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The pharmacokinetic assessment of sodium cromoglycate

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The plasma concentration of sodium cromoglycate (SCG) was measured in four healthy subjects by radioimmunoassay after a 4 mg intravenous dose and after inhaling from 20 mg capsules, and from 10 and 30 mg ml^{-1} nebulizer solutions. The mean absorption constant (K_1) after inhalation was 0·43 h^{-1}. The mean elimination constant from the plasma (K_{elim}) after intravenous administration was 11·5 h^{-1}, and that after inhalation was similar. The apparent volume of distribution of SCG ($V_{d\beta}$) was 0·2 litre kg^{-1} and the mean plasma clearance was 0·35 litre $h^{-1}kg^{-1}$. The amount of SCG absorbed after inhalation varied according to the method of inhalation and dose. After the inhalation of powder from 20 mg capsules, 1·30–3·96 mg reached the plasma, after inhalation of SCG produced by nebulizing a 10 mg ml^{-1} solution for 5 min at 10 psi using a Minineb nebulizer 0·19–0·31 mg reached the plasma and when the solution was increased to 30 mg ml^{-1} the figure was 0·33–0·45 mg.

Sodium cromoglycate (SCG) is an effective and commonly used treatment of asthma. However little is known about the dose reaching the lungs after inhalation or about its absorption, distribution or excretion characteristics. Early studies using ^{14}C-labelled SCG (Walker et al 1972) showed that the drug was absorbed from the lungs and rapidly excreted in the urine and bile but detailed pharmacokinetic analysis was not given. More recently a radioimmunoassay technique has been developed (Brown et al 1983 in the press). The results using this technique (Brown et al 1981) gave useful pharmacokinetic details concerning SCG after inhalation, but were not sufficient to allow full assessment of bioavailability of the drug or its absorption and elimination because the results after inhalation were not compared with those following intravenous administration. In the present study we have measured plasma SCG concentration after both inhalation and intravenous administration in the same subjects. The pharmacokinetic constants derived from these data have been calculated and estimates made of the bioavailability of the drug after inhalation.

METHODS

Subjects

Four subjects (three male) gave their informed consent before taking part in this study which had local Ethical Committee approval. Each subject took part in all of the studies which were performed under the same laboratory conditions.

Intravenous studies

Each subject received a 4 mg dose of SCG dissolved in 0·9% NaCl (saline) given over 1 min through a vein in the forearm. 10 ml samples of blood from a vein in the opposite arm were drawn into heparin tubes for measurement of SCG; samples were taken at 1, 3, 5, 10, 15, 20, 30, 60 and 120 min after the injection.

Inhalation studies — capsules

Pelleted SCG from standard 20 mg capsules was inhaled from a Spinhaler attached to a Fleisch head which measured inspiratory flow. Each subject inhaled the drug by sucking at such a rate as to give a Peak Inspiratory Flow (PIF) of greater than 140 litres min^{-1}. Breath was held for 10 s after inhalation. The capsules were 95% emptied, at the first attempt, as assessed by weight reduction of each capsule; some of the drug will have remained in the Spinhaler. At this flow rate 34% of the particles of SCG are less than 8.5 μm in diameter (from manufacturer). Blood samples for SCG estimation were then taken using the same time schedule as for the intravenous study.

Nebulizer solution

Solutions containing 10 mg ml^{-1} and 30 mg ml^{-1} SCG were nebulized by a Minineb driven by compressed air at 10 psi. Each subject inhaled the drug through the mouth using tidal breathing for

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5 min during which time 1 ml of the solution was nebulized. Blood was sampled for estimation of SCG using the same time schedule as for the previous experiments. The particle size of the aerosol measured by an impaction method was 2–10 μm. The optical density of the solution at a wavelength of 325 nm was the same before and after inhalation indicating that the concentration of SCG in the solution did not change with nebulization.

SCG assay

The blood samples were analysed by using the radioimmunoassay technique of Brown et al (1983). In our hands it had a detection limit of 0·5 ng of SCG per ml of plasma, and when estimations were repeated on the same sample the results obtained were subject to a 10% variation.

Pharmacokinetic analysis

Data obtained from the *intravenous studies* were analysed on a digital computer by a least squares curve fitting technique. They were best described by the double exponential equation $C = Ae^{-\alpha t} + Be^{-\beta t}$ associated with a two compartment disposition model. The elimination constant (K_{elim}) was derived from the α and β disposition constants using the equation $K_{elim} = (A + B)/(A/\alpha + B/\beta)$ (Saunders 1974). The area under the curve (AUC) from 0 to infinity was calculated by the trapezoidal method up to 120 min and thereafter by the expression C_{120}/β. The apparent volume of distribution based on β ($V_{d\beta}$) was calculated from $V_{d\beta} = Xo/AUC.\beta$ where Xo is the dose given divided by body weight which gives a volume of distribution related to body mass. The plasma clearance was calculated from $Cl_p = X_o/AUC$ and this was also related to body weight.

