- ing agent, practolol. *J. Pharmac. exp. Ther.*, **175**, 338–347.
- SMITH, L.H. (1980). The chemistry of beta-adrenergic blocking agents relative to cardioselectivity. *Royal Society of Medicine, International Congress & Symposium Series No. 19*. pp. 93–96.
- VERMEIJ, P., EL SHERBINI-SCHEPERS, M. & VAN ZWIETEN, P.A. (1978). The disposition of timolol in man. *J. Pharm. Pharmac.*, **30**, 53–55.
- WOODS, P. & ROBINSON, M.L. (1981). An investigation of the comparative liposolubilities of β -adrenergic blocking agents. *J. Pharm. Pharmac.* in press.

KINETICS OF INTRAVENOUS PYRIDOSTIGMINE IN MAN

In anaesthetic practice, anticholinesterase drugs are widely used to reverse non-depolarising neuromuscular block. In Great Britain, neostigmine methylsulphate (Prostigmin) is most commonly employed for this purpose. Occasionally, pyridostigmine bromide is used, since its duration of action is approximately 30% longer than neostigmine (Miller, Van Nyhuis, Eger, Vitez & Way, 1974), and it has been suggested that it is less likely to induce significant bradycardia (Katz, 1967). This paper is concerned with the kinetics of pyridostigmine after intravenous administration of relatively small doses of the drug to anaesthetised patients. The study was approved by the hospital ethical committee, and the nature of the procedure was explained to each patient before anaesthesia, and their informed consent was obtained.

Studies were carried out in ten patients, aged 16–64 years, during plastic surgical procedures. Their body weight ranged from 49.9–93.4 kg, and none of them had clinical or biochemical evidence of hepatic or renal disease. One subject (patient 2) was receiving concurrent treatment with anticonvulsant drugs (phenytoin sodium 300 mg/day and phenobarbitone 90 mg/day). All patients were premedicated with nitrazepam (10 mg orally, given on the previous night) and diazepam (5–10 mg orally) on the day of operation. Anaesthesia was induced by thiopentone sodium (200–400 mg); suxamethonium (100 mg) with tubocurarine chloride (15 mg) was used for incubation. Anaesthesia was maintained with nitrous oxide (60–70%) and halothane (1–2%) in oxygen, using intermittent positive pressure ventilation. During the course of the operation, a polyethylene cannula was placed in a superficial vein, attached to a three-way tap, and kept patent by the infusion of saline. Pyridostigmine bromide (200 nmol/kg; 3.65 mg/70 kg) was injected intravenously over a 15 s period. Blood samples (approximately 8 ml) were removed at 2, 3, 4, 5, 7, 10, 15, 20, 30, 40, 50, 60, 70, 80 and 90 min, and added to lithium heparin. Plasma was removed by centrifugation as soon as possible, and stored at -20°C . Pyridostigmine was extracted from plasma as an iodide complex, and its concentration was determined by gas-liquid chromatography using a nitrogen detector (Chan, Williams, Batty & Calvey, 1976).

In the ten patients studied, the plasma concentration of pyridostigmine decreased from 212 ± 25 ng/ml to 32 ± 5 ng/ml (mean $\pm$ s.e. mean) between 2 and 10 min (Table 1). Subsequently, the plasma concentration declined more slowly to 6 ± 1 ng/ml at 60 min. In two patients, the drug was still detectable in plasma at 90 min (Table 1). The relation between the plasma concentration of pyridostigmine and time was invariably expressed as a biexponential equation of the form

$$C_{p(t)} = Ae^{-\alpha t} + Be^{-\beta t}$$

where $C_{p(t)}$ is the plasma concentration at time t , and A , B , α and β are constants. Values for the fast disposition half-life ($T_{1/2\alpha}$) and the slow disposition half-life ($T_{1/2\beta}$) were derived from each biexponential function; total body clearance (C) and the total apparent volume of distribution (V_d) were determined by standard methods (Gibaldi & Perrier, 1975).

The fast disposition half-life of pyridostigmine ranged from 0.61–1.78 min, and the terminal half-life from 14.81–37.01 min (mean half-life = 22.79 min; Table 2). Pyridostigmine clearance (9.3 – 26.5 ml min^{-1} kg^{-1}) was invariably greater than the presumptive value for glomerular filtration rate, and the volume of distribution of the drug ranged from 246.5–833.9 ml kg^{-1} (Table 2). In the one subject studied, these kinetic parameters were not apparently affected by concurrent therapy with phenytoin and phenobarbitone.

