effect. Neale *et al.* (1986) have reported that absorption of SCG from the airways involves two different rates. It is possible that the initial rapid phase of SCG absorption that they have observed may have resulted from inspiratory manoeuvres prior to or at the time of SCG inhalation.

Table 1 The influence of respiratory manoeuvres on the pharmacokinetics of sodium cromoglycate

Subject	FEV ₁ (l)	Initial peak		AUC(0,240) (ngml ⁻¹ min)	Half-life ¹ (min)	Peak after FEV ₁ manoeuvres at 120 min		Peak after deep inspiration at 240 min	
		C _{max} (ng ml ⁻¹)	t _{max} (min)			C ₁₂₀ (ng ml ⁻¹)	C _{peak} (ng ml ⁻¹)	C ₂₄₀ (ng ml ⁻¹)	C _{peak} (ng ml ⁻¹)
1	6.2	13.65	10	1982	88	6.15	17.80	—	—
2	4.2	42.20	15	4786	106	16.02	29.60	—	—
3	4.5	85.58	10	8779	75	26.94	40.75	—	—
4	5.8	39.20	15	5657	77	17.70	52.20	5.70	17.20
5	3.8	35.60	7	4408	80	16.10	22.90	5.10	7.20
6	2.9	38.50	10	4874	90	19.25	25.60	6.95	8.85
Mean	4.6	42.46	11	5081	86	17.03	31.48	5.92	11.08
s. e. mean	0.5	9.60	1	898	5	2.73	5.21	0.54	3.10

C-plasma drug concentration

t-time;

1 calculated omitting the peaks produced by respiratory manoeuvres, i.e. using data for 30–120, 220 and 240 min only

2 calculated as $\frac{C_{120}}{C_{peak} - C_{120}} \times 100$ or $\frac{C_{240}}{C_{peak} - C_{240}} \times 100$

3 calculated from the AUC for the complete data to 240 min and the AUC derived omitting the peaks produced by FEV₁ manoeuvres i.e.

$$\frac{AUC^{(0-240)} - AUC^{(0-120; 220-240)}}{AUC^{(0-240)}} \times 100$$

Figure 1 Plasma concentration-time curves for sodium cromoglycate in volunteers given a single dose of 20 mg via a Spin-haler. All subjects undertook a series of FEV₁ manoeuvres starting at 120 min after the dose and three subjects (4, 5 and 6) undertook a deep inspiration at 240 min after the dose. The times of FEV₁ manoeuvres are indicated by arrows.

The rapid increase in SCG absorption following repeated FEV₁ manoeuvres confirms that passage through the bronchial mucosa is the rate limiting step determining the plasma concentrations of this drug rather than its clearance from the circulation. The mechanism by which a forced expiratory manoeuvre accelerates SCG transport most likely relates to either mechanical distortion of the absorption sites within the airways or drug displacement to a more distal absorption site with different characteristics, e.g. the alveoli, since almost an identical change in plasma drug kinetics was observed with deep inspiration only. An increase in the surface area available for SCG absorption within the airways seems less likely to explain the accelerated absorption of SCG since we have shown previously that the pharmacokinetics of SCG are independent of the extent or site of drug deposition within the lung (Richards *et al.*, 1987, 1988b). Rizk *et al.* (1984) have reported that the bronchial blood flow is not an important factor in determining the absorption of polar drugs into the canine circulation. Marks *et al.* (1985) found that the absorption of ^{99m}Tc-DTPA is accelerated ex-

ponentially by increases in lung volume. It has also been shown that increases in absorption are limited to low molecular weight solutes (Egan 1980, 1982). The nature of the rapid absorption sites within the airways is not known but conceivably could be the opening of gap junctions, since inhaled histamine has also been shown to accelerate SCG absorption and opens epithelial gap junctions (Richards *et al.*, 1988a).

Nedocromil sodium is another disease-modifying drug used in the treatment of asthma which is also absorbed slowly from the bronchial mucosa (Neale *et al.*, 1987). After inhalation of an aqueous aerosol a period of vigorous exercise has been shown to increase plasma drug concentrations (Neale *et al.*, 1988). Hyperventilation with increased tidal volume during the exercise task will have a similar effect of 'stretching' the lung and as a consequence reveal more sites for the rapid absorption of drug. In addition the protocol used in their study involved repeated measurements of FEV₁ after drug administration which alone could have accounted for increased drug absorption.

There are important conclusions that can be

drawn from this study. The absorption of drugs from the bronchial epithelium is subject to mechanical influences produced by deep inspiration. In patients using SCG therapeutically repeated forced expiratory manoeuvres may accelerate removal of drug from the airways and therefore diminish the duration of its effect. When relating plasma drug concentrations of

SCG to clinical efficacy care should be taken to remove samples of venous blood prior to the patient undertaking inspiratory or forced expiratory manoeuvres. The influence of inspiratory manoeuvres on the absorption of other bronchoactive drugs is a factor which clearly deserves further study.

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