J. Pharm. Pharmacol. 1985, 37: 38–41
Received 11 July, 1984

The nasal absorption of sodium cromoglycate in the albino rat

A. N. FISHER*, K. BROWN, S. S. DAVIS†, G. D. PARR† AND D. A. SMITH

Metabolic Studies Department, Fisons plc, Pharmaceutical Division, Bakewell Road, Loughborough, Leicestershire LE11 0RH, and †Pharmacy Department, Nottingham University, University Park, Nottingham NG7 2RD, UK

The intranasal absorption of sodium cromoglycate has been investigated in the adult male COBS/Wistar rat. Sodium cromoglycate (1 mg kg^{-1}) was instilled into the nasal cavities and for comparison animals were also similarly dosed intravenously or sub-lingually. Serial samples of blood or bile were collected. After intravenous administration, the area under the plasma concentration curve ($AUC_{0-\infty}$) was 32 μg min ml^{-1} corresponding to a plasma clearance of 13 ml min^{-1} and an elimination rate constant of 0·049 min^{-1}. Plasma concentrations of radioactivity after intranasal administration rose to a mean peak of 0·3 μg ml^{-1} approximately 20 min after dosing and fell to 0·03 μg ml^{-1} at 3 h. The AUC_{0-3} was 19 μg min ml^{-1} corresponding to an absorption of 60% over 3 h. The absorption rate constant (ka) was 0·059 min^{-1}. The total amount of sodium cromoglycate excreted in bile after intravenous administration was 56%. The amount of compound excreted in the bile was 30% after intranasal administration corresponding to an absorption of 53%. Plasma and bile data therefore show good agreement. Total excretion in the bile over 3 h after sub-lingual administration was 3%, demonstrating that this route made no significant contribution to the intranasal results. The absorption of sodium cromoglycate is independent of variations in the technique including changes in the orientation of the rat or blocking of the nasopalatine. The techniques used minimized other competing nasal clearance processes such as mucociliary clearance.

A wide range of compounds have been administered intranasally to man including steroids, peptides, decongestants, antibiotics, antihistamines (Parr 1983), cocaine (Van Dyke et al 1976) and nicotine (Temple 1976). Some of these compounds are known to be absorbed through the nasal mucosa but only a limited amount of systematic work has been performed to measure such absorption. The use of animal models in quantifying nasal absorption has been demonstrated with propranolol (Hussain et al 1979, 1980b), the results of which were directly extrapolatable to man (Hussain et al 1980a). In further investigations, the nasal absorption of a range of compounds, including salicylic acid, aminopyrine, bucolome, phenol red, sulbenicillin, cefazolin, cephacetrile and insulin was studied in the rat using in-situ recirculating and in-vivo methods (Hirai et al 1981).

Sodium cromoglycate (Rynacrom) is administered intranasally to man for the treatment of seasonal rhinitis. It is a highly water-soluble compound with low oral absorption but good pulmonary absorption. The compound is excreted unchanged in the urine and bile by most species including the rat (Ashton et al 1973). There are no published studies describing the absorption of sodium cromoglycate after intranasal administration. This report describes the simplification and modification of the in-vivo method of Hirai et al (1981) for studying the absorption of sodium cromoglycate by the adult male COBS/Wistar rat. The extent of absorption has been determined by comparison of plasma and biliary excretion data obtained following intranasal and intravenous administration.

* Correspondence.

MATERIALS AND METHODS

Sodium cromoglycate. Sodium cromoglycate ^{14}C-labelled, synthesized from diethyl [U-^{14}C]oxalate, with a specific activity of 15 μCi mg^{-1} was supplied by Dr W. J. S. Lockley of Fisons plc.

Preparation of animals

Male COBS/Wistar rats (Charles River, Manston, Kent, UK), 270 ± 34 g (mean ± s.d.) were used. All experiments were on animals anaesthetized with sodium pentobarbitone (Sagatal, May & Baker, Dagenham, Essex, UK) administered via an indwelling needle implanted in a caudal vein. Blood was collected from a cannula implanted into the dorsal aorta. The ease of collection, the constant flow experienced during experiments and the extremely

rapid transfer of compound (Buckley et al 1982) made bile the obvious choice for determining excretion data for sodium cromoglycate. Bile was collected from a cannula implanted into the common bile duct.

