Efficacy, duration, and absorption of a paediatric oral liquid preparation of ranitidine hydrochloride

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The objectives of this study were to assess the clinical efficacy of a new oral ranitidine liquid preparation in reducing gastric acidity and volume, to determine the degree of absorption of the drug, and to determine the duration of drug effect. Eighty preoperative children between the ages of one and six years were enrolled in each of three centres. Each subject was allocated to one of the following groups: Group A – apple juice, 5 ml · kg⁻¹ plus placebo liquid; Group B – apple juice, 5 ml · kg⁻¹ plus ranitidine hydrochloride 2 mg · kg⁻¹; Group C – water, 5 ml and placebo liquid; or Group D – water, 5 ml and ranitidine liquid 2 mg · kg⁻¹. All study agents were administered at least two hours before surgery along with a dye marker, sulfobromophthalein 1 ml (50 mg · ml⁻¹). Following induction of anaesthesia, gastric fluid was aspirated, and analyzed for pH, volume, and sulfobromophthalein content (as an index of the ingested fluids). A serum sample was also drawn and analyzed for ranitidine content by high performance liquid chromatography. Groups B and D had

fewer subjects with pH below 2.5 and gastric volume >0.4 ml · kg⁻¹. The duration of reduced volume and acidity was shown to be greatest from two to four hours after drug administration. Thirty-three percent of subjects receiving oral ranitidine, 2 mg · kg⁻¹ hydrochloride as a single dose demonstrated no measurable effect on gastric pH and volume; 28 of those subjects had adequate ranitidine serum levels.

Les objectifs de cette étude clinique portent sur l'évaluation d'une nouvelle préparation liquide de ranitidine et en particulier sur sa capacité de réduction de l'acidité et du volume gastrique, son degré d'absorption et sa durée d'action. En pré-opératoire, quatre-vingts enfants âgés d'un à six ans de trois centres hospitaliers font partie de l'étude. Ils sont distribués en quatre groupes: le groupe A ingère du jus de pomme 5 ml · kg⁻¹ avec un placebo liquide; le groupe B, du jus de pomme avec de l'hydrochlorure de ranitidine 2 mg · kg⁻¹; le groupe C, de l'eau 5 ml avec un placebo liquide; le groupe D, de l'eau avec de la ranitidine liquide 2 mg · kg⁻¹. Toutes les préparations à l'étude sont administrées au moins deux heures avant la chirurgie avec un colorant servant de marqueur, la bromesulfonephthaléine 1 ml (50 mg · ml⁻¹). Après l'induction de l'anesthésie, le liquide gastrique est aspiré et on en détermine le pH, le volume et le contenu en bromesulfonephthaléine. On prélève un spécimen de sérum et analyse son contenu en ranitidine par chromatographie en phase liquide à haute performance. Les groupes B et D comprennent moins de sujets avec un pH sous 2,5 et un volume gastrique plus grand que 0,4 ml · kg⁻¹. La durée de la diminution de volume et de pH est plus importante entre la deuxième et la quatrième heure qui suivent l'administration de la drogue. Trente-trois pourcent des sujets qui ont reçu 2 mg · kg⁻¹ de ranitidine orale ou l'hydro-chlorure en une dose ne présentent pas d'effets quantifiables sur le pH et le volume gastrique: 28 pourcent de ceux-ci ont des niveaux adéquats de ranitidine sérique.

Key words

ANAESTHESIA: paediatric;
COMPLICATIONS: aspiration;
GASTROINTESTINAL TRACT: stomach, gastric pH,
gastric volume;
HISTAMINE: receptor antagonists, ranitidine;
PHARMACOLOGY: ranitidine HCl.

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Because it reduces gastric acid secretion, the use of ranitidine has been suggested as an option for reducing the severity of aspiration pneumonitis, should aspiration of

gastric contents occur during general anaesthesia. Previous studies using ranitidine have evaluated the effects of an intravenous preparation administered via the oral route. This investigation is an evaluation of an oral preparation of ranitidine hydrochloride for its absorption, its effectiveness in reducing gastric acid secretion, and its duration of effect.

