Plasma concentrations of sodium cromoglycate given by nebulisation and metered dose inhalers in patients with exercise-induced asthma: relationship to protective effect

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Plasma sodium cromoglycate (SCG) concentrations were measured in 11 patients at regular intervals before and after exercise in a double-blind study to assess the protective effect in exercise-induced asthma (EIA) of 2, 10 and 20 mg SCG aerosol and placebo, and (on an open basis) nebulised SCG (10 g l⁻¹). There was a dose related increase in plasma concentration and AUC (0–1 h) with the aerosol formulations; values with nebulised SCG were significantly higher than with any aerosol dose. Protection from EIA increased to a maximum of 66% at plasma concentrations of 4 ng ml⁻¹ and above. Thus measurement of plasma concentration can allow a comparison to be made between the protective effects of SCG following different methods of inhalation. It is important to note, however, that plasma concentration *per se* is almost certainly not related directly to protective effect.

Keywords exercise asthma plasma sodium cromoglycate

Introduction

Sodium cromoglycate (SCG) has been shown to inhibit exercise-induced asthma (EIA) when given using a Spinhaler® device, nebuliser or metered dose inhaler.

Studies comparing inhaled dry powder with nebuliser solution and with metered dose inhalers are difficult to interpret because the dose of the drug and the site at which it is deposited in the airways may vary with different methods of administration. As SCG is relatively poorly absorbed from the mucosa of the mouth and gastrointestinal tract (Moss *et al.*, 1971; Walker *et al.*, 1972) the concentrations of the drug in the plasma reflect the absorption from the pulmonary epithelium (Brown *et al.*, 1981).

During a double-blind comparison of the effects on EIA of 2, 10 and 20 mg SCG aerosol and placebo, and nebulised SCG (10 g l⁻¹) on an open basis, plasma concentrations of the drug were measured at regular intervals before and after exercise, using a sensitive radioimmuno-

assay. The dose-response effect has already been reported (Tullett *et al.*, 1985). The present study concerns the plasma concentrations of SCG and their relationship to protective effect.

Methods

Eleven patients aged 19–51 (mean 32 years) with extrinsic and exercise asthma were studied. The patients demonstrated at least 40% protection from exercise asthma with 1 ml nebulised SCG (10 g l⁻¹). Details of the patients and the exercise test method have already been described (Tullett *et al.*, 1985).

The effect of SCG nebuliser solution (10 g l⁻¹) was studied first, the estimated dose nebulised being 12 mg (Patel *et al.*, 1982). Then in randomised double-blind fashion, using a placebo aerosol and aerosols delivering 1 mg and 5 mg SCG per shot, each patient inhaled four puffs

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from two identical-looking inhalers (two puffs from each), 30 min before exercise. The doses of SCG administered were 2, 10 and 20 mg.

An indwelling venous catheter was introduced into the antecubital vein following infiltration with local anaesthetic (1% lignocaine). Venous samples (5 ml) were drawn into heparinized syringes before treatments and 5, 15, 30, 45 and 60 min after dosing. The blood samples were centrifuged immediately, and plasma was separated and stored at -20°C until analysed. The plasma concentrations of SCG were determined using radioimmunoassay (Brown *et al.*, 1983).

Results

The effect of SCG aerosol on EIA was dose related, i.e. protection increased from 2–20 mg. Nebulised SCG gave similar protection to 20 mg aerosol (Tulleit *et al.*, 1985).

Mean plasma concentrations of SCG for the various treatments are illustrated in Figure 1. The mean peak plasma concentrations (C_{max} (s.e. mean) with 2, 10 and 20 mg aerosol were 1.3 (0.2), 3.4 (0.9), and 6.2 (1.1) ng ml^{-1} , respectively. C_{max} increased in a dose related manner with the aerosol preparations, with a significant linear correlation between C_{max} and dose ($r = 0.56$, $P < 0.001$, Student's *t*-test). Mean areas under the curves (AUC) (0–1 h) with 2, 10 and 20 mg SCG aerosol were 0.75 (0.11), 2.20 (0.39) and 4.41 (0.82) $\text{ng ml}^{-1} \text{ h}$, respectively. The highest values were observed with nebulised SCG, with mean C_{max} 14.2 (1.6) ng ml^{-1} and mean AUC 9.69 (1.30) $\text{ng ml}^{-1} \text{ h}$.

The plot of mean response (% protection relative to placebo) and mean plasma concentration at 30 min after dosing (Figure 2) showed that the protection increased with plasma con-

Figure 1 Mean plasma concentrations of sodium cromoglycate in patients after different treatments (● nebuliser, ▼ 2 by 1 mg, ○ 2 by 5 mg and ▲ 4 by 5 mg).

Figure 2 The relationship of the mean percentage protection ($\pm$ s.e. mean) and 30 min plasma concentration ($\pm$ s.e. mean) of SCG in 11 patients with exercise asthma.

centration to reach a maximum of 66% at plasma concentrations above about 4 ng ml^{-1} .

Discussion

Although a sensitive assay for measuring plasma SCG has been available for about 3 years, this is the first study which relates SCG plasma concentration to protection observed in a challenge experiment.

The inclusion of nebuliser solution and the measurement of plasma concentrations allow the dose-response curve to be extended in the form of a plasma concentration-response curve, which reached a maximum around 66% protection (Figure 2). A semilog transformation of this curve gave a typical sigmoid pattern, although more points would be needed for a definitive fit.

Since plasma concentrations are related to absorption, our results indicate that in the present study more than twice as much SCG was absorbed after the nebulised dose than after the 20 mg aerosol dose. The greater absorption with nebulisation may possibly relate to smaller particle size and low inspiratory flow rates at tidal breathing giving deeper penetration and better absorption through the pulmonary epithelium (Dolovich *et al.*, 1979). In contrast, the particle size can be larger with pressurised aerosols, and poor inhalation techniques may cause greater impaction in the throat with less deposition in the lung (Newman *et al.*, 1981).

The nebuliser result from this study fits well on the aerosol plasma-response curve. So too does the data from previous nebuliser studies (Patel *et al.*, 1982; Patel & Kerr, 1984) if the plasma concentrations are extrapolated from the dose nebulised, a reasonable assumption since similar methodology was used. Thus measurement of plasma concentration can allow a comparison to

be made between the protective effects of SCG following different methods of inhalation. It is important to note, however, that plasma concentration *per se* is almost certainly not related directly to protective effect.

The higher plasma concentrations following nebulised SCG and 10 and 20 mg aerosol compared with 2 mg aerosol suggest that the higher doses may provide a longer duration of effect,

hence reducing the frequency of administration. With respect to nebulised administration it is important to note, however, that different nebulisation techniques and equipment may well not give the same high absorption as that reported in this study.

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