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The pharmacokinetics of sodium cromoglycate in man after intravenous and inhalation administration

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1 The pharmacokinetics of sodium cromoglycate in four healthy volunteers after slow intravenous infusion have been evaluated following measurement of plasma concentrations by radioimmunoassay. The results confirm earlier findings that sodium cromoglycate is rapidly eliminated from the body and that the data can be fitted to a two compartment open model.

2 The pharmacokinetic parameters derived from the intravenous administration were used to evaluate the pharmacokinetics after inhalation administration via the Spinhaler. A model for absorption from the lungs is described which involves absorption at two different rates; this gives a better fit to the observed data than a single absorption rate.

3 A fast absorption rate constant with a mean value of 0.54 min^{-1} and a slower rate constant with a mean value of 0.0097 min^{-1} were found. Of a mean total of 2.84 mg absorbed from a 20 mg inhaled dose, 0.68 ± 0.15 (s.e. mean) mg were absorbed at the fast rate and 2.17 ± 0.37 mg at the slower rate. These rates probably reflect absorption from different sites within the lungs.

4 The results may have important implications for interpretation of clinical findings.

Keywords sodium cromoglycate pharmacokinetics inhalation

Introduction

Sodium cromoglycate is a water soluble, strongly acidic drug that has been used by inhalation for the treatment of asthma for over 15 years (Altounyan, 1967). Its metabolism and pharmacokinetics in animals have been studied by the use of radiolabelled drug (Moss *et al.*, 1970; Ashton *et al.*, 1973) given by various routes. Studies in man have been few, due to the lack of suitable analytical methodology, though Walker *et al.* (1972) did investigate the metabolic profile of the drug in asthmatic patients using [^{14}C]-sodium cromoglycate administered intravenously, orally and by inhalation. All of these studies demonstrate that sodium cromoglycate is poorly absorbed orally, is rapidly eliminated and is not metabolised. Although absorption from the gastro-intestinal tract is poor, that fraction of the drug that reaches the lungs is well absorbed (Gardiner & Shanker, 1974). Early work by Moss *et al.* (1971) described a colourimetric assay for sodium cromoglycate in the urine and this has been used in several studies (Benson *et al.*, 1973; Morrison-Smith & Pizarro, 1972; Marks, 1977; Morrison-Smith, 1973) to monitor the urine of patients treated with the drug. Of particular relevance was the study by Benson *et al.* (1973) who carried out a detailed investigation of urinary excretion in patients with different types of respiratory disease. Their work was the first to highlight the importance of inspiratory flow rate in determining the dose delivered from the Spinhaler. They also tentatively suggested that absorption following inhalation might occur at more than one rate.

Moss *et al.* (1971) measured plasma concentrations in three volunteers using a fluorimetric

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assay method but they had to give a dose of three capsules to obtain measurable concentrations, and the results were not detailed enough to allow pharmacokinetic evaluation. A radioimmunoassay (RIA) method has been developed in our laboratories (Brown *et al.* 1983a) and this has been used to study plasma concentrations in volunteers and patients after inhalation (Brown *et al.*, 1981, 1983b). Recently Fuller & Collier (1983) have used our method to evaluate the pharmacokinetics of sodium cromoglycate after both intravenous and inhalation administration. These reports support the earlier findings that sodium cromoglycate is well absorbed from the lung and that the elimination is rate limited by absorption. We have carried out an intravenous study in man using the RIA method for analysis of plasma concentrations and have applied these data to a more detailed interpretation of the inhalation findings. The results confirm earlier intravenous findings but show that a more complex model of absorption than that previously reported is required to describe adequately the inhalation findings.

Methods

Outline

Four healthy volunteers each received a single dose of sodium cromoglycate by slow intravenous infusion on one occasion. Plasma and urine concentrations were measured and the results analysed pharmacokinetically. The data were used to evaluate plasma concentrations measured in the same subjects previously dosed by inhalation via the Spinhaler (Auty *et al.*, submitted for publication; Brown *et al.*, 1983b).

Subjects

Four healthy volunteers (two males aged 35 and 42 years, weighing 73 and 92 kg; two females aged 25 and 26 years, weighing 57 and 52 kg) gave written informed consent to take part in the study, the protocol for which had been approved by an independent Ethics Review Committee. All values on routine biochemical and haematological testing were within the normal range.

