J. Pharm. Pharmacol. 1981, 33: 744–745
Communicated February 16, 1981

0022–3573/81/110744–02 $02.50/0

Hepatic and renal clearance of sodium cromoglycate

B. CLARK*, M. G. NEALE, *Fisons Limited—Pharmaceutical Division, Loughborough, Leicestershire, U.K.*

The polar anti-allergic drug sodium cromoglycate is rapidly excreted unchanged in bile and urine after intravenous injection (Moss et al 1970; Ashton et al 1973) and is reversibly bound to plasma proteins to a variable extent depending upon the species (Clark et al 1978). However, clearance was not reported nor was sufficient detail given to allow calculations to be made. We have therefore reviewed the original laboratory data and estimated the hepatic and renal clearances of the drug in several species to determine whether or not clearance was flow-dependent (Rowland 1972; Wilkinson & Shand 1975) and whether or not restricted elimination occurred (Shand et al 1976). Some data on man has been added.

Methods

The clearances and extraction ratios after intravenous injection of sodium cromoglycate in several species were calculated from results on rat, rabbit, dog, marmoset, stump-tailed macaque monkey and baboon given briefly by Ashton et al (1973), and from results on three male volunteers in whom the urinary excretion accounted for 41, 62 and 53% respectively of the dose given. 51, 50 and 63% respectively appeared in the faeces and was presumed to have been excreted in bile without being reabsorbed.

The plasma clearances (Cl_{Pl}) were estimated from the AUC's of the plasma concentration/time plots according to the relationship: Cl_{Pl} = Dose/AUC.

AUC was estimated by the method of residuals (Gibaldi & Perrier 1975). Two (in some cases three) exponentials were required to fit the data. The clearances for liver (Cl_H) and kidney (Cl_R) are proportional to the percentages of the dose excreted in bile or urine respectively. (These proportions are listed in Table 4 of Ashton et al 1973). Numerical values for Cl_H and Cl_R were then calculated from the relationships:

$$Cl_H = Cl_{Pl} \times F_B \ (F_B = \text{Fraction of dose excreted in bile}),$$

$$\text{and } Cl_R = Cl_{Pl} \times F_U \ (F_U = \text{Fraction of dose excreted in urine}).$$

Thus $Cl_{Pl} = Cl_H + Cl_R$ (since sodium cromoglycate is excreted unchanged).

The maximum renal clearances (Cl_{gf}) which could be due to glomerular filtration (GFR) were calculated from:

$$Cl_{gf} = GFR \times \text{free drug fraction in plasma}$$

Where GFR was assumed to be 2 ml min^{-1} kg^{-1}. The renal clearances due to tubular secretion (Cl_{ts}) were calculated from:

$$Cl_{ts} = Cl_R - Cl_{gf}$$

* Correspondence.

Sodium cromoglycate is known to be present in blood entirely in the plasma fraction (Clark et al 1978) and therefore organ plasma flow (P) rather than blood flow was used. Organ plasma flow values (ml min^{-1} kg^{-1}) assumed for conscious animals were: renal plasma flow—rat, 20, rabbit and marmoset, 15, dog, other monkeys and man, 10; hepatic plasma flow—rat and baboon, 30, rabbit and marmoset, 20, dog, 19, macaque, 14, man, 12. These representative flow rates were reached after consideration of several published values (Altman & Dittmer 1974; Shaw et al 1977).

The extraction ratio (E) is the fraction of drug removed from blood during one passage through the organ. Since sodium cromoglycate is restricted to plasma, time-averaged values for E were calculated from the relationship: E = Cl/P where P is the plasma flow to the organ. Clearance terms were determined in relation to plasma as described above.

The percentage (A) of the sodium cromoglycate present in plasma which would be removed during one circulation, assuming 20 and 30% of the cardiac output reaches the kidneys and liver respectively, is given by the equation:

$$A = (20\% \times E_R) + (30\% \times E_H)$$

Results and discussion

Clearance data are presented in Table 1 which also shows values for the unbound fraction of sodium cromoglycate in plasma for several species (Clark et al 1978). Plasma clearances (Cl_{Pl}) varied between 6·1 ml min^{-1} kg^{-1} in the marmoset to 34·7 in the baboon. The clearance (7·6 ml min^{-1} kg^{-1}) in man was similar to that found in marmosets and stump-tailed macaques. With only a small number of animals for any given species (Ashton et al 1973) it was not possible to assess accurately the interspecies variability. However, where mean data from two animals of a species are quoted, the individual values were of the same order. Thus the observed variations in clearances give some indication of the interspecies differences and do not simply reflect intraindividual variation.

The hepatic extraction (E_H) was lowest in the rabbit (0·08) and highest in the baboon (0·75). Other species including man were in the range 0·16–0·47. The low value of E_H in the rabbit is due to the poor ability of this species to excrete sodium cromoglycate in the bile (Ashton et al 1973). The rabbit relies on renal excretion (E_R = 0·98) which involves active tubular secretion (Cl_{ts} = 13·4 ml min^{-1} kg^{-1}).