Ranitidine hydrochloride, an H_2 blocker, is a potent inhibitor of both gastric acid secretion and volume.¹⁻³ Previous studies in children have shown that ranitidine is effective in increasing gastric pH and reducing gastric volume following oral administration, prior to the induction of anaesthesia.^{4,5} Unfortunately, because an oral liquid preparation of ranitidine was not previously available, these studies used the intravenous preparation administered orally. Further, ranitidine hydrochloride was not 100% effective in these trials, as a considerable percentage of subjects failed to demonstrate an increase in their gastric pH, despite an appropriate ingestion-to-sampling (of gastric fluid) interval. It is unknown if the lack of response to ranitidine as an intravenous preparation administered orally was the result of poor drug absorption or lack of effect on receptors – could inclusion in an oral preparation alter the absorption of the drug?

The present investigation was initiated to answer three questions: Is the oral preparation of ranitidine hydrochloride as effective as previously used intravenous ranitidine hydrochloride administered orally; how efficient is the absorption of the oral ranitidine hydrochloride preparation; and over what period of time does the oral preparation of the drug act?

Methods

Experimental protocol

This three-centre, randomized, single blind, comparative trial was conducted between the months of March and December, 1988 at the Alberta Children's Provincial Hospital, Calgary, Alberta; The Hospital for Sick Children, Toronto, Ontario; and the Izaak Walton Killam Children's Hospital, Halifax, Nova Scotia.

The study was carried out according to the Declaration of Helsinki (Venice Amendment, 1983), and Ethics Committee approval was obtained from institutional ethics review committees of all three centres before commencing the study. The study was fully explained to each parent and/or patient by one of the investigators, and informed, written consent was obtained before surgery.

Elective ASA Physical Status Class I and II surgical patients aged one to six years were eligible for inclusion in the study. Patients with known gastrointestinal disease, patients taking any medications during the course of the study, and patients requiring premedication (with the

TABLE Group assignment and incidence of high risk for aspiration pneumonia, should aspiration of gastric contents occur. Criteria used are gastric aspirate volume $>0.4 \text{ ml} \cdot \text{kg}^{-1}$ and gastric aspirate pH <2.5 .

Treatment	Number	High risk
Juice and placebo	48	15 (31%)
Juice and ranitidine	53	6 (11%)
Water and placebo	51	20 (39%)
Water and ranitidine	47	7 (15%)
All treatments	191	84 (24%)

exception of benzodiazepines) were all excluded from participation.

Patients who met the evaluability criteria but who were administered any of the study agents less than two hours before surgery were deemed non-evaluable for the determination of efficacy of the drug.

A total of 240 patients were enrolled in the study, with 80 patients at each of the three participating centres. Each patient was randomized to receive either ranitidine or placebo with or without apple juice as an oral fluid.

This was a randomized trial in which investigators and subjects were unaware of the formulation used. Ranitidine hydrochloride was supplied as an oral formulation ($15 \text{ mg} \cdot \text{ml}^{-1}$) by Glaxo Canada Inc. Synthetic sweetener (sodium cyclamate) and mint flavouring additives were blended into the oral liquid formulation to mask the bitter taste of ranitidine. The ranitidine liquid was bottled in 25 ml size bottles. The placebo liquid was identical, except that it did not contain the ranitidine hydrochloride.

Bromosulphthalein (BSP-intravenous preparation) was obtained from Allen & Hanburys (item #23380) as a $50 \text{ mg} \cdot \text{ml}^{-1}$ solution and was used as a marker to differentiate between ingested fluid and gastric fluid secretions in the subsequent aspirated fluid. BSP was used because it is not absorbed in the stomach.