Treatment

Intravenous infusion Each subject received a dose of sodium cromoglycate of 1 $\mu g\,kg^{-1}\,min^{-1}$ for a period of 30 min giving a total of 30 $\mu g\,kg^{-1}$ (due to technical problems subject 1 received the infusion over 36 min). A 0.004% sterile solution of sodium cromoglycate in saline was used so that 25 $\mu l\,min^{-1}\,kg^{-1}$ was infused, the dose being administered via a cannula inserted into a forearm vein.

Procedure

Having fasted from 22.00 h the night before, subjects reported to the laboratory in the early morning when a cannula was inserted into a forearm vein for blood sampling; a second cannula was inserted into the other arm for dosing. Control urine and blood samples were collected before the particular treatment was administered.

Blood samples (5 ml) for drug determinations were collected at the following times: 0, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55 min and 1, 1.25, 1.5, 2, 3, 4, 5 and 6 h after the start of the infusion.

Blood samples were collected in heparinised tubes, then centrifuged to separate the plasma which was stored at −20° C until analysed. All urine produced over the periods 0–1, 1–2, 2–4, 4–6, 6–24 h was collected: volumes were measured and aliquots (20 ml) were frozen and stored at −20° C until analysed.

Analysis of samples

Aliquots (10 or 100 µl) of plasma samples were analysed for content of sodium cromoglycate by a RIA method previously described (Brown *et al.*, 1983a). Urines (10 ml aliquots) were analysed by high performance liquid chromatography (Gardner, 1984).

Inhalation data

The four subjects had all received previously, on three separate occasions, single doses of sodium cromoglycate (20 mg) via the Spinhaler. Plasma concentrations were measured by RIA and the data generated were interpreted pharmacokinetically using the intravenous findings.

Pharmacokinetic analysis (see Appendix for further details)

The post-infusion intravenous plasma data were analysed using the method of Wagner (1975) for a two compartment open-model with elimination from the central compartment, using the following equation

$$C = I_1 e^{-\alpha(t-T)} - I_2 e^{-\beta(t-T)} \qquad \text{Equation 1}$$

Initial parameter estimates were made via an automated stripping procedure run on a microcomputer. Subsequent analysis on a VAX computer using the non-linear, least squares iterative

procedure FITFUN, part of Bolt, Beranek and Newman's RS1 package, yielded computer fitted values for α, β, I_1 and I_2 from which the k_{10}, k_{12}, k_{21}, V_1 and V_{dss} (apparent volume of distribution at steady state) were calculated (Wagner, 1975).

The pharmacokinetic parameters derived from the intravenous data were then used in the analysis of the inhalation data. As with the intravenous data, all equations were analysed using the FITFUN iterative procedure. Initially a two compartment open model with a single absorption phase was employed using the following equation

$$C = Ae^{-\alpha t} + Be^{-\beta t} - Ee^{-k_a t} \quad \text{Equation 2}$$

We also used the FLIP-FLOP model similar to Fuller & Collier (1983); this is described by the following equation

$$C = Ge^{-k_a t} - Ge^{-k_{10} t} \quad \text{Equation 3}$$

Improvements in the fit were obtained, however, by modification of the model to include two absorption components. The equation for this is

$$C = Me^{-\alpha t} + Ne^{-\beta t} - Ee^{k_{a_1} t} - Je^{-k_{a_2} t} \quad \text{Equation 4}$$

for the two compartment model whilst for the single compartment model the equation is

$$C = (G\text{–}P)e^{-k_{10} t} - Ge^{-k_{a_1} t} + Pe^{-k_{a_2} t} \quad \text{Equation 5}$$

Plasma concentration data from one subject (1) were fitted to equations 2–5. Data from the other subjects were fitted to equations 4 and 5 only. Thus, two absorption rate constants, k_{a_1} and k_{a_2}, were obtained. In addition, using equation 4, the fractions of the dose absorbed at these rates were calculated as described in the Appendix.