In previous experiments, the kinetics of approximately equimolar doses of neostigmine (i.e., 206–308 nmol/kg) have been studied during the reversal of neuromuscular block (Calvey, Wareing, Williams & Chan, 1979). When compared with the present results, it is clear that there are two important differences in the kinetics of the quaternary amines. In the first place, the volume of distribution of pyridostigmine is greater than neostigmine; this difference is probably due to the more extensive distribution and enhanced tissue sequestration of the former drug. Differences in the distribution and uptake of pyridostigmine and neostigmine by tissues probably reflect different steric and ionic properties of the two quaternary amines. Secondly, the clearance of pyridostigmine is at least five times greater than neo-

Table 1 Plasma concentration after intravenous injection of pyridostigmine (200 nmol/kg)

Time (min) Patient	Plasma concentration of pyridostigmine (ng/ml)										
	2	3	4	5	7	10	15	20	30	40	50
1	189	115	46	26	14	14	14	10	NS	9	6
2*	150	109	54	31	25	20	19	16	14	8	ND
3	227	101	49	27	23	15	NS	13	12	11	ND
4	237	106	53	39	31	17	9	8	7	5	ND
5	325	174	101	87	61	49	38	31	23	18	ND
6	206	100	65	NS	43	34	24	19	10	8	3
7	146	92	77	47	40	37	26	23	15	16	9
8	132	97	80	70	59	39	35	26	19	15	10
9	360	159	94	72	53	53	45	27	19	15	12
10	146	98	83	65	40	38	32	23	17	10	8
mean	212	115	70	52	39	32	27	20	15	12	8
s.e. mean	25	9	6	8	5	5	4	2	2	1	1

NS no sample was obtained

ND no pyridostigmine was detected in plasma

* concurrently treated with phenytoin sodium (300 mg/day) and phenobarbitone (90 mg/day)

Table 2 Pharmacokinetic parameters for intravenous pyridostigmine

Patient	$T_{1/2}\alpha$ (min)	$T_{1/2}\beta$ (min)	Cl (ml min ⁻¹ kg ⁻¹)	V_d (ml kg ⁻¹)
1	0.73	37.01	15.6	833.9
2*	0.74	23.66	17.7	604.5
3	0.61	29.12	12.4	519.8
4	1.35	20.44	26.5	781.8
5	0.91	19.34	10.7	297.5
6	0.70	14.81	16.2	347.8
7	1.14	25.42	17.4	636.5
8	1.78	23.33	17.1	574.5
9	0.69	18.43	9.3	246.5
10	1.35	16.35	19.7	465.7

 $T_{1/2}\alpha$ half-life of fast disposition phase $T_{1/2}\beta$ half-life of slow disposition phase

Cl total body clearance

 V_d total apparent volume of distribution

* concurrently treated with phenytoin sodium (300 mg/day) and phenobarbitone (90 mg/day)

stigmine; this difference is presumably related to the differential renal elimination of the two quaternary amines, since pyridostigmine is less extensively metabolised than neostigmine (Somani, Roberts & Wilson, 1972). Similar results have been observed in experimental animals (Baker, Calvey, Chan, MacNee & Taylor, 1978). In consequence, the elimination half-lives of pyridostigmine (22.79 ± 2.09 min; mean $\pm$ s.e. mean) and neostigmine (25.46 ± 2.74 min; mean $\pm$ s.e. mean) were similar, and the difference between the mean values was not statistically significant ($t = 0.777$; $0.50 > P > 0.40$).

It is generally assumed that pyridostigmine is eliminated more slowly than neostigmine, thus accounting for its longer duration of action. Nevertheless, the results of this study suggest that the clearance of pyridostigmine is greater than neostigmine, and that equal doses of the drugs have a similar half-life. When administered in man, the dose of pyridostigmine is normally 4–5 times greater than neostigmine, due to differences in their potency. Experimental evidence suggests that the half-life of larger doses of pyridostigmine is prolonged (Baker *et al.*, 1978), and we hope to investigate the kinetics of different doses of the drug in future studies.

