J. Pharm. Pharmacol. 1983, 35: 114–115
Communicated July 13, 1982

0022–3573/83/020114–02 $02.50/0

Pharmacokinetics of guanfacine in the rabbit

N. D. BARBER*, J. L. REID, *Department of Materia Medica, Stobhill General Hospital, Glasgow, G21 3UW, U.K.*

Guanfacine is a centrally acting antihypertensive drug with a similar mode of action to clonidine (Scholtysik et al 1975). It reduces central sympathetic outflow (Waite 1975) and produces a dose dependent reduction in blood pressure in a number of models of hypertension (Scholtysick et al 1980). Although it is only about one tenth as potent an antihypertensive as clonidine (Dollery & Davies 1980; Scholtysik 1980), its side effects of dry mouth and sedation appear to be less prominent in man (Dollery & Davies 1980) and animals (Kleinlogel et al 1975; Barber & Reid, in preparation).

A major objection to the widespread therapeutic use of clonidine is the rapid reversal of hypotension on interruption of treatment, associated with withdrawal phenomena. These are signs of increased sympathetic activity and are seen after abrupt cessation of clonidine treatment, but do not seem to occur with such frequency or severity after guanfacine is withdrawn (Jaattela 1980; Reid et al 1980a). A possible explanation for this and the longer duration of hypotensive action of guanfacine is that it has a longer elimination half life. This has been shown in man (Dollery & Davies 1980; Kiechel 1980) but no results in animals have been published yet. We have examined the kinetics of a single intravenous dose in the rabbit, a species in which we have studied the dynamic actions and kinetics of clonidine (Dollery & Reid 1973; Reid et al 1980b; Barber & Reid, in preparation).

Method

Five male New Zealand White rabbits (2·8–4·5 kg) were used. Under local anaesthesia, the central artery of the ear was cannulated to sample arterial blood; guanfacine was administered via the marginal ear vein. Guanfacine hydrochloride was made up in 0·9% w/v NaCl (saline) to a dose of 300 μg of the base kg^{-1}. Target times for blood withdrawal were 2, 4, 6, 15, 60, 90, 180, 360 and 540 min; actual times being recorded at the midpoint of withdrawal. The samples were stored in ice until centrifugation (2000 rev min^{-1}, 15 min, 4 °C), after which the plasma was removed and frozen until analysed.

For analysis the samples were made alkaline, extracted in diethyl ether and derivatized with hexafluoroacetyl acetone (Laplanche & Morin 1978). The samples were analysed on a Hewlett Packard gas chromatography with quadrupole g.c.-m.s. system HP 5982 and a HP 5934 data system. The g.c. separation was on a silicon phase OV1 at 3% on Gas-Chrom Q 100–120 mesh in a silanized glass column of 180 × 0·4 (i.d.) cm. Oven temperature was 220 °C, injector temperature 250 °C and transfer line 300 °C. The carrier gas was methane, regulated to maintain a pressure of 0·5 torr at the m.s. source. The mass spectrometry was carried out in chemical ionization using methane as reactant gas. The source was at 200 °C and the mass filter at 150 °C. The derivatives of guanfacine and of the labelled internal standard [^{13}C, $^{15}N_3$] guanfacine were detected in selected ion monitoring using the masses m/z 418 and 424 respectively, the latter corresponding to the molecular mass of [^{37}Cl, ^{13}C, $^{15}N_3$] guanfacine.

Linearity was tested within standards containing up to 200 ng guanfacine per ml of plasma. The detection limit was defined as the value which is significantly different ($P < 0·05$) from the blank value in a one side t-test; this was 0·4 ng ml^{-1} of plasma. Unknown concentrations were calculated with results obtained for external standards. They were prepared with blank plasma and contained 50, 100 or 200 ng or guanfacine hydrochloride ml^{-1} sample. Each sample was measured in duplicate.

Results and discussion

A bi-exponential equation adequately described the plasma concentration time profiles. The lines were fitted using a weighted non-linear least squares fitting program on a Varian computer. The parameters for each animal were calculated and are presented in Table 1. The mean of each parameter (with s.d.) are A: 533 (404) ng ml^{-1}; α: 0·288 (0·196) min^{-1}; B: 34·2 (5·9) ng ml^{-1}; β: 0·00621 (0·000651) min^{-1}. From these parameters the following were calculated: $t_{½\alpha}$ = 2·4 min; $t_{½\beta}$ = 111·5 min; Vd = 529 ml kg^{-1}; Clp = 40·8 ml min^{-1} kg^{-1}.

These results show guanfacine, with an elimination half life of 112 min, exists in rabbit plasma for a much

Table 1. Parameters of two compartment model fitted to data from each rabbit. A α B β are constants in the equation $C = Ae^{-\alpha t} + Be^{-\beta t}$ where C is the plasma concentration at time t. Values given are mean (with s.d.), as calculated by a weighted non-linear least squares line fitting programme. R^2 is the coefficient of determination of the line. The means (with s.d.) of these parameters are A: 533·1 (403·5); α: 0·2875 (0·1956); B: 34·21 (5·906); β: 0·006214 (0·0006512).