Results

The mean plasma concentration data obtained following intravenous infusion are illustrated in Figure 1, whilst the derived pharmacokinetic parameters are shown in Table 1. Mean concentrations rose rapidly during infusion, reached a maximum of 88.7 ± 15.1 ng ml^{-1} at the cessation and thereafter declined in a biphasic manner so that by 4 h the concentration was around 1.0 ng ml^{-1}. Clearance of the drug from the plasma was consistently high (mean 7.9 ± 0.9 ml min^{-1} kg^{-1})

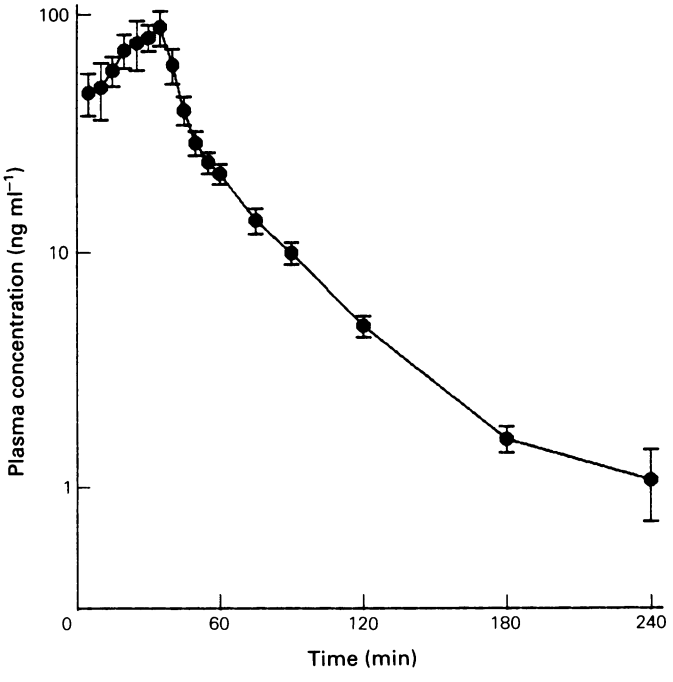


Figure 1 Mean (± s.e. mean) plasma concentrations of cromoglycate in four subjects after slow intravenous administration of a dose of 30 μg kg^{-1} over 30 min.

Table 1 Pharmacokinetic parameters of sodium cromoglycate after intravenous infusion in four subjects at a dose of 30 μg kg^{-1} over 30 min. Results expressed as mean ± s.e. mean

α (min^{-1})	0.079 ± 0.021
β (min^{-1})	0.011 ± 0.004
Dose (mg)	1.77 ± 0.16
k_{10} (min^{-1})	0.051 ± 0.007
k_{12} (min^{-1})	0.019 ± 0.01
k_{21} (min^{-1})	0.02 ± 0.01
V_1 (l kg^{-1})	0.16 ± 0.03
V_{dss} (l kg^{-1})	0.32 ± 0.06
AUC (ng ml^{-1} h)	55.9 ± 5.9
Clearance (ml min^{-1} kg^{-1})	7.9 ± 0.9

in all subjects. This was due largely to very rapid excretion, the mean half-life calculated from k_{10} being 13.5 min. Correspondingly 91 ± 5% of the total urinary excretion (43.8 ± 4.1% of the dose) occurred within 90 min of cessation of the infusion. In all cases a good fit of the observed data to that calculated for the two compartment model was obtained.

Some detail of plasma concentrations obtained in the inhalation part of the study have been reported (Auty *et al.*, submitted for publication; Brown *et al.*, 1983b); mean data relevant to this paper are shown in Table 2. The extent of intersubject variation is illustrated in Figure 2 which shows the different shapes of curves obtained in the four subjects. The early time of the peak concentration (2–5 min) is particularly noticeable.

Table 2 Mean ± s.e. mean plasma concentrations of sodium cromoglycate in four volunteers after administration of a single dose of 20 mg by inhalation (each subject received a single dose on three separate occasions)

Time (min)	*Plasma concentration (ng ml^{-1})*
0	0 ± 0
2	37 ± 8
5	46 ± 7
10	43 ± 5
15	36 ± 4
30	32 ± 3
60	22 ± 2
120	13 ± 2
180	8.9 ± 1.6
240	6.5 ± 1.6
360	2.9 ± 1.2
480	2.7 ± 1.2

Similarly (see Figure 3) even the same subject can show marked differences from one occasion to another: on one occasion an early peak was followed by a steady decline; on a second the early peak was followed by a rapid fall; whilst on the third a lower plateau concentration was maintained for an hour before the steady decline. A suitable pharmacokinetic model, therefore, has to be able to fit these different shaped curves.

