Plasma ranitidine concentrations after intravenous administration in normal volunteers and haemodialysis patients

A. P. ROBERTS
B.Sc., Ph.D., M.I.Biol.

G. T. DIXON†
B.Sc., Ph.D., M.B.B.S.

C. HARRISON†
F.I.M.L.S.

J. R. CURTIS*
M.D., F.R.C.P.

*Departments of Microbiology and Medicine,
Charing Cross Hospital Medical School, London W6 8RF and
†Glaxo Group Research Ltd, Ware, Herts SG12 0DJ*

Summary

A comparison was made of the plasma concentrations of ranitidine base in 12 normal volunteers after the administration of 100 mg intravenously and in 6 patients with terminal renal failure after 40 mg intravenously off and then during haemodialysis. The plasma ranitidine concentrations were determined by radioimmunoassay. The results suggest that reduced elimination of the drug occurs in patients with severe renal failure and that there is significant removal of the drug during haemodialysis. It is suggested that dosage reduction is advisable in patients with severe renal failure and a suitable schedule for such patients is described.

KEY WORDS: ranitidine, haemodialysis, H₂-receptor.

Introduction

Ranitidine is a relatively new H₂-receptor antagonist which is highly water soluble with a log *P* value of 0.2 and pK_a values of 8.2 and 2.7. A mean urinary excretion, after intravenous injection, of 68.2% as unchanged drug together with less than 10% as the N-oxide, desmethyl derivative and S-oxide during the first 24 hr has been reported in normal volunteers (Carey, Martin and Owen, 1981). The elimination half-life of ranitidine after intravenous injection ranged from 110-248 min and the mean renal clearance value was 512 ml/min in normal subjects indicating extensive tubular excretion of ranitidine in addition to glomerular filtration (Carey *et al.*, 1981). Reduced elimination of the drug was therefore anticipated in patients with severe renal failure.

Material and methods

Subjects

Twelve normal volunteers and six patients with terminal renal failure were studied. The endogenous creatinine clearance in the 6 patients was less than 5 ml/min and all 6 were undergoing regular haemodialysis treatment using disposable Gambro Dialysers for 6-8 hr twice weekly. The normal volunteers and the patients all gave their informed consent to the study and the experimental protocol had been approved by the ethical subcommittee of Charing Cross Hospital.

Procedures

Each normal subject was given 100 mg of ranitidine base intravenously (i.v.) over 1 min and blood samples obtained through an indwelling i.v. needle at 1, 2, 3, 4, 5 and 12 hr.

The patients with renal failure were each studied on two separate occasions, once on a non-dialysis day and then on another occasion during haemodialysis. On each occasion, 40 mg of ranitidine base was given i.v. over 1 min and blood samples obtained at 1, 2, 3, 4 and 5 hr. In 4 patients during the non-dialysis study, a final blood sample was taken 24 hr after the dose. During the haemodialysis study, the 40 mg of ranitidine base was given at the start of haemodialysis.

The plasma ranitidine concentrations were determined by radioimmunoassay (Jenner *et al.*, 1981). Statistical analysis was by Wilcoxon sum of ranks test of difference and signed ranks test of difference.

*Correspondence to Dr J. R. Curtis.

TABLE 1. Plasma ranitidine base concentrations (ng/ml) after 100 mg i.v. (normals) and 40 mg i.v. (patients)

		Time of sample collection (hr)					
		1	2	3	4	5	12 24
Normal subjects (A)	Mean	557	389	272	190	136	20
	s.d.	74	46	53	32	30	8
Patients	Off dialysis (B)	Mean	330	268	237	208	199
		s.d.	88	72	79	71	87
	On dialysis (C)	Mean	276	217	181	151	132
		s.d.	44	33	32	25	34
	AvB	$P<0.01$	$P<0.01$	N.S.	N.S.	N.S.	
	AvC	$P<0.01$	$P<0.01$	$P<0.01$	$P<0.05$	N.S.	
				$P<0.05$	$P<0.05$	$P<0.05$	35* 13

*n = 4.

N.S.: not significant.

