Effects of cirrhosis and ageing on the elimination and bioavailability of ranitidine

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SUMMARY The plasma concentrations of ranitidine after oral and intravenous administration have been measured in 10 healthy young adults, nine cirrhotic patients, and eight healthy elderly people. In the first of these bioavailability was $51 \pm 4\%$ and half life 161 ± 11 minutes after oral and 124 ± 5 minutes after intravenous administration. In the cirrhotics bioavailability was increased to $70 \pm 7\%$, clearance was reduced, and there was a modest increase in half life. In the elderly bioavailability was similar to that in young adults, clearance was markedly reduced, and half life was prolonged to 243 ± 7 minutes after oral and 194 ± 11 minutes after intravenous administration. It is predicted that blood levels in cirrhotics and the elderly would be 50 to 60% higher than in healthy young adults after repeated oral administration of similar doses.

Ranitidine is a new H_2 receptor antagonist for the treatment of peptic ulcer disease. In contrast with cimetidine, which is predominantly excreted as unchanged drug in the urine,¹ approximately 50% of ranitidine is eliminated by hepatic metabolism and it undergoes significant pre-systemic metabolism ('first-pass effect').² It is to be expected therefore that impaired capacity to metabolise drugs in the liver would result in raised blood levels of ranitidine because of both increased bioavailability and decreased elimination. Reduced renal function would be expected only to prolong the drug's elimination. In this study we have examined the pharmacokinetics of ranitidine in two clinically relevant situations – that is, in cirrhotic patients and in old age. In patients with chronic liver disease impaired hepatic function leads to reduced pre-systemic metabolism of certain drugs and consequently high blood levels after oral administration.^{3,4} The elderly have reduced hepatic and renal function, both of which have been shown to alter drug pharmacokinetics.^{5,6} Both groups of patients are particularly liable to peptic ulcer disease and it is important therefore to determine the extent of the dosage adjustment that might be required in these groups.

Methods

PATIENTS

All participants gave their informed consent for the

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study, which was approved by the hospital ethics committee. Three groups of individuals were studied.

Normal subjects

These were 10 healthy individuals aged between 20 and 40 years. All were non-smokers and none was taking significant drug therapy. Five were women.

Cirrhotics

These were nine hospital inpatients with histologically proven chronic liver disease. All had been admitted for investigation or treatment of their liver complaint, but their clinical condition was judged to be stable at the time of the study. None was receiving drugs known markedly to influence hepatic microsomal enzymes and none had undergone surgical portosystemic anastomosis. Relevant details of the cirrhotic patients are given in Table 1.

Elderly

These were 10 healthy individuals aged between 65 and 80 years. They were recruited with the assistance of general practitioners. The elderly had no known active disease or significant biochemical abnormality. None was taking drugs known markedly to influence hepatic enzymes.

The pharmacokinetics of ranitidine were measured in all subjects using the same protocol. Each subject was studied on two separate days at least five days apart, when ranitidine was given

Table 1 Details of cirrhotic patients

Age (yr) and sex	Diagnosis	Serum albumin (g/l)	BSR	Ascites
54F	Alcoholic cirrhosis	37	1.0	—
72M		32	1.3	+
58M		32	1.3	+
42F	Micronodular cirrhosis	36	1.0	+
54M	Cryptogenic cirrhosis	16	1.9	+
51M	Alcoholic cirrhosis	29	1.1	—
60M		35	1.4	+
60F		30	1.4	+
60M	Micronodular cirrhosis	36	1.0	—

either orally or intravenously. The order of administration was alternated between participants. Subjects fasted overnight and after insertion of an intravenous cannula and withdrawal of baseline blood sample, they received either ranitidine 100 mg orally or 50 mg intravenously as a constant infusion over one hour. Venous blood samples were collected at 0.5, 1, 1.5, 2, 2.5, three, four, five, six, eight, 10, and 24 hours after drug administration. Plasma was immediately separated from red blood cells and stored frozen for subsequent measurement of drug concentration by a radioimmunoassay at Glaxo Group Research Laboratories. Heart rate and blood pressure were measured before and hourly for four hours after drug administration.

Physical examination, urinalysis, full blood count, plasma viscosity, urea and electrolyte concentrations, liver function tests, prothrombin time (expressed as British Standard Ratio:BSR), and electrocardiogram were performed on all subjects at the beginning of the study and after the second dose of ranitidine. Creatinine clearance was also measured in all participants using a 24 hour urine collection. In addition, antipyrine clearance was measured in the normal subjects and the cirrhotic patients using the procedure previously described.⁷

Calculations

Plasma ranitidine half-life was calculated using least squares linear regression analysis of the terminal exponential of the log plasma concentration time profile. The area under the plasma concentration time curve (AUC) was calculated as follows. The area up to the end of sampling (A) was calculated using the trapezoidal rule. Subsequent area extrapolated to infinity (B) was calculated from regression analysis of the terminal log concentration time slope. The total area was the sum of A+B. Volume of distribution was calculated as $\text{dose}_{iv}/C_{\beta,0}$ where $C_{\beta,0}$ is the plasma concentration of ranitidine

at time zero derived from back extrapolation of the terminal exponential of the log concentration time profile. Systemic bioavailability was calculated as $\frac{\text{AUC oral}}{\text{AUC IV}} \times \frac{\text{Dose IV}}{\text{Dose oral}} \times 100$.

Systemic clearance was calculated as

$$\frac{\text{Dose IV}}{\text{AUC IV}}$$

Statistical analysis was by one-way analysis of variance.

Results

Ranitidine was well tolerated and there were no significant changes in heart rate or blood pressure. No deterioration in hepatic function occurred in cirrhotics after ranitidine. Ranitidine caused no haematological or biochemical abnormalities in the young adults or the elderly.