The results of the application of equations 2 to 5 to the plasma concentration data obtained

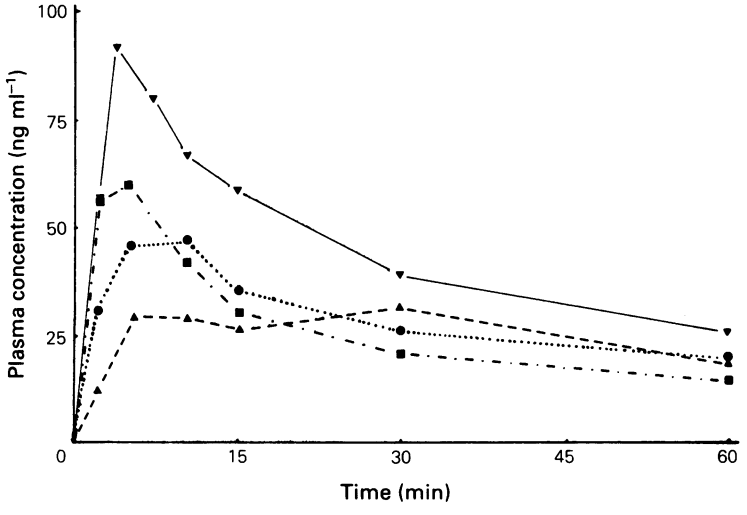


Figure 2 Intersubject variation in plasma concentration of cromoglycate. The data represent observations for four individuals all doses with 1 × 20 mg cromoglycate via a Spinhaler. ·—■·— Subject 1, —▼— Subject 2, ····●···· Subject 3, --▲-- Subject 4.

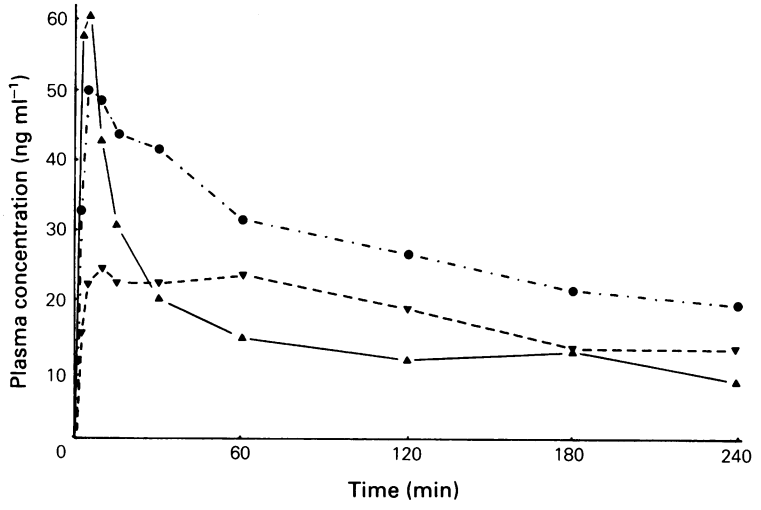


Figure 3 Intrasubject variation in plasma concentration of cromoglycate. The data represent plasma concentrations for subject 1 given a single dose of 20 mg cromoglycate via a Spinhaler on three different occasions. Conditions of inhalation were similar each time. —▲— First occasion, ·—●—· Second occasion, --▼-- Third occasion.

from subject 1 are shown in Table 3. The residual mean square values indicate that the models based on equations 2 and 3 give very poor fits. In subsequent analyses for the other subjects using equations 4 and 5 good fits were obtained in all cases. Figure 4 shows a representative application of this model (using equation 4) to the plasma concentration data from one of the subjects on one occasion. Application of equation 4 to all the subjects yielded absorption rate constants as shown in Table 4. Although the number of sampling points was insufficient to assign an accurate figure to the rapid phase it is quite clear that the rate constant of absorption for this phase is high, giving a mean value of 0.54 min^{-1}, corresponding to an absorption half-life of around 1 min. The second absorption phase had a mean rate constant of 0.0097 min^{-1} which corresponds to a half-life of 71 min. Also shown in Table 4 are the amounts deposited at the sites corresponding to the fast and slow absorption rates. In every case the amount deposited at the slower absorption site was higher than at the rapid site, although the ratio ranged from just over 1 to nearly 21. The mean total deposition was 2.84 ± 0.41 mg which represents 14% of the nominal dose of 20 mg.

