

RANITIDINE DISPOSITION IN PATIENTS WITH RENAL IMPAIRMENT

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Ranitidine disposition has been studied in 12 patients with renal impairment following 50 mg given intravenously and 150 mg given by mouth on separate occasions. The clearance of ranitidine from plasma (y) was correlated with creatinine clearance (x): $y = 10.47 + 0.289x$, $r^2 = 0.751$, but there was no significant correlation of creatinine clearance with distribution volume or bioavailability. The mean (s.e. mean) distribution volume was 1.62 (0.08) l/kg and the mean bioavailability 0.81 (0.05). These data suggest that in order to obtain similar ranitidine plasma concentrations in anephric patients and patients with normal renal function, the maintenance dose in the anephric patients should be 25-30% of that for patients with normal renal function.

Introduction

Ranitidine is cleared predominantly by urinary excretion of unchanged drug (Brogden *et al.*, 1982) but there is little information on the effect of renal dysfunction on ranitidine disposition. McGonigle *et al.* (1982) studied the disposition of ranitidine in patients with poor renal function, but the majority of the data from this study was reported in terms of half-life changes. The aim of the present study was to investigate relationships between creatinine clearance and the major determinants of ranitidine disposition: plasma clearance, distribution volume, half-life and bioavailability.

Methods

One female and 11 male patients of mean (s.e. mean) age 67.9 (1.5) years with mild to severe impairment of renal function took part in this study which was approved by the Human Ethics Committee of Flinders Medical Centre and the Daw Park Repatriation Hospital. Patients gave written consent to take part in the study after its nature and purpose had been explained to them by one of the investigators. Each patient received on separate occasions 5-7 days apart oral ranitidine (150 mg) and intravenous ranitidine (50 mg), six patients receiving the oral dose first and six the intravenous dose first. Patients were fasted overnight before receiving ranitidine at approximately 08.00 h or in the case of patients with severe renal dysfunction on haemodialysis, for approximately 6 h prior to dosing with ranitidine. Patients on haemo-

dialysis received their doses approximately 2 h after the completion of their dialysis. Oral ranitidine was taken with 50 ml of water and the intravenous dose was given by constant infusion into a peripheral arm vein over 25 min. Peripheral venous blood samples (5 ml) were obtained before each dose and 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 h after the oral dose and the above times from the start of the intravenous infusion with an additional sample taken at 0.5 h. Blood samples were obtained via an indwelling catheter not used for drug administration during the first 10 h of the study and by venepuncture thereafter.

Plasma was stored at -20°C until analysed for ranitidine using a specific high performance liquid chromatographic method (Mihaly *et al.*, 1980). The 12 sets of calibration standards analysed concurrently with this study had a mean coefficient of variation (C.V.) of 6.6%. Total urine was collected during the first 8 h following each dose in order to determine creatinine clearance, except in the case of the haemodialysis patients who were unable to provide urine samples. Plasma and urinary creatinine concentrations were measured by a standard method (Finley *et al.*, 1978).

The area under the plasma ranitidine concentration-time curve from zero to infinite time (AUC) was calculated using the trapezoidal rule. The area beyond the last plasma concentration measurement (C_L) was obtained as C_L/k where k is the rate constant from unweighted regression of the terminal log-linear portion of the data. The slow half-life ($t_{1/2}$) was calculated as $0.693/k$. The clearance of ranitidine from

plasma was determined as the quotient of the intravenous dose and its AUC. The distribution volume of ranitidine at steady-state was calculated by a model independent method (Benet & Galeazzi, 1979). Ranitidine bioavailability (F) was obtained as:

$$F = \frac{\text{AUC oral}}{\text{AUC intravenous} \times 3}$$

The magnitude (C_{\max}) and time (t_{\max}) of maximum ranitidine concentration after oral doses was determined by inspection. If values were within $C_{\max} \pm 2.C.V.$ for the concurrently analysed calibration standards, then all such values were averaged.

The significance of relationships between creatinine clearance and the above parameters of ranitidine disposition were assessed using the correlation coefficient. For the purpose of these analyses, a creatinine clearance of 0.5 ml/min has been assigned to each patient on haemodialysis, as urine samples to enable direct determination of creatinine clearance could not be obtained in these patients. A t -test for paired data was used to evaluate differences in half-life following oral and intravenous doses. All values are presented as means (s.e. mean) and $P < 0.05$ is considered significant.

Results

The creatinine clearance, body weight, plasma ranitidine clearance, steady-state distribution volume and half-life following the intravenous dose are listed for each patient in Table 1. Patient 2 has a bioavailability of 1.7 and abnormally high values for clearance and steady-state distribution volume that suggest that

less than 50 mg of ranitidine was administered intravenously. For this reason the data from this patient has been excluded from further analysis. There is a significant correlation between the clearance of ranitidine (y) and creatinine clearance (x): $y = 10.47 + 0.289x$, $r^2 = 0.751$ ($P < 0.01$), shown in Figure 1. A similar but slightly weaker correlation exists for creatinine clearance and ranitidine clearance normalised for body weight. The data in the figure indicate that the clearance of ranitidine is approximately 10 l/h in the absence of any renal function. Neither the steady state distribution volume or the bioavailability of ranitidine showed a significant correlation with creatinine clearance.

