Br. J. clin. Pharmac. (1985), **20**, 699–702

Pharmacokinetics of ranitidine in acute upper gastrointestinal haemorrhage

O. VAROQUAUX[1], J. M. TRAWALE[2], J. DOLL[3], J. ANDRIEU[3], S. GROSBUIS[2], M. PAYS[4] & C. ADVENIER[1]

[1]Laboratoire de Pharmacologie, [2]Service de Réanimation Médicale et d'Urgences et [3]Service de Médecine Interne, Centre Hospitalier de Versailles, F-78150 Le Chesnay et [4]Laboratoire de Chimie Analytique, UER des Sciences Pharmaceutiques, Université de Caen, F-14000 Caen, France

A pharmacokinetic study of ranitidine was performed in 14 patients with haematemesis divided into two groups according to the severity of blood loss. Pharmacokinetic values were calculated from plasma concentrations after the first of three daily injections (100 mg) and compared with those obtained in five healthy volunteers (50 mg i.v.). There were no significant differences between patients in the two haemorrhage groups and controls. The low, or even questionable, effectiveness of histamine H_2-receptor antagonists in the treatment of upper gastrointestinal haemorrhage does not seem to be due to pharmacokinetic factors.

Keywords ranitidine pharmacokinetics gastrointestinal haemorrhage

Introduction

Numerous attempts have been made at evaluating the effectiveness of histamine H_2-receptor antagonists in the treatment of upper gastrointestinal haemorrhage. With regard to ranitidine Nowak *et al.* (1982) found it superior to conventional treatment, especially in patients with gastric ulcer; Dawson & Cockel (1982) showed that it reduced the incidence of rebleeding in duodenal ulcer; Thomson *et al.* (1984) compared it with cimetidine and concluded that both were equally effective. In contrast, Coraggio *et al.* (1984) did not find any significant difference between ranitidine and a placebo in the control of iatrogenic gastroduodenal haemorrhages.

Thinking that these conflicting or poor results might be due, at least in part, to kinetic disturbances, we carried out a comparative pharmacokinetic study of intravenous ranitidine in patients with severe or mild upper gastrointestinal bleeding and in healthy volunteers.

Methods

Patients

Fourteen patients with haematemesis entered the study; all had given verbal, informed consent to the study. There were 12 men and two women ranging in age from 22 to 83 years and in weight from 46 to 87 kg. As in the Barer *et al.* (1983) and Thomson *et al.* (1984) studies, the patients were divided into two groups according to the severity of blood loss and its haemodynamic consequences. The 'severe haemorrhage' group consisted of six patients who required more than five

Correspondence: Dr O. Varoquaux, Laboratoire de Pharmacologie, Centre Hospitalier de Versailles, 177, rue de Versailles, F-78150 Le Chesnay, France

transfusion units (packed red blood cells or fresh frozen plasma) and presented with a heart rate in excess of 100 beats min^{-1} and with a blood pressure equal or inferior to 110/70 mm Hg. The 'mild haemorrhage' group consisted of eight patients with normal blood pressure and a heart rate of 100 beats min^{-1} or less; they required fewer perfusions, less than five transfusion units or even none.

The cause of the haemorrhage was gastric ulcer (n = 9) or duodenal ulcer (n = 5). Six patients were taking non steroidal anti-inflammatory drugs and two, antivitamin K drugs.

Patients with haemorrhage from ruptured oesophageal varicosities or ulcerated tumour and patients with organic renal failure or liver dysfunction were excluded from the study.

Starting on the day of admission, all patients received 100 mg of ranitidine intravenously three times daily for 3 consecutive days. They were then put on oral ranitidine 150 mg morning and afternoon. Topical anti-acid treatments were discontinued.

Blood samples were taken from all patients on the first day of parenteral dosing 10, 20, 30, 45 min and 1, 2, 4, 6 and 8 h after the first intravenous injection of ranitidine.

All samples were collected on lithium heparinate. Plasma was separated by centrifugation and kept at −80° C pending assay.

Controls

Five healthy volunteers (four men and one woman) aged from 25 to 52 years and weighing from 60 to 76 kg received one single 50 mg dose of ranitidine by intravenous injection. Since it has been clearly demonstrated that the kinetics of ranitidine are dose-independent (McNeil *et al.*, 1981), the pharmacokinetic values measured in volunteers after a 50 mg i.v. dose could legitimately be compared with those obtained in patients after a 100 mg i.v. dose.

Blood samples from controls were collected and treated as described above for patients.

A high performance reversed phase liquid chromatography method was used for the determination of ranitidine in plasma.

Calculations

Plasma ranitidine concentration data were subjected to an open two-compartment model analysis of an Apple IIe microcomputer according to Wagner's (1975) equations.

Comparison between the groups were made by means of Student's t-test for unpaired data.