From the estimated values of E_H, hepatic extraction of sodium cromoglycate appears to be only partially dependent upon hepatic plasma flow in these species (including man) with the possible exception of the baboon. Renal extraction (E_R) was high in the rabbit (0·98) and in the

Table 1. Hepatic and renal clearances and extraction ratios of sodium cromoglycate in several species. All doses were administered i.v. at 1 mg kg^{-1} except in man, where the i.v. dose was 0·024 mg kg^{-1}. Clearances are in ml min^{-1} kg^{-1}. The definitions and calculations of Cl_{Pl}, Cl_H, Cl_R, Cl_{gf} and Cl_{ts} are given in the text. Extraction ratios were calculated as described in the text. Mean values are given.

Species (Strain, no, sex)	Free drug fraction in plasma‡	Cl_{Pl}	Cl_H	Cl_R	Cl_{gf}	Cl_{ts}	Extraction ratios Liver (E_H)	Kidney (E_R)
Rat (Sprague Dawley) 4 M, 4 F)	0·60	19·3	14·05	5·29	1·2	4·1	0·47	0·26
Rabbit (Dutch, 2 M)	0·64	16·3	1·61	14·7	1·3	13·4	0·08	0·98
Dog (Beagle, 2 M)	0·75	14·2	9·64	4·56	1·5	3·1	0·51	0·46
Marmoset (Mico argentatus, 2 M)	*	6·1	3·25	2·85	<2*	>0·9*	0·16	0·19
Stump-tailed macaque monkey (Macaca arctoides 1 M, 1 F)	0·64	6·4	3·36	3·04	1·3	1·7	0·24	0·3
Baboon (Papio cyancephalus 1 M, 1 F)	*	34·7	22·5	12·2	<2*	>10*	0·75	1·2
Man (3 male subjects)	0·37**	7·6†	3·9	3·6	0·7	2·9	0·33	0·36

* Binding unknown ** Binding data was not from the volunteers in whom clearances were estimated.
‡ Binding data from Clark et al (1978).

baboon (apparently greater than 1). The apparently high value for E_R in the baboon is likely to be due to an underestimate of the renal flow. The renal extraction in other species including man varied from 0·19 to 0·46. After allowing for glomerular filtration of the free drug fraction in plasma, tubular secretion of sodium cromoglycate is seen to be important in all species. The clearance values (Cl_{ts}) are typical of polar anionic compounds which are actively secreted. For example the clearance of phenol red in man is approximately 5 ml min^{-1} kg^{-1} (Smith 1951). Sodium cromoglycate thus appears to be eliminated at a comparable rate in man (Cl_{ts} = 2·9 ml min^{-1} kg^{-1}). An earlier study (Cox et al 1970), also concluded that sodium cromoglycate was actively secreted in man after inhalation doses. Tubular secretion of sodium cromoglycate in animals has also been proposed (Cox et al 1970).

Extraction by the liver or kidneys did not usually exceed the free fraction of sodium cromoglycate in plasma (Table 1). However, since virtually complete extraction occurs in the baboon (hepatic or renal) and rabbit (renal) protein binding should not be considered to be a restriction upon elimination. The plasma protein binding is relatively weak.

These hepatic and renal extractions result in a substantial fraction of the sodium cromoglycate in plasma being removed by these organs in one circulation of the plasma. The extent of this varied from 9% in the marmoset to 50% in the baboon (man was approximately 20%).

Sodium cromoglycate is therefore a drug with a high clearance due solely to excretion.

We thank Professor Charles S. Lieber for data to enable us to estimate hepatic blood flow in baboons.

REFERENCES

Altman, P. L., Dittmer, D. S. (1974) Respiration and Circulation, Second Ed. Vol. III, Federation of American Society for Experimental Biology, Bethesda, (Maryland), pp 1701–1706

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

Clark, B., Moss, G. F., Neale, M. G. (1978) J. Pharm. Pharmacol. 30: 386–387

Cox, J. S. G., Beach, J. E., Blair, A. M. J. N., Clarke, A. J., King, J., Lee, T. B., Loveday, D. E. D., Moss, G. F., Orr, T. S., Ritchie, J. T., Sheard, P. (1970) Adv. Drug Res. 5: 115–196

Gibaldi, M., Perrier, D. (1975) in Pharmacokinetics, Marcel Dekker, Inc. New York, pp 281–292

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

Rowland, M. (1972) Eur. J. Pharmacol. 17: 352–356

Shand, D. G., Cotham, R. H., Wilkinson, G. R. (1976) Life Sci. 19: 125–139

Shaw, S., Heller, E. A., Friedman, H. S., Baraona, E., Lieber, C. S. (1977) Proc. Soc. Exp. Biol. Med. 156: 509–513

Smith, H. W. (1951) The kidney; structure and function in health and disease. Oxford University Press. New York, pp 171–177

Walker, S. R., Evans, M. E., Richards, A. J., Paterson, J. W. (1972) J. Pharm. Pharmacol. 24: 525–531

Wilkinson, G. R., Shand, D. G. (1975) Clin. Pharmacol. Ther. 18: 377–399