Ranitidine pharmacokinetics in newborn infants

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Abstract
Few data are available for ranitidine pharmacokinetics in the first few days of life. Twenty seven newborn infants were treated with intravenous ranitidine because they were vomiting blood, although they had a negative Apt's test. Each infant provided two blood samples at randomly selected times 30–360 minutes after a 2·4 mg/kg intravenous bolus of ranitidine. A single exponential equation for the concentration-time graph was fitted to the mean serum concentrations at different times. From this model the following mean (SD) measurements were derived: elimination half life, 207·1 (19·1) minutes; total volume of distribution, 1·52 (0·91) l/kg; and total plasma clearance, 5·02 (0·46) ml/kg/min. Assuming that these measurements do not change with different administered doses, regimens can be derived to assist in planning ranitidine treatment in newborn infants.
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Despite the wide use of ranitidine to treat upper gastrointestinal bleeding from mucosal lesions in the neonatal period or to prevent bleeding in critically ill infants, data about its pharmacokinetics in the first few days of life are not available; dosage regimens are largely empirical and derived from studies conducted in older children or adults. This study was undertaken to explore ranitidine pharmacokinetics in the neonatal period.

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Patients and methods
Twenty seven term infants, born in four different hospitals in the Milan area between 1 May 1990 and 30 September 1991 were studied. Vomiting of blood with a negative Apt's test was the clinical indication for intravenous H_2 antagonist treatment. No infant showed clinical or laboratory signs of renal or liver dysfunction, sepsis, or respiratory distress. Their mean (SD) postnatal age was 21·2 (9·6) hours (range 18–27). A single ranitidine bolus of 2·4 mg/kg was administered intravenously over five minutes at a concentration of 2 mg/ml in dextrose 5% water. The ranitidine concentration was determined by high performance liquid chromatography[1] on frozen serum samples drawn 30–360 minutes after the completion of the infusion. For ethical reasons no more than two blood samples were drawn from each patient. Nine different pairs of sampling times were scheduled to be repeated three times each; individual patients were then randomly allocated to a pair. The interval between the two samples ranged from 120 to 300 minutes with a mean (SD) of 187 (64·1).

Informed consent was given by the legal guardians of the patients and approval of the local ethics committee was obtained.

PHARMACOKINETIC ANALYSIS
Pharmacokinetic indices were estimated on the basis of mean serum concentrations at the various sampling times. Explorative data analysis was performed by the peeling method,[2] and Akaike's test[3] was used to select the best model for the concentration-time graph. An interpretative model was then constructed on the basis of analysis of residuals. Data were analysed by a specific computer program for pharmacokinetic analysis (SIPHAR, Simed-Creteil). Standard equations[4] were used to estimate the regimens necessary to attain selected serum concentrations.

Results
Table 1 shows the mean serum concentrations at the various sampling times.

A single exponential model with three points in the terminal phase of the concentration-time graph was selected

$$y = A \times exp(-a \times t)$$

where y=calculated serum concentration, A=1583·8 (95·4) ng/ml (95% confidence interval (CI) 1338·6 to 1828·9) and a (elimination constant)=0·0033(0·0003) 1/min (95% CI 0·0015 to 0·0041).

In the interpretative model, A=administered dose/total volume of distribution (V_d) and a=total plasma clearance (Cl)/V_d; this equation then became: y=(dose/V_d)×(exp $(-Cl/V_d \times t)$).

Table 2 summarises the pharmacokinetic indices derived from this model.