The data obtained from the *inhalation studies* were best described by the equation $C = Co\ (e^{-K1.t} - e^{-K2.t})$ associated with the 'flip-flop' model. The AUC was calculated in the same manner as for the intravenous studies substituting the slowest rate constant for β. The amount of drug absorbed from the lungs into the plasma was calculated by comparing the AUC for the intravenous studies with that following inhalation using the formula $dose_{inhalation} = (dose_{i.v.}/AUC_{i.v.})\ AUC_{inhalation}$.

RESULTS

Intravenous studies

The plasma concentration time graphs were well described by the two compartment model. The mean real and computed values for all the subjects with the standard errors are shown in Fig. 1. The mean α and β disposition constants from the computation together with the calculated elimination constants are shown in Table 1. The Table also shows the calculated mean AUC, clearance and the $V_{d\beta}$ for all the four subjects.

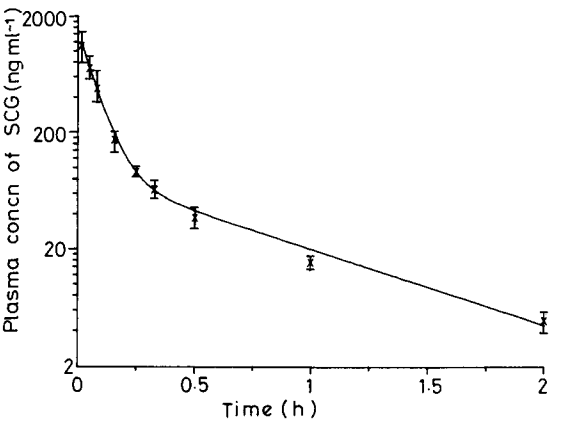

FIG. 1. The points (×) on the graph show the mean ± s.e. measured plasma concentrations for sodium cromoglycate following a 4 mg i.v. injection in 4 subjects.

Inhalation studies

In none of the studies was a delay seen before SCG could be measured in the plasma. All but one of the plasma concentration-time graphs were well described by the 'flip-flop' model. The results for the mean computed rate constants for eleven of the studies are shown in Table 2. One set of values obtained from subject 4 could not be analysed by the computer using this model, probably because of the error in the assay method at the low concentrations seen in this subject. The results from this study have not been included. Table 2 shows the mean calculated values of AUC and the estimation of the actual

Table 1. Mean ±1 standard deviation for the disposition and elimination constants, Area under the curve (AUC) apparent volume of distribution ($V_{d\beta}$) and plasma clearance after intravenous administration of 4 mg of sodium cromoglycate in 4 subjects.

Body weight (kg)	80 ± 14
$\alpha(h^{-1})$	22·5 ± 10
$\beta(h^{-1})$	1.85 ± 0.13
$K_{elim}(h^{-1})$	11.5 ± 3
AUC(ng ml h^{-1})	150 ± 80
$V_{d\beta}$(litres)	16 ± 4
$V_{d\beta}$ kg^{-1} (litres kg^{-1})	0·2 ± 0·04
Clp (litres h^{-1})	28·8 ± 10·8
Clp kg^{-1} (litres h^{-1} kg^{-1})	0·35 ± 0·1

dose absorbed after inhalation for each study. In all subjects the values for the plasma concentration at 30 and 60 min fell on the slow decay part of the concentration time graph. By extrapolating a line through these two points to zero and infinity, it was possible to calculate an AUC. The dose calculated from this new AUC was linearly related ($r = 0{\cdot}81$) to that calculated using all the data. The slope of this line ($b = 2{\cdot}4$) was significantly different from zero ($P < 0{\cdot}001$), Fig. 2.

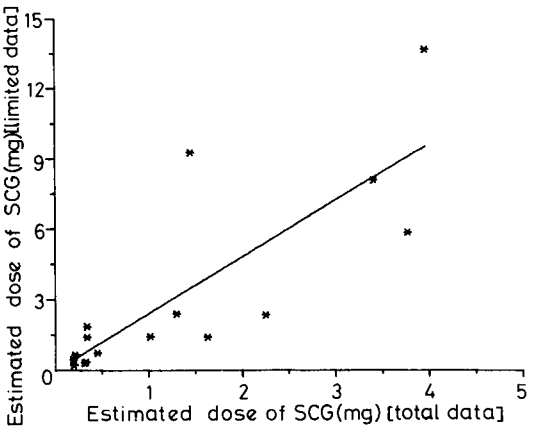

FIG. 2. A graph of the dose received (mg) after inhalation of sodium cromoglycate calculated from all the available data on the horizontal axis and from the plasma samples at 30 and 60 min on the vertical axis. The line of best fit is estimated by the least squares method.