Subjects received either ranitidine hydrochloride or placebo, and either apple juice or a small volume of water. Subjects were randomly allocated to one of the following groups: (Table) Group A: apple juice ($5 \text{ ml} \cdot \text{kg}^{-1}$) plus placebo liquid; Group B: apple juice ($5 \text{ ml} \cdot \text{kg}^{-1}$) plus ranitidine liquid ($2 \text{ mg} \cdot \text{kg}^{-1}$); Group C: 5 ml water and placebo liquid; Group D: 5 ml water and ranitidine liquid ($2 \text{ mg} \cdot \text{kg}^{-1}$).

Each subject underwent a general anaesthetic according to the preference of the attending anaesthetist. Details concerning the type of induction and types of maintenance anaesthetic were recorded. At least two hours before surgery each subject received the study agent orally, according to the randomization code. At the same time, each subject also received 1 ml bromosulphthalein ($50 \text{ mg} \cdot \text{ml}^{-1}$), *po*. The time of administration of the study agents was recorded. The volume of placebo liquid

administered was based on the assumption that it also contained 15 mg · ml⁻¹ active ingredient. Sampling of gastric contents was standardized in all three centres as follows: following induction of anaesthesia, a size 14 French ×48 cm Salem-Sump[®] tube was passed into the stomach and its position confirmed by auscultating for insufflated air. Gastric fluid was then aspirated into a 60 ml syringe with the patient in the supine position. Retrieval of gastric contents was maximized by repeating gastric fluid aspiration following two partial withdrawals and readvancing of the oral gastric tube. The total volume of gastric aspirate was recorded. An aliquot was allowed to equilibrate to room temperature one hour before pH measurement with an analogue pH meter, which was calibrated with pH 1 and pH 7 standards at all three centres. Gastric aspirate samples were shipped frozen to laboratories at the University of Calgary, and stored at -70°C until analyzed. Bromosulphthalein concentration was measured using a CU-50 Beckman Spectrophotometer according to the method of Shaffer and Small.⁶ At the time of aspiration of gastric contents, a 5 ml sample of the subject's blood was drawn, centrifuged and frozen. Samples were shipped on dry ice to Glaxo Canada Inc. and later analyzed for ranitidine content by high performance liquid chromatography. Results from subjects who met the inclusion criteria and who were deemed evaluable were included in the analysis of efficacy.

Data analysis

Statistical analyses were performed using the statistical analysis system PC/SAS, and results are reported as mean ± SEM. All significance tests were performed at the $P < 0.05$ level, as follows:

- 1 Demographics – the demographic data (age, weight, height, and sex) were analyzed to evaluate the possibility of randomization biases. For the continuous dependent variables, two-way analysis of variance was performed with liquid and drug as the two independent factors. The ratios of boys to girls were also compared by centre using the chi-square test.
- 2 Efficacy was defined in terms of mean gastric volume aspirated per body weight, gastric fluid pH, and % BSP recovered. For these continuous dependent variables, a two-way analysis of variance was used with the two factors, drug (ranitidine or placebo) and liquid (water or fruit juice), as the independent variables. These analyses are hierarchical in nature with a significance test of overall differences among any of the treatments performed first. If the overall test was significant, the interaction between drug and liquid and the main effects of drug and liquid were subsequently tested. The interaction effect is a measure of whether or not there is a particular combination of drug and liquid which leads

to an "extraordinary" response unexplained by simple drug and/or liquid effects. If the interaction was not significant, a focus on the simple main effects of drug and liquid was made.

The % BSP dye recovered was calculated as follows:

$$\text{BSP recovered} = \frac{\text{concentration of BSP} \times \text{gastric volume}}{50} \times 100\%$$

The concentration of BSP was converted to mg · ml⁻¹ before being used in the above equation. The value 50 represents the 50 mg of BSP administered orally. If no gastric fluid was aspirated, the percentage of BSP recovered was given a value of 0.

The relationship between serum ranitidine concentrations versus gastric volume and pH was assessed using correlation analysis.