Assuming the elimination constant does not change with different administered doses, the doses necessary to maintain the serum ranitidine concentration above a chosen value for a chosen period could be calculated from these indices. So, for example, single intravenous boluses of 1·6 and 3·3 mg/kg are expected to result in serum concentrations greater than 100

Table 1   Serum concentrations of ranitidine at the various sampling times

Time (min)	No of samples	Rantidine serum concentration (ng/ml)	
		Mean (SD)	95% CI for the mean
30	6	1458 (620)	808 to 2109
60	9	1519 (424)	1193 to 1846
90	6	901 (298)	587 to 1214
120	6	922 (480)	418 to 1426
180	9	952 (397)	647 to 1257
240	9	637 (181)	498 to 776
360	9	499 (315)	257 to 742

Table 2   Rantitidine pharmacokinetic indices estimated after a single intravenous bolus in newborn infants

	Estimated mean (SD)	95% CI
Elimination half life ($t_{1/2}$) (min)	207·1 (19·1)	170·3 to 450·1
Total volume of distribution (l/kg)	1·52 (0·91)	1·31 to 1·79
Total plasma clearance (ml/kg/min)	5·02 (0·46)	2·34 to 6·19

and 200 ng/ml respectively for at least 12 hours.

As Css=R/Cl is the relationship between the average serum steady state concentration (Css) and the rate of continuous intravenous infusion (R), it can be estimated that Css values between 100 and 200 ng/ml are expected to be reached with R values between 0·03 and 0·06 mg/kg/hour.

Discussion

To our knowledge this is the first study exploring the pharmacokinetics of ranitidine in the first few days of life. Wiest *et al* studied nine infants aged 2 to 21 months and found the mean values for $t_{1/2}$, V_d, and Cl to be 125·4 minutes, 1·61 l/kg, and 13·9 ml/kg/min, respectively.[5] The V_d value found here compares well with their value and with values from studies in older children[6] and adults[7] (2·3 and 1·6 respectively); this finding suggests that ranitidine binding to plasma proteins and its tissue distribution are similar at different ages.

In contrast, the $t_{1/2}$ value in our study (207 minutes) is longer than that in the study of Wiest *et al*; Cl is consequently lower. Mallet *et al*[8] found the ranitidine $t_{1/2}$ value to be 168 minutes in 11 infants aged 6 weeks to 6 months; $t_{1/2}$ values of 108 and 114 minutes were also described in older children[6] and adults[7] respectively. About 70% of the intravenously administered ranitidine was found to be excreted unchanged in the urine of adults.[7] In our opinion, therefore, the long $t_{1/2}$ observed here mainly reflects the well known low glomerular filtration rate of newborn infants: as the glomerular filtration rate is low at birth and sharply increases thereafter, doubling after the first two weeks of life,[9] major differences in the $t_{1/2}$ value are expected to occur between newborn infants and infants several months old.

The pharmacokinetic indices found here are in good agreement with our previous observations; in another series of 27 term newborn infants aged 70 (11) hours, a serum ranitidine concentration of 642 (376) ng/ml was found after a 48 hour continuous intravenous infusion at the rate of 0·2 mg/kg/hour (unpublished data); this concentration is close to the value of 664 ng/mg expected from the present work. With the same infusion rate, Rosenthal and Miller,[10] after 24 hours of

treatment in a critically ill preterm infant aged 96 hours, observed a plasma concentration of 789 ng/ml, which also compares well with our expected value.

Target serum ranitidine concentrations, effective in reducing gastric acid output probably vary with the gestational and postnatal age of the patient and with the underlying medical disorder (for example, acute stress). In adults, concentrations from 94 to 165 ng/ml have been reported to inhibit stimulated gastric acid output by 50%,[11] [12] whereas concentrations between 40 and 60 ng/ml were found to suppress unstimulated gastric secretion by 90% in children aged 3·5 to 16 years with peptic ulcer disease[6]; Eddlestone *et al* found the gastric pH to be maintained above 3·5 by serum concentrations greater than 200 ng/ml.[13] On the basis of the pharmacokinetic indices found here, concentrations greater than 100 and 200 ng/ml could be expected for at least 12 hours after a single intravenous bolus of 1·6 and 3·3 mg/kg respectively; the same average concentration range could be obtained at the steady state by continuous intravenous infusion at a rate between 0·03 and 0·06 mg/kg/hour. These findings could be helpful in assisting ranitidine treatment in newborn infants, for short as well as for long term purposes.

It must be remembered, however, that our results refer to term newborn infants without overt renal or liver disease; their application to preterm infants or to infants with renal or liver failure must be regarded cautiously.

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