Results

Figure 1 shows the plasma ranitidine concentration curves obtained after intravenous injection of 50 mg to controls and 100 mg to patients with upper gastrointestinal haemorrhage. Pharmacokinetic values calculated from plasma concentrations are given in Table 1.

There were no significant changes in pharmacokinetic values in patients with either severe or mild haemorrhage as compared with controls. However, individual values were more scattered and mean volume of distribution and total clearance values were higher in the severe haemorrhage group than in the mild haemorrhage and control groups.

Discussion

The pharmacokinetic values of ranitidine observed in controls after intravenous injection were in close agreement with those reported in the literature (see the review paper by Roberts, 1984).

There were no significant differences in pharmacokinetic values between patients with severe or mild haemorrhage and controls. However, patients with severe bleeding had a distinct, though non-significant, increase in volume of distribution, possibly due to ranitidine depletion through blood loss. Individual values were also more scattered in this group. Thus, in two patients plasma ranitidine concentrations 4 h after the intravenous dose of 100 mg were lower than those required to reduce gastric acid output by 50% and which have been reported as ranging from 0.095 $\mu g\ ml^{-1}$ (Holloway *et al.*, 1984) to 0.166 $\mu g\ ml^{-1}$ (Lebert *et al.*, 1981).

This lack of significant differences between patients and controls after intravenous administration of ranitidine, suggests that the kinetic abnormalities observed in a few patients were most probably of minor importance and transient.

However it must also be noted that although ranitidine pharmacokinetic values were very similar in patients and controls, tissue perfusion might have been differently distributed in patients, with subsequent perturbations in drug tissue uptake and concentrations at the site of action. It has been shown that in spite of 'normal' plasma levels, drug distribution can be profoundly altered in patients with severe haemodynamic disturbances (Wilkinson, 1975).

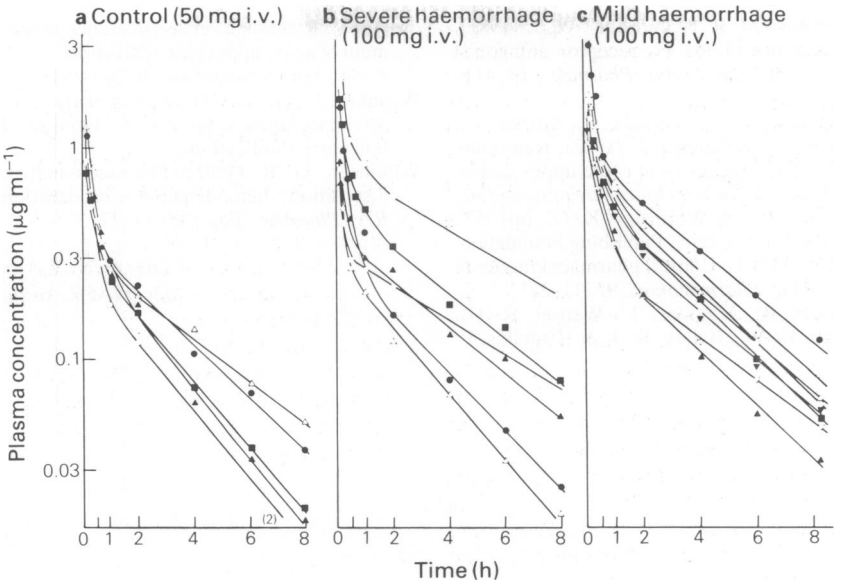

Figure 1 Plasma ranitidine concentrations after intravenous injection of 50 mg (controls) or 100 mg (patients with severe or mild upper gastrointestinal haemorrhage).

Table 1 Ranitidine pharmacokinetic values (mean ± s.e. mean) calculated from plasma concentrations

	Controls (50 mg i.v.)	*Severe haemorrhage patients (100 mg i.v.)*	*Mild haemorrhage patients (100 mg i.v.)*
n	5	6	8
$t_{½,z}$ (h)	2.24 ± 0.27	3.00 ± 0.37	2.48 ± 0.21
AUC (mg l^{-1} h)	1.16 ± 0.13	2.30 ± 0.68	2.44 ± 0.26
V (l kg^{-1})	2.14 ± 0.16	4.08 ± 0.82	2.44 ± 0.48
CL_T (l h^{-1} kg^{-1})	0.69 ± 0.10	1.06 ± 0.31	0.65 ± 0.09

In conclusion, the low, or even questionable, effectiveness of histamine H_2-receptor antagonists in the treatment of upper gastrointestinal haemorrhage does not seem to be due to pharmacokinetic factors.

The authors thank Dr C. Alexandre (Glaxo, Paris) for her generous supply of ranitidine and Dr G. Roux for his English translation.

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(*Received 9 April 1985, accepted 7 August 1985*)