Five different groups of animals were prepared for studies on intranasal absorption:

1. The animal was placed on its back and a cannula was inserted into the oesophagus to the back of the nasal cavity and a second cannula inserted into the trachea to maintain respiration. The nasopalatine and, after dosing, both nostrils were sealed with tissue adhesive ('Superglue-3', Loctite, Welwyn Garden City, Herts, UK). Serial blood (n = 4, where n = number of animals) or bile (n = 5) samples were collected. This method was essentially that of Hirai et al (1981).
2. The technique for Group 1 was simplified by inserting a cannula into the trachea to maintain respiration, and the oesophagus was occluded by tying it on to this cannula. Serial blood (n = 4) or bile (n = 3) samples were collected.
3. Two cannulae were inserted into the trachea, one towards the head to collect mucus and secretions expelled from the nasal cavity and one towards the lungs to maintain respiration. A cannula was inserted into the oesophagus towards the head to collect secretions. Serial bile samples and total secretions into the tracheal and oesophageal cannulae were collected (n = 3).
4. This group of animals were treated as for Group 3 except that the animals were placed on their stomachs for dosing and sample collection (n = 6).
5. This group of animals were treated as for Group 4 with the addition of sealing the nasopalatine and, after dosing, the nostrils as for Group 1 (n = 3).

Dosing of animals

Animals were dosed into the nasal cavity, via a nostril, with ^{14}C-labelled sodium cromoglycate (1 mg kg^{-1}) dissolved in 0·9% NaCl (saline) (50 µl) using a microsyringe (100 µl capacity) with approximately 40 mm of pp 10 cannula (Portex, Hyde, Kent, UK) attached to the needle.

For comparison, a group of animals were dosed intravenously, via a caudal vein, with ^{14}C-labelled sodium cromoglycate (1 mg kg^{-1}) dissolved in saline (0·5 ml) and serial blood (n = 3) or bile (n = 3) samples were collected. Other animals, on their stomachs, received a dose of ^{14}C-labelled sodium cromoglycate (1 mg kg^{-1}) dissolved in saline instilled under the tongue (50 µl) and serial bile samples were collected (n = 4).

Determination of radioactivity

The various aliquots of plasma, bile and secretions were adjusted to a volume of 0·5 ml with distilled water, 5 ml of Fisofluor mpc liquid scintillation cocktail (Fisons, Loughborough, Leics, UK) was added and the radioactivity present determined by liquid scintillation spectrometry. Efficiency of counting was determined by the external standard channels ratio method.

Calculation of pharmacokinetic parameters

Plasma concentration data from the intravenously dosed animals were fitted to a two compartment model using the method of residuals and linear least squares regression analysis and conventional equations. The areas under the plasma concentration-time curves were calculated using the trapezoidal method. The plasma concentration data from the intranasally dosed animals was analysed by the method of Loo & Riegelman (1968) to obtain a value for the absorption rate constant. All values are expressed as means ± s.d.

RESULTS

Sodium cromoglycate is not metabolized (Ashton et al 1973) and consequently radioactivity detected in the plasma, bile or secretions represents the unchanged drug. The mean plasma concentrations of sodium cromoglycate after intravenous administration are shown in Fig. 1. The $AUC_{0-\infty}$ was 32 ± 9 µg min ml^{-1} corresponding to a plasma clearance of 13 ± 4 ml min^{-1} and an elimination rate constant of 0·049 ± 0·002 min^{-1}. Mean plasma concentrations after intranasal administration, to Groups 1 and 2 are shown in Fig. 1. Plasma concentrations of sodium cromoglycate after intranasal administration using both the original method of Hirai et al (1981) (Group 1) and the simplified version (Group 2) were similar, rising to a peak of approximately 0·3 µg ml^{-1} at about 20 min after dosing and falling to approximately 0·03 µg ml^{-1} at 3 h. The AUC_{0-3} was 19 ± 6 µg min ml^{-1} which when compared to the intravenous $AUC_{0-\infty}$ corresponds to an absorption of 60% over 3 h. The absorption rate constant was 0·059 ± 0·009 min^{-1}.