The applicability of the model represented by equation 4 is illustrated in Figure 5 which shows the resultant fits of the mean absorption rates (ref. Table 4) for subject 1 to the intrasubject variation illustrated in Figure 3.

Table 3 Goodness of fit of the models described in the text to the data from subject one dosed on three separate occasions

Occasion	*Equation used*	*Residual mean square*	F *value*
1	2	88.4	31
1	3	202.4	24
1	4	3.8	1031
1	5	3.3	1197
2	4	2.4	1471
2	5	6.8	510
3	4	1.6	746
3	5	1.4	842

After intravenous administration, a mean (± s.e. mean) of 43.6 ± 2.1% of the dose of sodium cromoglycate was eliminated in the urine within 48 h. After administration via inhalation mean urinary excretion was 6.4 ± 1.3% of the nominal dose of 20 mg. Extent of absorption calculated by comparison of this excretion with that after intravenous dosing gives a similar figure (15%) to that calculated for deposition using the plasma data.

Discussion

Plasma concentrations of sodium cromoglycate following intravenous administration in man have been studied previously using ^{14}C-labelled

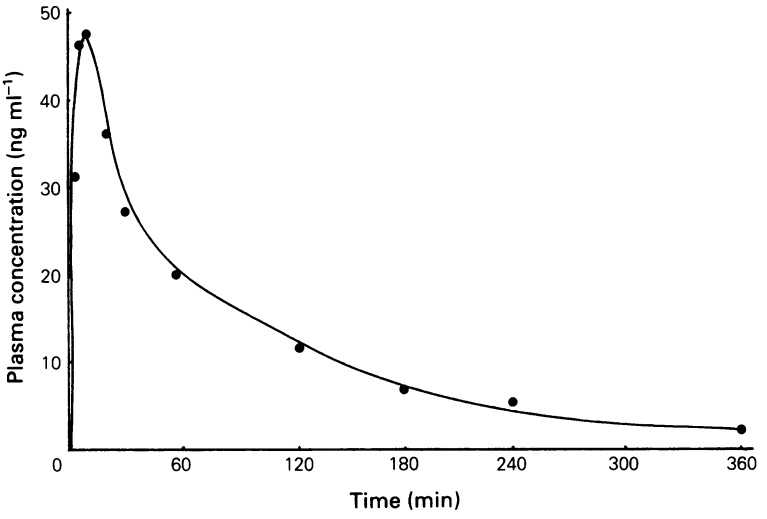


Figure 4 Representative fit of inhalation absorption model described in the text to the observed data for subject 3 on one occasion after inhalation of 20 mg cromoglycate via the Spinhaler. Closed circles (●)— observed points, solid line — fitted by model.

Table 4 Absorption rate constants and dose to different sites

Subject	*Occasion*	k_{a_1} *(min^{-1})*	k_{a_2} *(min^{-1})*	D_1 *(mg)*	D_2 *(mg)*	$D_1 + D_2$ *(mg)*
1	1	0.36	0.0041	0.40	5.01	5.41
1	2	0.81	0.0030	0.54	1.80	2.34
1	3	0.40	0.0034	0.16	3.87	4.03
2	1	0.81	0.0129	1.19	2.91	4.00
2	2	31.10*	0.0107	1.60	2.24	3.84
2	3	317.00*	0.0100	1.70	2.10	3.80
3	1	0.80	0.0135	0.28	1.02	1.30
3	2	0.32	0.0102	0.75	1.38	2.13
3	3	0.53	0.0090	0.52	2.44	2.96
4	1	0.76	0.0093	0.53	1.94	2.47
4	2	0.23	0.0148	0.33	0.74	1.07
4	3	0.40	0.0156	0.14	0.53	0.67
Mean		0.54	0.0097	0.68	2.17	2.84
s.e. mean		0.07	0.0012	0.15	0.37	0.41

*omitted from mean

compound (Walker *et al.*, 1972). Recently Fuller & Collier (1983) reported the pharmacokinetics of sodium cromoglycate after bolus intravenous administration and related this to a simple model for their inhalation data. We now report the pharmacokinetics after intravenous infusion and have used the information to derive a more detailed model found necessary to describe adequately our inhalation data. Our intravenous results, in agreement with these other studies, show a biphasic decline and are suitably fitted by a two compartment model. It is apparent that elimination from the plasma into the urine and probably the bile is extremely rapid and occurs largely during what is normally regarded as the 'distributive' phase. Recent animal studies (Buckley *et al.*, 1982) confirm the rapid elimination. The terminal half-life represents the rate-limited elimination from the tissues which accounts for only a small fraction of the dose. The intravenous data also confirm that sodium cromoglycate is a drug with a high clearance due to excretion, the results from this study (7.9 ml min^{-1} kg^{-1}) being in close agreement with

