Pharmacokinetics of ranitidine in quadriplegics

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In a previous study we observed that quadriplegic patients were unresponsive to ranitidine given in high dose (600 mg day^{-1} intravenously) for prophylaxis of stress ulceration. The pharmacokinetics of 100 mg of intravenous ranitidine have therefore been studied in six male quadriplegic patients. Plasma drug concentrations declined in a biexponential fashion. The mean ($\pm$ s.e. mean) distribution half-life was $9.42 (\pm 1.04)$ min. The terminal plasma elimination half-life $1.79 (\pm 0.12)$ h, the volume of distribution $103 (\pm 17)$ litres and total body clearance $663 (\pm 86)$ ml/min. These values are similar to those described in two published studies performed in normal male volunteers. This suggests that there is no pharmacokinetic reason for the quadriplegics to be resistant to ranitidine and the defect is likely to be related to vagal control of acid secretion.

Keywords quadriplegia ranitidine pharmacokinetics

Introduction

Patients who have suffered serious spinal cord injuries, especially those with cervical cord lesions, have an excess risk of developing upper gastro-intestinal bleeding compared with other patients who have suffered equally serious injuries not involving the spinal cord (Perret & Solomon, 1969; Leramo *et al.*, 1982).

In recent study we noted that quadriplegic patients consistently failed to respond to H_2 -receptor antagonists given in high dose for stress ulcer prophylaxis (More *et al.*, 1985). We therefore performed the present study to ascertain if quadriplegic patients had unusual ranitidine pharmacokinetics

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Methods

Patient group

Six male quadriplegic inpatients in the Spinal Injuries Unit of the Royal North Shore Hospital,

St Leonards, N.S.W., Australia were studied. They were in hospital for primary rehabilitation or management of some complication of their quadriplegia. All were clinically stable with normal hepatic and renal function, and were not receiving H_2 -receptor antagonists. Ages ranged from 19 to 56 years, the time since injury ranged from 1 to 36 months and all had cervical cord lesions which were at or higher than C7-8. The study was approved by the Medical Ethics Review Committee of the Royal North Shore Hospital and each patient gave informed consent.

Study protocol

The patients were allowed their normal food and fluid intake during the study. A baseline sample of blood was taken, then 100 mg of ranitidine (Glaxo Australia Pty Ltd) was infused (in 10 ml of normal saline) over 10 min via an intravenous line with a heparin lock. This line was then flushed with 10 ml of 0.9% saline. Blood was taken, via the indwelling cannula at 5, 15, 30 and 45 min and at 1, 1.5, 2, 3, 4, 5 and 6 h after the infusion was complete. The blood samples were

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separated and then the plasma frozen and stored at -20°C until just prior to analysis. BP and pulse were taken at 0, 5, 10 and 60 min and then hourly.

Ranitidine assay

Ranitidine in plasma was measured by a reverse phase h.p.l.c. method (Boutagy *et al.*, 1984). The detection limit for ranitidine was 20 ng ml^{-1} and the coefficient of variation less than 5% at 74 and 285 ng ml^{-1} .

Pharmacokinetic analysis

A bi-exponential function was fitted to the individual drug concentration-time data from the six patients. This was of the form:

$$C = C_{1e}^{-\lambda_1 t} + C_{2e}^{-\lambda_2 t}$$

where C is the concentration at time t after the intravenous injection and λ_1 and λ_2 represent the two first order rate constants. C_1 and C_2 are The two zero-time intercepts of the biexponential. The curve fitting was done using a digital computer, and the least squares analysis was done using a simplex algorithm with a weighting function of $1/C^2$ being applied to the sum of squares of the residuals.

The area under the time-concentration curve (AUC) was determined by numerical integration to infinity of the function derived from the Curve fit. The 'elimination' half-life was obtained Using the expression:

$$t_{1/2,z} = 0.693/\lambda_2$$

The 'distribution' half-life was obtained using the expression:

$$t_{1/2,\alpha} = 0.693/\lambda_1$$

The volume of distribution (area) and total clearance was calculated by standard methods.

The duration for which the plasma drug concentration was above a specified level was derived numerically using a digital computer program that solved the equation fitted to each of the individual sets of concentration-time data.

An estimate of mean steady state plasma drug concentration was obtained using the expression:

$$D/CL \cdot \tau = Cov$$

where CL is the total clearance and τ is the dosage interval.

Statistical methods

The results of the present study were compared with results of two published studies performed with six and five normal male subjects, respectively, (McNeil *et al.*, 1981; Van Hecken *et al.*, 1982) These two studies were selected as they described young male subjects and provided adequate individual patient data to allow statistical comparison. The individual data from each of the previously published studies was compared using a two tailed non-paired Student's t -test.