The total amount of sodium cromoglycate excreted in bile after intravenous administration was 56 ± 13%, the rate of excretion in bile is shown in Fig. 2. After intranasal administration the data for all groups were similar. The peak concentration in the bile appeared in the 15 or 30 min sample being approximately 10% of the dose declining to 1% for the 2½ or 3 h sample. Table 1 summarizes the data in

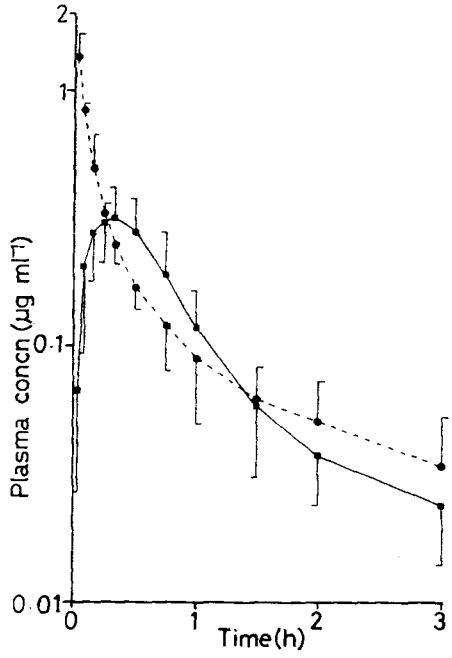

FIG. 1. Plasma concentrations (mean ± s.d.) of sodium cromoglycate after intravenous ● and intranasal ■ administration at a dose of 1 mg kg^{-1}.

terms of the amount of sodium cromoglycate excreted in bile over 3 h and the percentage of the dose absorbed calculated by comparison with the data obtained after intravenous administration. The amount of sodium cromoglycate excreted in bile over 3 h was similar for all groups with a mean of 30 ± 8% corresponding to an absorption of 53%. After sub-lingual administration 3·1 ± 2·2% of the dose was excreted in bile corresponding to 5·6% absorption. The mean rate of excretion in bile after intranasal and sub-lingual administration is also shown in Fig. 2.

Where applicable (animal Groups 3, 4 and 5) the recovery of dose in the oesophageal or tracheal cannulae was generally low. The amount of dose recovered in the oesophageal cannula was small and variable being 2·3 ± 3·9%, 1·5 ± 2·2% and 0·003 ± 0·005% in Groups 3, 4 and 5 respectively. In Groups 3 and 5, both comprised animals on their backs, only 2·2 ± 1·2% and 3·7 ± 2·8% respectively of the dose was recovered from the tracheal cannula. In contrast, for the animals on their stomachs (Group 4) 22·4 ± 14·8% was recovered in the tracheal cannula.

DISCUSSION

After intranasal administration of sodium cromoglycate to anaesthetized adult male albino rats at 1 mg kg^{-1}, 53% or greater of the dose was absorbed

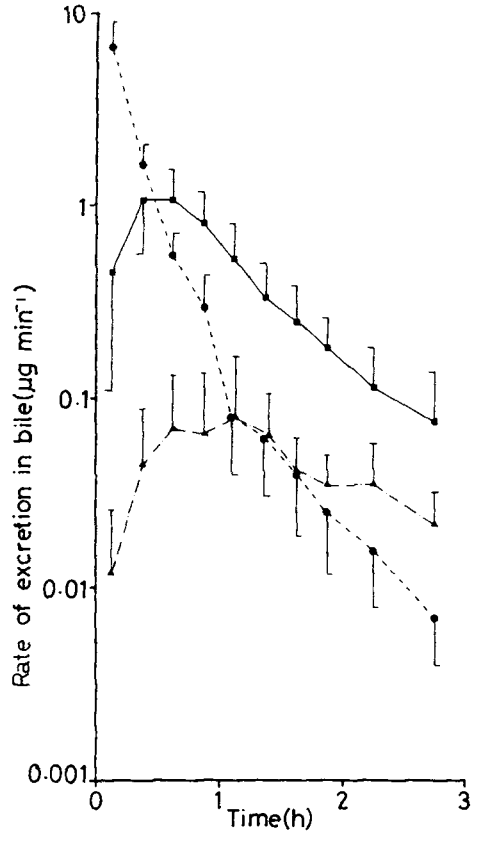

FIG. 2. Rate of biliary excretion (mean ± s.d.) of sodium cromoglycate after intravenous ●, intranasal ■ and sub-lingual ▲ administration at a dose of 1 mg kg^{-1}.