Following the intravenous dose, the mean half-life was 5.32 (0.75) h and was not different from that following the oral dose, 5.51 (0.77) h. There was a significant correlation between the reciprocal of the intravenous half-life and creatinine clearance ($r^2 = 0.59$). Mean maximum ranitidine plasma concentration was 866.6 (81.8) $\mu\text{g/l}$ and the mean time to peak concentration was 2.93 (0.27) h.

Plasma ranitidine concentration profiles after intravenous and oral doses of ranitidine are shown in Figure 2 for patient 10 who had a creatinine clearance of 25 ml/min and patient 11 who was on haemodialysis.

Discussion

The data in Figure 1 indicate that in the absence of any renal function the clearance of ranitidine is approximately 10.5 l/h. This value is in agreement with the mean of 11.27 (1.83) l/h for non-renal clear-

Table 1 Ranitidine disposition as a function of creatinine clearance

Patient	Creatinine clearance (ml/min)	Weight (kg)	Ranitidine clearance* (l/h)	Distribution volume* (l/kg)	F	Half-life* (h)
1	32	70.9	15.74	1.67	0.96	4.47
**2	34	64.0	41.85	3.41	1.70	3.52
3	0.5	77.0	12.64	1.48	0.91	6.54
4	0.5	90.0	17.83	1.66	0.81	6.79
5	28	61.5	13.91	2.0	0.57	7.29
6	34	59.8	18.40	1.74	0.49	4.36
7	64	81.4	23.86	1.51	0.66	3.38
8	100	77.0	38.67	2.08	0.79	2.90
9	65	84.4	39.44	1.46	0.80	2.09
10	25	61.6	22.23	1.62	1.01	2.99
11	0.5	82.0	8.21	1.42	0.92	10.04
12	12	82.0	8.71	1.15	0.98	7.62
Mean		75.2		1.62	0.81	5.32
s.e mean		3.1		0.08	0.05	0.75

* i.v. data

** Data from this patient has been excluded from all averages

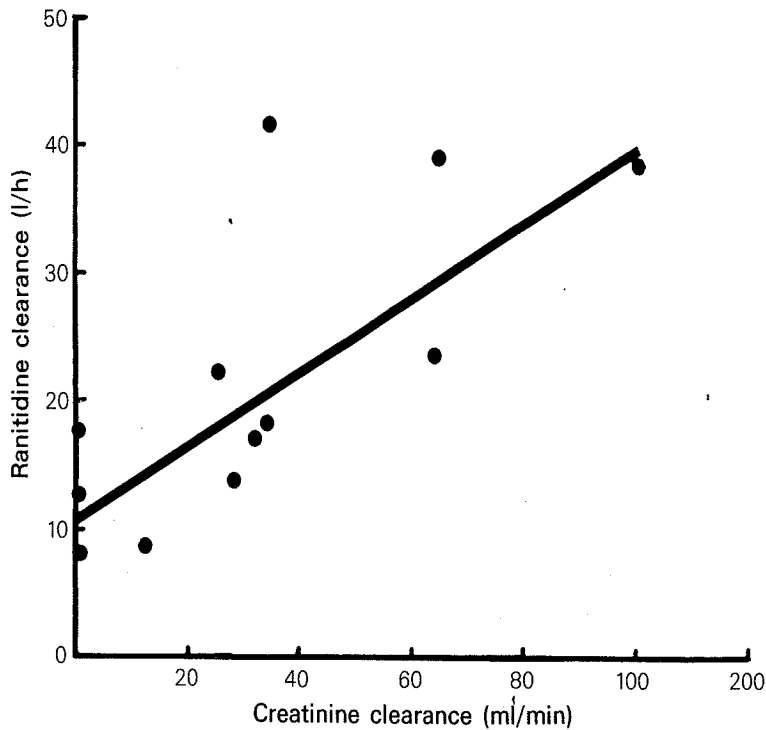


Figure 1 The relationship between plasma ranitidine clearance and creatinine clearance.

ance obtained from three studies with intravenous doses in renally healthy subjects: 13 l/h (Chan *et al.*, 1982), 7.62 l/h (Van Hecken *et al.*, 1982) and 13.2 l/h (McNeil *et al.*, 1982). Non-renal clearance accounts for 25–31% of the range of plasma clearances of