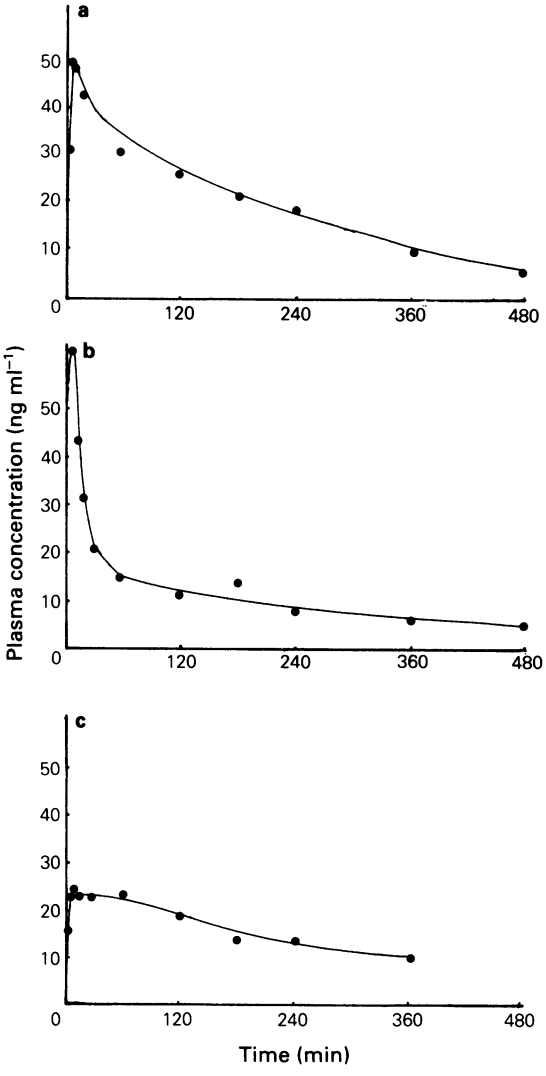


Figure 5 Data from Figure 3 showing fitted curves obtained by varying the amounts deposited at the two sites of absorption (Table 4).
$C = Me^{-0.101t} + Ne^{-0.019t} - Ee^{-0.52t} - Je^{-0.0035t}$
(a) first occasion, (b) second occasion and (c) third occasion

earlier findings (Clark & Neale, 1981; 7.6 ml min^{-1} kg^{-1}).

An understanding of the intravenous pharmacokinetic behaviour of sodium cromoglycate has allowed confirmation of the belief that following inhalation, absorption becomes rate-limiting and therefore 'flip-flop' kinetics apply (Gibaldi & Perrier, 1975).

The results of the study following inhalation demonstrate that the plasma concentrations of sodium cromoglycate administered via the Spinhaler reach peak level generally within 5 min of administration. The concentration can remain at a plateau for a while or fall gradually with a terminal half-life that is longer than the β phase following intravenous dosing. The inhalation plasma half-life is in general agreement with that of 91 min reported by Walker *et al.* (1972) and represents the absorption half-life. However, given the observed intravenous pharmacokinetics,

the rapid rise to peak concentration and a comparatively slow absorption, a single absorption rate constant (Fuller & Collier, 1983) cannot adequately account for the findings. By introducing the concept of more than one absorption site, as suggested originally by Benson *et al.* (1973), a model that can explain the observed data has been established.

This is shown particularly well in explaining the intrasubject plasma profile variations (Figure 5) where the different plasma patterns are explained by varying the amounts absorbed at the two rates. The model can account for the very early time to reach peak concentration and also the observed plateau effects (Brown *et al.*, 1983b) in intersubject variations. In order to define more accurately the faster absorption rate more data points around the peak concentration would be required.