Results

Clinical data

There were no significant changes in heart rate or blood pressure noted in any of the subjects during the study. No side-effects of any type were noted by the subjects.

Pharmacokinetic data

The results are shown in Table 1. The drug concentration-time curves obtained from all six subjects were fitted adequately by biexponential function. Table 2 shows the average data derived from all six individuals compared with that from two previously published studies of ranitidine kinetics in normal male volunteers. It will be noted that the results of all three studies are similar. The only parameter that appears not to be similar to that reported in the two published studies is the 'distribution' half-time. This may be artificially prolonged in the present study due to the fact that the drug infusion was given much more slowly.

Table 1 Pharmacokinetic parameters of ranitidine in the six quadriplegics.

Patient	V (l)	$t_{1/2,\alpha}$ (min)	$t_{1/2,z}$ (h)	CL (ml min ⁻¹)
1	151	11.58	1.81	966
2	73.9	7.20	1.78	479
3	87.8	5.22	1.39	730
4	96.6	11.04	2.02	553
5	55.7	10.32	1.51	425
6	158	11.04	2.22	825
Group means	103	9.42	1.79	663
s.e. mean	17	1.04	0.12	86

Table 2 Principal mean (s.e. mean) pharmacokinetic parameters of i.v. ranitidine from the present study, and from two previously published studies using normal male subjects.

	Current study 100 mg	Normal subjects Study 1 150 mg	Normal subjects Study 2 20 mg
Dose			
$t_{1/2\alpha}$ (min)	9.4 (1.04)	6.61	6.1
$t_{1/2\beta}$ (h)	1.8 (0.12)	1.7	1.9
AUC (ng ml ⁻¹ h)	2739 (354)	3934 (2622)+	488 (2438)+
CL (ml/min)	663 (86)	647	709
V (l)	103 (17)	96	115

Study 1. Van Hecken *et al.* (1982)

Study 2. McNeil *et al.* (1981)

+ AUC corrected for dose of 100 mg.

Analysis of the drug concentration-time data showed that high concentrations of ranitidine were present in plasma after a single intravenous dose for a long period. A plasma drug concentration of approximately 200 ng ml⁻¹ has been shown to decrease pentagastrin stimulated acid output by 50% (Broegden *et al.*, 1982). In the present study this level was achieved after a single dose for an average of 3.2 h (s.e. mean = 0.34). Extrapolation from the single dose data, assuming first order kinetics, indicates that on repeated dosing of 100 mg 4 hourly intravenously, the mean plasma drug concentration over a Dosage interval would be 627 ng ml⁻¹. This plasma drug concentration can be expected to block pentagastrin stimulated gastric acid output by more than 95% in normal volunteers (Brater *et al.*, 1982).

Statistical comparisons

Analysis of the power of this study to detect differences in the other parameters shows that a study of this type, using the number of subjects involved has a greater than 80% chance of detecting a difference of two standard deviations or more in the means of the parameters examined at the 0.05 level (Johnson & Leone, 1964).

Discussion

The previous demonstration in quadriplegic patients of resistance to H₂-receptor antagonists suggested that it was worthwhile to examine the kinetics of ranitidine in this group.

However we found that the kinetics of i.v. ranitidine (including corrected AUC) were

similar in quadriplegics to those in two published studies using normal male volunteers. After i.v. injection ranitidine is largely excreted in the urine (McNeil *et al.*, 1981; Van Hecken *et al.*, 1982) and it is therefore reasonable to equate renal and total clearance. The kinetics obtained also suggest that the plasma drug concentrations that would be obtained in quadriplegics on repeated dosing are well above the known effective inhibitory concentrations. The unresponsive quadriplegic patients who prompted this study received at least three doses of 100 mg of ranitidine before being categorized as resistant to the drug (More *et al.*, 1985), and the majority had received additional doses.

This suggests that there cannot be a kinetic explanation for the reduced responsiveness to ranitidine observed previously and an alternative explanation must be found. One possibility is that it is due to the alterations in the innervation of the stomach that occur with quadriplegia. An injury which divides the spinal cord above the T1 level will result in the disconnection of sympathetic innervation to the stomach. The role of the sympathetic nervous system in the regulation of gastric acid production is not fully understood, but there is a general consensus that the net effect is inhibitory and in balance with the stimulatory effects of the vagus (Sanders, 1976).

Therefore unopposed vagotonia is possibly of considerable significance for the therapeutic resistance noted in these patients. This observation also provides evidence in humans for the view that there are physiological pathways regulating gastric acid production which bypass histamine as the final common pathway (Soll & Walsh, 1979).

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