The authors are indebted to Mr D.O. Maisels for permission to study patients admitted under his care.

T.N. CALVEY, K. CHAN, A. DEGHAN & N.E. WILLIAMS

Department of Pharmacy, Liverpool Polytechnic, Liverpool L3 3AF, Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool L69 3BX, and Whiston Hospital, Prescot, Merseyside L35 5DR

Received November 21, 1980

References

- BAKER, P.R., CALVEY, T.N., CHAN, K., MACNEE, C.M. & TAYLOR, K. (1978). Plasma clearance of neostigmine and pyridostigmine in the dog. *Br. J. Pharmac.*, **63**, 509–512.
- CALVEY, T.N., WAREING, M., WILLIAMS, N.E. & CHAN, K. (1979). Pharmacokinetics and pharmacological effects of neostigmine in man. *Br. J. clin. Pharmac.*, **7**, 149–155.
- CHAN, K., WILLIAMS, N.E., BATY, J.D. & CALVEY, T.N. (1976). A quantitative gas-liquid chromatographic method for the determination of neostigmine and pyridostigmine in human plasma. *J. Chromatogr.*, **120**, 349–358.
- GIBALDI, M. & PERRIER, D. (1975). *Pharmacokinetics*, pp. 48–69. New York: Marcel Dekker, Inc.
- KATZ, R.L. (1967). Pyridostigmine (Mestinon) as an antagonist of d-tubocurarine. *Anesthesiol.*, **28**, 528–534.
- MILLER, R.D., VAN NYHUIS, L.S., EGER, E.I., VITEZ, T.S. & WAY, W.L. (1974). Comparative times to peak effect and durations of action on neostigmine and pyridostigmine. *Anesthesiol.*, **41**, 27–33.
- SOMANI, S.M., ROBERTS, J.B. & WILSON, A. (1972). Pyridostigmine metabolism in man. *Clin. Pharmac. Ther.*, **13**, 393–399.

THE EFFECT OF RANITIDINE, A NEW HISTAMINE H₂-RECEPTOR ANTAGONIST, ON THE AMYLASE/CREATININE CLEARANCE RATIO

A recent article in your correspondence columns reported the effect of cimetidine on the amylase/creatinine clearance ratio (ACCR, a sensitive test for pancreatic dysfunction) because of the possibility of exocrine pancreatic damage with this histamine H₂-receptor antagonist (Murie, Murray & Roberts, 1980). No evidence of ACCR elevation during long term oral cimetidine therapy was found.

A new histamine H₂-receptor antagonist, ranitidine hydrochloride, has recently become available. This drug is reported to be several times more potent than cimetidine on a molar basis (Peden, Saunders & Wormsley, 1979; Domschke, Lux, Domschke & Demling, 1979) and, hence, the theoretical possibility exists that this more potent drug may cause pancreatic damage.

We have estimated the ACCR of 15 patients with active duodenal ulceration prior to treatment with

ranitidine by a clinically relevant oral dose of 300 mg daily. The ACCR was repeated after 2 and 4 weeks of therapy. The mean control ACCR of the group was 2.55 ± 0.25 . The ACCR at week 2 and week 4 of treatment were 2.31 ± 0.13 and 2.45 ± 0.20 , values not significantly different from control using Student's *t*-test for paired values.

We have thus found no evidence of ACCR elevation during one month's treatment with ranitidine. This suggests that ranitidine does not damage the exocrine pancreas.

R. MOHAMMED & K. MITCHELL

University Department of Surgery, Western Infirmary, Glasgow G11 6NT

Received December 24, 1980

References

- DOMSCHKE, W., LUX, G., DOMSCHKE, S. & DEMLING, L. (1979). New histamine H₂-receptor antagonist inhibits human gastric acid secretion more strongly than cimetidine. *Gut*, **10**, A450–A451.
- MURIE, J.A., MURRAY, W.R. & ROBERTS, L.B. (1980). Cimetidine and the amylase/creatinine clearance ratio. *Br. J. clin. Pharmac.*, **9**, 279.
- PEDEN, N.R., SAUNDERS, J.H.B. & WORMSLEY, K.G. (1979). Inhibition of pentagastrin stimulated and nocturnal gastric secretion by ranitidine. *Lancet*, **i**, 690–692.