DISCUSSION

In this study a radioimmunoassay technique has been used to measure the plasma concentration of circulating SCG after administration both by intravenous injection and inhalation. The absolute values following inhalation are similar to those reported by Brown et al (1981) who developed the technique. The results obtained after intravenous injection show the drug to be rapidly eliminated with elimination constants of around 10 h^{-1}. This finding is consistent with that of Walker et al (1972) who showed that 2 h after i.v. administration most of the drug had appeared in the urine. It is not however in keeping with their conclusion that the late phase of the plasma concentration time graph after both inhalation and intravenous administration is a reflection of elimination.

Table 2. Results of the mean ± 1 standard deviation for the absorption (K_1), and elimination (K_2) constants, AUC and estimated dose received for 4 subjects inhaling a 20 mg capsule and from a 10 and 30 mg ml^{-1} solution of sodium cromoglycate.

	K_1 (h^{-1})	K_2 (h^{-1})	AUC ($ng\,ml^{-1}\,h^{-1}$)	Dose (mg)
Capsule 20 mg	0·43 ± 0·21	29 ± 37	73 ± 28	2 ± 1·3
Solution 10 mg ml^{-1}	0·31 ± 0·16	18 ± 35*	88 ± 3·8	0·23 ± 0·06
Solution 30 mg ml^{-1}	1·12 ± 1·15	34 ± 26	14 ± 6	0·37 ± 0·06

* Mean of 3, see text for details.

Analysis of the inhalation data using the one compartment absorption, and two compartment disposition model, could not be used because the slow decay phase of the graph was an order of magnitude slower after inhalation than after intravenous administration, and a second component to the decay was not always obvious. The data were therefore subjected to analysis by the 'flip flop' model, where the absorption rate is slower than the elimination rate, and this was found to describe the data well. The elimination constants (K_2) derived by this method are compatible with the urine collection data of Walker et al (1972) which suggested rapid elimination of the drug, and in general are of a similar order of magnitude to the elimination rate after intravenous administration. The interpretation by Brown et al (1981) that the slow decay rate was due to the drug's absorption is born out by the finding of a slow absorption constant (K_1). This constant (K_1) is of a similar order of magnitude to that implied by the $t_{1/2}$ found after inhalation of SCG by Walker et al (1972) up to 4 h and by Brown et al (1981) up to 8 h. The higher mean absorption rate after the 30 mg ml^{-1} dose was due to one high value which was not in keeping with the other values. This slow absorption may explain the long duration of action of a drug which is rapidly eliminated. SCG is a water-soluble molecule and not absorbed from the gut. That the drug is found to be absorbed from the lungs in this study and also in that of Walker et al (1972) and Brown et al (1981) is surprising, but is consistent with the finding in animals (Enna & Shanker 1980) that other water soluble molecules can be absorbed through the epithelium of the airways.

It is not possible to measure directly the amount of SCG reaching the lungs after inhalation but it is feasible to estimate this figure using calculations based on the pharmacokinetic constants described above. Calculation of a bioavailability ratio from comparison of the AUC after parenteral and non-parenteral administration require that the dose, distribution and the decay characteristics of the drug given in both conditions are the same. In this study

the dose reaching the lungs was unknown but the elimination rate is the same and it is reasonable to assume that the apparent volume of distribution is also the same. We therefore calculated the estimated dose using a ratio of dose to AUC from the intravenous data and the AUC calculated from the inhalation data. This shows that the dose received by the lungs after inhalation of pelleted SCG from a Spinhaler was 1·30 to 3·96 mg; that is 7–20% of the dose leaving the capsule. The wide range shows that even using the optimum conditions of a high PIF and breath holding, standardized dosing is difficult. The dose received from the nebulizer ranged from 0·33 to 0·45 mg for the 30 mg ml^{-1} solution and 0·19 to 0·31 mg for the 10 mg ml^{-1} solution, these are more consistent presumably because this is an easier technique for the subject to use.

The variation of the dose underlines the importance of knowing the dose received rather than dose given if comparison of the drug's effect amongst subjects is to be made. However a formal pharmacokinetic investigation is not practical for most studies involving patients. Here we demonstrate that measurement of the plasma concentration at 30 and 60 min only, is sufficient to allow an estimate of the amount of drug adsorbed from the lungs and so overcome this problem. Although this gives an over estimate it is linearly related to and of the same order of magnitude as the dose obtained from the full data. It can therefore be used for dose comparisons between subjects. Since the amount absorbed from the lungs must correlate with the amount reaching the lungs this technique will provide a way of improving the reliability of dose-response relationships for inhaled SCG, and so help in the investigation of its mechanism of action.

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