up to 3 h after dosing. The plasma data (60% absorbed) and the bile data (53% absorbed) are in good agreement. The absorption was independent of the orientation of the rat or the blocking of the nasopalatine and nostrils. The techniques used will maximize the absorption process and minimize competing clearance mechanisms such as mucociliary clearance or drainage. Little of the dose was swallowed in any of the groups as demonstrated by the low recovery in the oesophageal cannula. There

Table 1. Intranasal administration of sodium cromoglycate (1 mg kg^{-1}). Excretion in bile and percentage absorbed.

Group	Percentage excreted in bile over 3 h mean ± s.d.	Percentage absorbed
1	30 ± 2	53
2	28 ± 5	50
3	41 ± 10	73
4	26 ± 10	47
5	27 ± 7	48
Mean all groups	30 ± 8	53

was little mucociliary clearance or drainage into the tracheal cannula when the animals were on their backs (Group 3) or on their stomachs with sealed nasopalatine and nostrils (Group 5). However, approximately 20% of the dose was recovered in the tracheal cannula when the animals were on their stomachs with unsealed nasopalatine and nostrils (Group 4), indicating that the mucociliary clearance of this water soluble drug can still be important. Mucociliary clearance and drainage would be expected to be much higher in the conscious rat or man, and consequently the total absorption of an intranasal dose of sodium cromoglycate under clinical conditions is likely to be considerably lower. Sublingual absorption of the drug was low and made no significant contribution to the intranasal absorption.

Sodium cromoglycate has a molecular weight of 512 and is highly water-soluble. It is a strong dibasic acid; both acid groupings having pK_a values of less than two. The ionized compound has negligible lipophilicity. These physicochemical properties prevent the drug from being well absorbed from the gastrointestinal tract (Moss et al 1970; Smith & Fisher 1980). In contrast, the drug is rapidly absorbed from the lung (Moss & Ritchie 1970) and after subcutaneous administration (Smith & Fisher 1980). The rapid absorption of the compound through the nasal mucosa suggests that the permeability of this tissue is governed by similar factors to those controlling absorption from the lung or subcutaneous sites.

REFERENCES

Ashton, M. J., Clark, B., Jones, K. M., Moss, G. F., Neale, M. G., Ritchie, J. T. (1973) Tox. Appl. Pharm. 26: 319–328

Buckley, G. A., Murphy, A. J., Neale, M. G. (1982) Br. J. Pharmacol. 77: 569P

Hirai, S., Yoshiki, T., Matsuzawa, T., Mima, H. (1981) Int. J. Pharm. 7: 317–325

Hussain, A. A., Hirai, S., Bawarshi, R. (1979) J. Pharm. Sci. 68: 1196

Hussain, A., Foster, T., Hirai, S., Kashihara, T., Battenhorst, R., Jones, M. (1980a) Ibid. 69: 1240

Husaain, A. A., Hirai, S., Bawarshi, R. (1980b) Ibid. 69: 1411–1413

Loo, J. C. K., Riegelman, S. (1968) Ibid. 57: 918–928

Moss, G. F., Jones, K. M., Ritchie, J. T., Cox, J. S. G. (1970) Tox. Appl. Pharm. 17: 691–698

Moss, G. F., Ritchie, J. T. (1970) Ibid. 17: 699–707

Parr, G. D. (1983) Pharm. Int. 4: 202–205

Smith, D. A., Fisher, A. N. (1980) J. Pharm. Pharmacol. 32: 823–827

Temple, D. J. (1976) Arch. Pharm. 309: 984–987

Van Dyke, C., Barash, P. G., Jatlow, P., Byck, R. (1976) Science 191: 859–861