Rabbit	1	2	3	4	5
A	352·7	394·8	117·7	66·53	733·7
	(45·87)	(68·31)	(34·68)	(2·865)	(113·0)
α	0·2861	0·3482	0·115	0·1061	0·582
	(0·03673)	(0·05801)	(0·06102)	(0·005645)	(0·05977)
B	42·37	30·99	31·03	28·29	38·38
	(5·284)	(5·969)	(14·66)	(0·5475)	(4·492)
β	0·007169	0·006516	0·005978	0·005825	0·005556
	(0·001053)	(0·00132)	(0·002916)	(0·0001129)	(0·0009212)
R^2	0·996	0·999	0·879	1·000	0·998

* Correspondence and present address: Department of Pharmacology, Chelsea College, Manresa Road, London, SW3 6LX, U.K.

shorter period than it does in man. Half life estimates in man vary from about 12–22 h (Weiss et al 1979; Dollery & Davies 1980; Kiechel 1980), most estimates being in the upper end of that range. This species difference in half lives has also been reported with clonidine, which has an elimination half life in the rabbit of about 30 min (Reid et al 1980) and a half life in man of about 9 h (Davies et al 1977). Although estimates of half lives vary between workers, it seems that the elimination half lives of these two drugs are about 10 to 20 times longer in man than in rabbit, emphasizing that care is needed in 'between species' comparisons of doses or effects, but showing the validity in this case of between drug comparisons in the same species.

Guanfacine's longer plasma half life is a possible explanation of its longer duration of action in animals and man, and the lower frequency with which a withdrawal syndrome occurs.

We gratefully acknowledge the help of Dr Pacha, Dr Laplanche and Dr Jean of Sandoz, Basle in assaying these samples.

REFERENCES

Davies, D. S., Wing, L. M., Reid, J. L., Neill, E., Tippett, E., Dollery, C. T. (1977) Clin. Pharmacol. Ther. 21: 593–601

Dollery, C. T., Davies, D. S. (1980) Br. J. Clin. Pharmacol. 10 (Suppl. 1) 5S–12S

Dollery, C. T., Reid, J. L. (1973) Ibid. 47: 206–216

Jaattela, A. (1980) Ibid. 10 (Suppl. 1) 67S–70S

Kiechel, J. R. (1980) Ibid. 25S–32S

Kleinlogel, H., Scholtysik, G., Sayers, A. C. (1975) Eur. J. Pharmacol. 33: 159–163

Laplanche, R., Morin, Y. (1978) Quant. Mass-Spectrom. Life Sci. II: 339–345

Reid, J. L., Barber, N. D., Davies, D. S. (1980b) Arch. Int. Pharmacodyn. Ther. (Suppl. 1): 11–16

Reid, J. L., Zamboulis, C., Hamilton, C. A. (1980a) Br. J. Clin. Pharmacol. 10 (Suppl. 1): 183S–188S)

Scholtysik, G., Lauener, H., Eichenberger, E., Burki, J., Salzmann, R., Muller-Schweinitzer, E., Waite, R. (1975) Arzneim. Forsch. 25: 1483–1491

Scholtysik, G. (1980) Br. J. Clin. Pharmacol. 10 (Suppl. 1) 21S–24S

Scholtysik, G., Jerie, P., Picard, C. W. (1980) in: Scriabine, A. (ed.) Pharmacology of antihypertensive drugs. pp 79–98, New York, Raven Press

Waite, R. (1975) in: Milliez, P., Safar, M. (eds): Recent Advances in Hypertension Vol. II. Eds pp 27–31 Ingleheim, Boehringer

Weiss, Y. A., Lavene, D. L., Safar, M. E., Simon, S. C., Loria, Y., Georges, D. E., Milliez, P. L. (1979) Clin. Pharmacol. Ther. 25 (3): 283–293

J. Pharm. Pharmacol. 1983, 35: 155–117
Communicated June 25, 1982

0022–3573/83/020115–03 $02.50/0

Concentration-dependence of salicylate distribution

GERALD M. RUBIN, THOMAS N. TOZER*, SVEIN ØIE, *Department of Pharmacy, School of Pharmacy, University of California, San Francisco, CA 94143, U.S.A.*

Salicylate shows saturable binding to plasma albumin in man, as evidenced by a concentration-dependent unbound fraction (Shah et al 1974; Borgå et al 1976; Furst et al 1979). Accordingly, the apparent volume of distribution in man is expected to be concentration-dependent. This dependence has been observed in children who have taken an overdose of salicylate (Levy & Yaffe 1974), but no quantitative relationship between volume of distribution and unbound fraction in plasma has yet been established.

Øie & Tozer (1979) developed a model for relating the volume of distribution of a drug to its binding to plasma proteins, distributed both intravascularly and extravascularly, and to other constituents in the body. For a healthy 70 kg man, in whom the extracellular volume minus plasma volume is 12 litres, the plasma volume is 3 litres and the extravascular/intravascular ratio of albumin distribution is 1·4 (Jusko & Gretch 1976), the model can be expressed as:

$$V = 7{\cdot}2 + 7{\cdot}8 \cdot fu + \frac{V_R}{fu_R} \cdot fu \qquad (1)$$

where fu is the fraction of drug unbound in plasma, fu_R is the fraction of drug outside the extracellular fluids which is unbound, and V_R is the cellular fluid space. The units are in litres.

Using data from various published experiments on salicylate kinetics, we have examined whether or not the increase in the volume of distribution associated with an increase in the fraction unbound to albumin at elevated plasma salicylate concentrations can be described by the proposed model by Øie & Tozer (1979).

Method

The average initial volumes of distribution of salicylate after seven different dose sizes (ranging from 0·5 to 20 g, expressed as sodium salicylate) were calculated from literature data (Smith et al 1946; Swintosky 1956; Schachter & Manis 1958; Hollister & Levy 1965; Rowland & Reigelman 1968; Ventafridda & Martino 1976). For five of the seven dose sizes, volume of distribution was determined by dividing the intravenously administered dose by the extrapolated intercept value for the concentration at time zero. The other doses (2 and 4 g) were given orally. Peak concentrations

* Correspondence.