Results

Demographic data

A total of 240 subjects were enrolled into the trial, 60 receiving apple juice and placebo (Group A), 60 receiving juice and ranitidine (Group B), 60 receiving water and placebo (Group C), and 60 receiving water and ranitidine treatment (Group D).

There was an even distribution of patients among all four groups, and the number of patients recruited by each of the three investigators was similar. The four treatment groups were found to be comparable with respect to the distribution of sex, age, weight, and height.

Evaluable patients

From the total population of 240 subjects, 41 patients were excluded from the efficacy analysis for the following reasons: gastric samples could not be taken, patients spat out treatment agents, induction of anaesthesia and aspiration of gastric contents occurred less than two hours after treatment administration, or case record forms were missing or ambiguous. A comparison of the proportion of subjects who were excluded among groups was not significant, as measured by the chi-squared test.

Volume and pH measurements

Analysis of variance for gastric acidity of the two groups receiving ranitidine was significantly different ($P < 0.0001$) from the two groups receiving placebo (mean pH: ranitidine 3.91 (SE 0.23) versus placebo 1.95 (SE 0.11)).

Administration of juice did not affect intragastric pH. Mean values for pH of patients receiving ranitidine with juice or water were 4.09 (SE 0.31) and 3.70 (SE 0.34) respectively. Those patients who received the placebo

FIGURE 1 Relative volumes ($\text{ml} \cdot \text{kg}^{-1}$) and pH values of gastric aspirate for all subjects, indicating fewer subjects in the high-risk category ($\text{pH} < 2.5$ and volume $> 0.4 \text{ ml} \cdot \text{kg}^{-1}$) for those groups in which subjects received ranitidine.

versus those who received juice plus placebo had mean pH values of 1.94 (SE 0.13) and 1.96 (SE 0.17), respectively (NS). The pooled mean pH data for patients in all treatment groups who received water was compared with the pooled mean pH data for patients in all treatment groups who received juice. Fluid effects were found not significant ($P = 0.46$).

Ranitidine decreased the mean gastric volume, based on examination of pooled mean gastric volume data for ranitidine treatment groups versus placebo treatment groups. Mean gastric volume was $0.42 \text{ ml} \cdot \text{kg}^{-1}$ (0.04) for placebo groups and $0.30 \text{ ml} \cdot \text{kg}^{-1}$ (0.03) for ranitidine groups. In comparing juice versus water, there was no significant effect on gastric volume. There were no differences in the aspirated gastric volume between treatments. No significant interaction effect could be demonstrated for any combination of drug and liquid.

For the purposes of this study, variables used to identify patients potentially at higher risk of aspiration pneumonitis, should aspiration of gastric contents occur, were a gastric aspirate volume of greater than $0.4 \text{ ml} \cdot \text{kg}^{-1}$

and a pH less than 2.5 (Table). The proportion of patients at risk was different among the four treatment groups (chi-squared test; $P = 0.002$). Ranitidine treatment substantially decreased the number of patients at risk, relative to those patients who had received placebo (Figure 1).

Dye recovery

A comparison of juice versus water administration showed that liquid effects on BSP recovery were insignificant. The mass of dye recovered from ranitidine-treated patients (0.27%) was higher than from patients who had received placebo (0.12%), ($P < 0.001$). Although there was a difference between groups with regard to BSP recovery, the recovery represented less than 0.3% of the original volume at the time of BSP administration.

Timing of drug and fluid administration

The mean duration of fasting before administration of study agents was 10.2 hr; it was not demonstrated to be different among the four treatment groups.

The time between drug administration and aspiration of

GASTRIC ASPIRATE PH Effects of Ranitidine

FIGURE 2 Variation of mean values of pH of gastric aspirate, grouped by hourly intervals, subsequent to placebo or ranitidine administration. The effect of ranitidine in increasing the mean pH values is most evident at 2-4 hours. Values within bars are the number of subjects for each time interval. Bars shown are mean pH of gastric aspirate $\pm$ SD.