It is suggested, therefore, that upon inhalation of sodium cromoglycate from the Spinhaler the drug is deposited in varying amounts at least two sites with different absorption rates. Such a hypothesis was put forward some time ago (Benson *et al.*, 1973) on the basis of rates of urinary excretion. It was suggested that material deposited in the alveoli would be absorbed rapidly, whilst that deposited higher in the airways would be absorbed more slowly. At present there is not enough evidence to substantiate this idea though two different rates of absorption have been shown for different size particles of p-aminohippuric acid administered by inhalation to anaesthetised rats (Brown *et al.*, 1982). The smaller particles, which presumably penetrate more deeply, were more rapidly absorbed. It is quite conceivable that two sites of absorption, whilst giving a good fit in the model described, are not representative of the real situation where there may be a series of different rates of absorption at the different levels of the lungs.

Detailed studies are in progress to identify the two postulated absorption sites of sodium cromoglycate and to relate its efficacy to deposition at one or both sites. When this has been achieved it will be possible to provide guidance about the inhalation technique which should be used by an individual patient in order to maximise delivery of the drug to its site of action, and so to optimise the extent and duration of the efficacy of the drug. Further, it may be possible to relate the plasma concentration of sodium cromoglycate to its efficacy, though it seems more likely that it will be the pattern of the plasma concentration time course (indicating site of deposition) which is more important in this respect.

Appendix

Abbreviations used throughout are defined below:

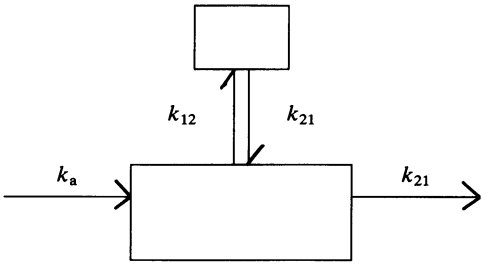
α and β, conventional hybrid rate constants as defined by Wagner (1975)
t, time after dose (min).
T, length of intravenous infusion (min).
C, plasma concentration (ng ml^{-1}).
FD, dose absorbed.

The standard two-compartment scheme described by Wagner (1975) was used for the intravenous model.

For the post-infusion data the relevant equation is

$$C = I_1 e^{-\alpha(t-T)} - I_2 e^{-\beta(t-T)} \qquad \text{Equation 1}$$

Simple alteration of the model to two compartments with first order absorption gives:



where $C = Ae^{-\alpha t} + Be^{-\beta t} - Ee^{k_a t}$ Equation 2

$$\text{where } A = \frac{k_a FD}{V_1}\left[\frac{(k_{21}-\alpha)}{(k_a-\alpha)(\beta-\alpha)}\right]$$

$$B = \frac{k_a FD}{V_1}\left[\frac{(\beta-k_{21})}{(k_a-\beta)(\beta-\alpha)}\right]$$

$$E = \frac{k_a FD}{V_1}\left[\frac{(k_a-k_{21})}{(\alpha-k_a)(\beta-k_a)}\right]$$

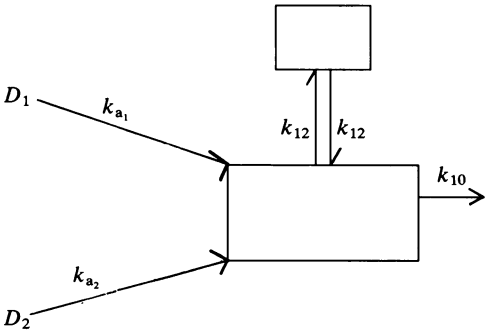
For the single compartment model with FLIP-FLOP kinetics i.e. $k_a < k_e$ the following equation applies:

$$C = Ge^{-k_a t} - Ge^{-k_{10} t} \qquad \text{Equation 3}$$

$$\text{where } G = \frac{FD}{V_1} \qquad \frac{k_a}{(k_{10}-k_a)}$$

As neither the two or single compartment models gave very good fits to the data a more complex

model was developed. This involved two first order absorption components as indicated in the following scheme:



The equation describing the concentration in the central compartment is obtained by adding together two appropriate equations *viz*:

$$C_1 = Ae^{-\alpha t} + Be^{-\beta t} - Ee^{-k_{a_1} t}$$

$$C_2 = \mathrm{H}e^{-\alpha t} + \mathrm{I}e^{-\beta t} - \mathrm{J}e^{-k_{a_2} t}$$

$$C_1 + C_2 = Me^{-\alpha t} + \mathrm{N}e^{-\beta t} - \mathrm{E}e^{k_{a_1} t} - Je^{k_{a_2} t}$$