Results

Table 1 shows the mean plasma ranitidine concentrations together with the standard deviations (s.d.) in normals and patients and also the results of the statistical evaluations. Figure 1 shows the mean values ± 2 s.d. in normals and patients.

FIG. 1. Mean plasma ranitidine base concentrations ± 2 s.d. in ng/ml after 100 mg ranitidine base intravenously in normal subjects; and after 40 mg intravenously in dialysis patients both off and on dialysis.

Comparison of normal volunteers with renal failure patients during a non-dialysis period

The mean plasma ranitidine concentrations were significantly higher in the normal volunteers at 1 and 2 hr but there were no significant differences at 3, 4 and 5 hr. At 4 and 5 hr, the mean values were in fact higher in the renal failure patients but not significantly so. In the 4 patients in whom 24-hr samples were obtained, the mean value at 24 hr was significantly higher than the mean value at 12 hr in the normal volunteers ($P<0.05$).

Comparison of normal volunteers with renal failure patients during haemodialysis

The mean plasma ranitidine concentrations in the

normal volunteers were significantly higher than in the patients during haemodialysis up to 4 hr, but at 5 hr the levels were almost identical.

Comparison of renal failure patients on a non-dialysis period and during haemodialysis

After the first hour, the mean plasma ranitidine concentrations were significantly lower during haemodialysis than the values obtained in the same patients in a non-dialysis period.

Discussion

In this study, the results suggest that reduced elimination of ranitidine occurs in patients with severe renal failure. Thus the mean concentration after the first 2 hr in the renal failure patients during a non-dialysis period and after only a 40 mg dose of ranitidine base were higher although not significantly so than in the normal volunteers given 100 mg of ranitidine base. In addition the 4 patients in whom 24-hr samples were obtained during the non-dialysis period had a mean concentration at 24 hr which was significantly higher than the mean concentration at 12 hr in the normal volunteers.

The comparison of ranitidine concentrations in the patients during a non-dialysis period and during haemodialysis suggests that significant amounts of ranitidine are removed by haemodialysis. After 1 hr the mean plasma ranitidine concentrations were all significantly lower during haemodialysis. This finding was also to be anticipated in view of the relatively low molecular weight (350-87 daltons) and small degree of protein-binding ($15 \pm 3\%$) of the drug.

Some attempts at correlation between plasma concentrations of ranitidine and pharmacological effects have been made and 50% inhibition of pentagastrin-induced acid secretion has been achieved at a mean plasma ranitidine concentration of 93.6 ng/ml (range 48-125) in patients with duodenal ulcer (Peden, Saunders and Wormsley 1979; Peden *et al.*, 1979). With this in mind and with

the results of the present study, it is tentatively suggested that some dosage reduction can be recommended in patients with terminal renal failure. A dose of 40 mg ranitidine base i.v. every 12 hr would seem to be adequate with an additional dose of 40 mg at the end of each dialysis.

Acknowledgments

Thanks are due to Sister Margaret Greatbatch and the Nursing Staff of the Renal Unit, Charing Cross Hospital who assisted with collection of some of the samples and to Mrs R. Thornley for processing of the blood samples.

References

- CAREY, P.F., MARTIN, L.E. & OWEN, P.E. (1981) Determination of ranitidine and its metabolites in human urine by reversed-phase ion-pair high performance liquid chromatography. *Journal of Chromatography*, **225**, 161.
- JENNER, W.N., MARTIN, L.E., WILLOUGHBY, B.A. & FELLOWS, I. (1981) The development of a radioimmunoassay for ranitidine in biological fluids. *Life Sciences*, **28**, 1323.
- PEDEN, N.R., RICHARDS, D.A., SAUNDERS, J.H.B. & WORMSLEY, K.G. (1979) Pharmacologically effective plasma concentrations of ranitidine. *Lancet*, *ii*, 199.
- PEDEN, N.R., SAUNDERS, J.H.B. & WORMSLEY, K.G. (1979) Inhibition of pentagastrin—stimulated and nocturnal gastric secretion by ranitidine. A new H_2 -receptor antagonist. *Lancet*, *i*, 690.

(Accepted 11 May 1982)