34.1–42.5 l/h reported for ranitidine after intravenous doses in healthy subjects (Brogden *et al.*, 1982). These data imply that in order to obtain similar plasma ranitidine concentrations in subjects with normal renal function and anephric patients the

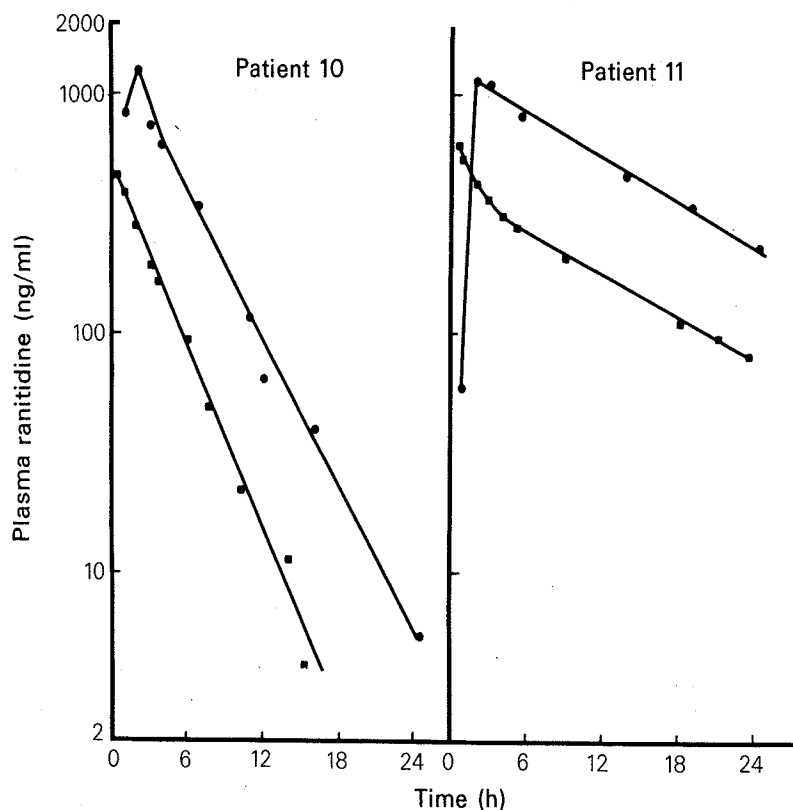


Figure 2 Plasma ranitidine concentration-time profiles following intravenous doses of 50 mg and oral doses of 150 mg of ranitidine to patient 10 who had a creatinine clearance of 25 ml/min and patient 11 who was on haemodialysis.

maintenance dose in anephric patients should be 25–30% of that for patients with normal renal function. The lack of any correlation between bioavailability and creatinine clearance indicates that the inferences made from intravenous data will also apply to oral dosing. These conclusions are similar to those of McGonigle *et al.* (1982) who suggested that oral maintenance doses of ranitidine in patients with plasma creatinine concentrations above 300 $\mu\text{mol/l}$ should be half those of patients with normal renal function.

In the absence of any change in distribution volume, the half-life in patients with poor renal function should increase to a maximum of 3–4 times that in subjects with normal kidneys. This increase is consistent with the half-lives of approximately 2 h reported for subjects with normal renal function (Brogden *et al.*, 1982) and the values of 6–10 h for the three patients on haemodialysis (Table 1) and are in reasonable agreement with the mean value of 8 h reported for patients with a median plasma creatinine of 200 $\mu\text{mol/l}$ (McGonigle *et al.*, 1982). Figure 2 shows the plasma ranitidine concentration time profile for patient 10 (creatinine clearance 25 ml/min) and patient 11 (creatinine clearance 0.5 ml/min). In healthy volunteers the range of half-lives of 1.6–2.1 h after intravenous dosing is shorter than that of

2.1–3.1 h after oral dosing (Brogden *et al.*, 1982) which presumably reflects the effect of absorption rate on the overall elimination of ranitidine. The mean half-life of 5.32 h after intravenous ranitidine in our patients is not different from that after oral dosing. The lack of a difference in half-lives with route of administration is consistent with the longer half-life in our patients and the above interpretation of the mechanism of this effect in healthy-subjects.

The bioavailability of ranitidine does not correlate with creatinine clearance and the mean bioavailability of 0.81 for patients with renal dysfunction is similar to the mean of 0.88 reported by McNeil *et al.* (1981) in healthy subjects but higher than the value of approximately 0.5 reported in the majority of studies (Brogden *et al.*, 1982). A bioavailability of 0.39 was reported on the basis of urinary excretion of unchanged ranitidine (Carey *et al.*, 1981). It is of interest to note that a similar value of 0.35 was also obtained by Van Hecken *et al.* (1982) from urinary excretion data although concurrent plasma concentration measurements in the same subjects yielded a value of 0.6. The reasons for this discrepancy are unclear but must involve differences in the renal clearance of ranitidine following these two doses.

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