Data collection was virtually complete. It was, however, necessary to exclude two of the elderly subjects from analysis as the results obtained were clearly erroneous. Ranitidine plasma concentrations in the three groups are shown in Figs. 1, 2 and 3. Oral administration of 100 mg produced mean ranitidine concentrations of 100 ng/ml or more in all groups after 30 minutes. A plateau in ranitidine concentrations was seen in all groups after oral dosing. The plateau concentrations differed little between the young normal subjects and the elderly, but were consistently higher in cirrhotics. The decay in ranitidine plasma concentrations began about three hours after dosing.

After intravenous administration the peak ranitidine concentrations occurred at the end of the infusion and were similar in the three groups. The concentrations then decayed in a biexponential manner.

The derived ranitidine pharmacokinetic measurements are shown in Table 2. Plasma ranitidine half-life was prolonged in cirrhotics and in the elderly. This was evident in the elderly after both oral and intravenous administration but found in cirrhotics only after the intravenous route. The volume of distribution of ranitidine was not significantly different in the three groups. Reduced ranitidine clearance was observed in the elderly and cirrhotics.

An increase in systemic bioavailability was seen only in cirrhotics. They demonstrated a 37% increase in mean ranitidine bioavailability and a 47% decrease in mean antipyrine clearance compared with normal subjects. Mean creatinine clearance was lower than that in normal subjects by 30% and 38% in cirrhotics and the elderly respectively.

Fig. 1 Plasma levels after oral (x) administration of 100 mg ranitidine and intravenous (.) infusion 50 mg ranitidine in 10 healthy young adults (mean $\pm$ SEM).

Fig. 2 Plasma levels after oral (x) administration of 100 mg ranitidine and intravenous (.) infusion 50 mg ranitidine in nine cirrhotic patients (mean $\pm$ SEM).

Discussion

This study has elucidated the effects of chronic liver disease and old age on the plasma concentrations of ranitidine. It has shown that the major change in chronic liver disease is a rise in peak plasma levels after oral administration due to an increased

systemic bioavailability. In contrast, a prolongation of half-life is the most notable finding in the elderly.

Ranitidine has a complicated pharmacokinetic profile, being both metabolised in the liver and excreted unchanged by the kidney. The exact percentage of drug which is reported to undergo hepatic metabolism differs between studies^{8 9} but

Table 2 Measurements in three groups of people (mean $\pm$ SEM)

Groups	Ranitidine pharmacokinetics					Antipyrine clearance (ml/min)	Creatinine clearance (ml/min)
	Half life (min)		Volume of distribution (litres)	Clearance (ml/min)	Bioavailability (%)		
	Oral	Intravenous					
Ten healthy young individuals	161±11	124±5	106±11	543±40	51±4	40±5	125±18
Nine cirrhotic patients	165±20	166±13	115±10	476±44	70±7	21±3	87±10
Eight healthy elderly individuals	243±7	194±11	142±29	322±31	48±7	—	77±8
F ratio	8.4	13.0	0.25	8.0	4.2	10.2	3.5
p value	<0.002	<0.001	N.S.	<0.005	<0.05	<0.01	<0.05

Fig. 3 Plasma levels after oral (x) administration of 100 mg ranitidine and intravenous (.) infusion 50 mg ranitidine in eight healthy elderly individuals (mean $\pm$ SEM).

we believe that it is just over 50% after intravenous administration. The metabolic process in the liver for ranitidine is avid, so that there is considerable presystemic metabolism. This accounts for the approximate 50% bioavailability seen in this study in young adults. In this group the results are closely similar to those in most previous studies. A recent study, however, using a less sensitive assay and shorter sampling period, suggested a greater bioavailability and shorter half-life.⁹ The findings in patients with chronic liver disease were consistent with predictions based on the known pharmacokinetics of ranitidine. It has been well established that, in cirrhotics, the bioavailability of 'high-clearance' agents is considerably increased because of reduced metabolic capacity and the presence of intra- and extrahepatic portosystemic shunting.^{3,4} Thus, in such patients, abnormally high blood concentrations are seen predominantly after oral administration of such drugs. Evidence that cirrhotics in the present study had impaired

metabolic capacity is provided by the significant reduction in antipyrine clearance. The latter is now established as a sensitive test of hepatic microsomal oxidative activity.¹⁰ In the absence of a change in the volume of distribution the moderate prolongation of ranitidine half-life seen in cirrhotics is due to a reduction in the systemic clearance. This can be attributed to impaired hepatic metabolism and the reduction in renal function seen in this group.

In the elderly hepatic drug metabolism is known to be reduced⁵ and decreased first-pass effect has been demonstrated.¹¹ Variability in drug metabolism is wide in the elderly, however, and not all elderly people show impairment.¹² The normal bioavailability of ranitidine in the elderly in this study suggests no reduction in drug metabolism. Unfortunately, we did not perform an independent measure of drug metabolism in this group, such as antipyrine clearance. The striking change in the elderly was the considerable prolongation in ranitidine plasma half-life, caused mainly by the large reduction in systemic clearance. If the drug metabolising capacity is assumed to be normal in these elderly subjects then the age related fall in renal function (as demonstrated by the reduced creatinine clearance) must be the major contributing factor. This change would therefore be similar to the marked prolongation of ranitidine plasma half-life reported in renal failure.¹³

One can predict from our data that, after repeated oral administration, ranitidine concentrations will be approximately 55% higher in the cirrhotics and approximately 60% higher in the elderly compared with the young adults. In these circumstances a minor dose adjustment would be appropriate for a drug with a low therapeutic ratio. Present evidence suggests, however, that ranitidine is substantially free of dose-related adverse effects, so that dose reduction in cirrhotics and the elderly is not mandatory.

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