Equation 4

where A, B and E are the same as in equation 2 but with $FD = F_1D_1$ and $k_a = k_{a_1}$

Also M = (A + H) and N = (B + I)

$$\text{where H} = \frac{k_{a_2} F_2 D_2}{V_1}\left[\frac{(k_{21} - \alpha)}{(k_{a_2}-\alpha)\,(\beta-\alpha)}\right]$$

$$\mathrm{I} = \frac{k_{a_2} F_2 D_2}{V_1}\left[\frac{(\beta-k_{21})}{(k_{a_2}-\beta)\,(\beta-\alpha)}\right]$$

$$\text{and J} = \frac{k_{a_2} F_2 D_2}{V_1}\left[\frac{(k_{a_2}-k_{21})}{(\alpha-\beta)\,(\beta-k_{a_2})}\right]$$

Equation 4 contains four exponential terms, but has six unknowns—M, N, E, J, k_{a_1} and k_{a_2}. Fitting of this function with FITFUN was difficult and it is more likely to get a meaningful fit if one reduces the number of variables. We, therefore, simplified the fitting procedure.

Now

$$\mathrm{M} = \frac{(k_{21}-\alpha)}{V_1\,(\beta-\alpha)}\left[\frac{k_{a_1} F_1 D_1}{(k_{a_1}-\alpha)} + \frac{k_{a_2} F_2 D_2}{(k_{a_2}-\alpha)}\right]$$

and from equation 1 $\dfrac{k_{a_1} F_1 D_1}{(\alpha-k_{a_1})} = \dfrac{\mathrm{E}V_1\,(\beta-k_{a_1})}{(k_{a_1}-k_{21})}$

$$\therefore \mathrm{M} = \frac{(k_{21}-\alpha)}{V_1\,(\beta-\alpha)}$$

$$\left[-\frac{\mathrm{E}V_1\,(\beta-k_{a_1})}{(k_{a_1}-k_{21})} - \frac{\mathrm{J}V_1\,(\beta-k_{a_2})}{(k_{a2}-k_{21})}\right]$$

k_{a_1} is large, $k_{a_1} >> \beta$ and $k_{a_1} >> k_{21}$

$$\therefore \mathrm{M} = \frac{(k_{21}-\alpha)}{(\beta-\alpha)}\left[\mathrm{E} - \mathrm{J}\quad\frac{(\beta-k_{a_2})}{(k_{a_2}-k_{21})}\right]$$

k_{a_2} is the terminal half-life of the inhalation curve and can, therefore be evaluated separately. Therefore, M can be evaluated in terms of E and J, using the known values of k_{21}, α and β from the i.v. data.

Similarly N can be evaluated in terms of E and J:

$$\mathrm{N} = \frac{(\beta-k_{21})}{(\beta-\alpha)}\left[\mathrm{E} + \mathrm{J}\quad\frac{(\alpha-k_{a_2})}{(k_{a_2}-k_{21})}\right]$$

We, thus, have an equation for $C_1 + C_2$ which contains four unknowns, E, J, k_{a_1} and k_{a_2}, although k_{a_2} can be separately estimated from the terminal portion of the inhalation curve.

The amounts, F_1D_1 and F_2D_2, absorbed at the different rates can then be calculated:

$$F_1D_1 = \frac{\mathrm{E}V_1\,(\alpha-k_{a_1})\,(\beta-k_{a_1})}{k_{a_1}\,(k_{a_1}-k_{21})}$$

$$F_2D_2 = \frac{\mathrm{J}V_1\,(\alpha-k_{a_2})\,(\beta-k_{a_2})}{k_{a_2}\,(k_{a_2}-k_{21})}$$

For the single compartment model

$$C_1 = \mathrm{P}e^{-k_{10} t} - \mathrm{P}e^{-k_{a_1} t}$$

$$\text{and } C_2 = \mathrm{G}e^{-k_{a_2} t} - \mathrm{G}e^{-k_{10} t}$$

$$\therefore C_1 + C_2 = (\mathrm{P}-\mathrm{G})e^{-k_{10} t} - \mathrm{P}e^{-k_{a_1} t} + \mathrm{G}e^{-k_{a_2} t}$$

Equation 5

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