VOLUME OF GASTRIC ASPIRATE Ranitidine vs Placebo

FIGURE 3 Variation of mean values of volume of gastric aspirate, grouped by hourly intervals, subsequent to placebo or ranitidine administration. Values within bars are the number of subjects for each time interval. Bars shown are mean volume of gastric aspirate in $\text{ml} \cdot \text{kg}^{-1} \pm$ SD.

gastric volume averaged 2.77 hr; this interval was not different among the four treatment groups. Data for pH (Figure 2) and volume (Figure 3) were grouped into one-hour time intervals for the periods from two hours after drug administration until six hours after drug admin-

SERUM RANITIDINE LEVELS

FIGURE 4 Variation of serum ranitidine concentrations with time, grouped in hourly intervals, subsequent to ranitidine administration. Values within bars are the number of subjects for each time interval. Bars shown are mean serum ranitidine levels in $\text{ng} \cdot \text{ml}^{-1} \pm$ SD.

istration. The mean volume of gastric aspirate peaked at three to four hours. The measured volume for the subjects who received ranitidine was reduced.

Serum ranitidine concentration

The coefficient of correlation between serum ranitidine concentration and intragastric pH was 0.47, but there was no correlation between serum ranitidine level and gastric volume per kg body weight. As expected, the mean serum ranitidine concentrations decreased with increasing time between ranitidine administration and aspiration of gastric contents (Figure 4). For those subjects who received ranitidine without demonstrable effect (defined by a pH value less than 2.5), the corresponding serum ranitidine concentrations varied over a wide range, from $17.8 \text{ ng} \cdot \text{ml}^{-1}$ to $330.6 \text{ ng} \cdot \text{ml}^{-1}$, with a mean of $128.8 \text{ ng} \cdot \text{ml}^{-1}$. Of the evaluable subjects who received ranitidine (98 subjects), 32 had a pH value of gastric aspirate less than 2.5; this represents 33% of the evaluable patients who had received ranitidine; of those 32 subjects with a pH < 2.5, all but 4 had a serum ranitidine level $> 60 \text{ ng} \cdot \text{ml}^{-1}$, the serum concentration of ranitidine required to suppress gastric acid secretion by $\geq 90\%$.⁷ The mean serum ranitidine for patients receiving juice was $170.0 \text{ ng} \cdot \text{ml}^{-1}$ (12.72) and for water $165.6 \text{ ng} \cdot \text{ml}^{-1}$ (13.8), showing that the liquid effects were non-significant.

Adverse events

Of the 240 subjects enrolled in the study, ten reported a minor adverse event. Eight subjects gagged and spat out or

vomited the treatment agents. One subject experienced unexplained flushing and diaphoresis ten minutes after administration of the treatment, and this spontaneously resolved with supportive therapy only; this patient was a quiet but apprehensive patient. The diaphoresis may have been a vaso-vagal response; because of the transient nature of the reaction, the aetiology is not clear. One other experienced coughing, regurgitation, and aspiration on induction of anaesthesia; this 13 kg patient received 65 ml of apple juice without ranitidine three hours and ten minutes before induction of anaesthesia. The coughing and regurgitation may have been related to the airway management, and is very unlikely to be related directly to the administration of ranitidine. Neither of the latter two complications were attributed to administration of the study drug by the anaesthetists responsible for each patient's care.

Two centres recorded reactions to the taste of the medication as an adverse event, but the taste of the oral preparation could not be differentiated from the taste of the bromosulphthalein. The BSP is bitter, and the test solution was made bitter when the BSP was added. The importance of this adverse event in relation to acceptability of the oral preparation could not therefore be determined.

Discussion

Pulmonary aspiration of gastric contents during general anaesthesia has been recognized as a life-threatening complication in both adults and children,^{8,9} and concerns about this have resulted in the introduction of strict fasting guidelines in the preoperative period. During general anaesthesia the normal protective gag and cough reflexes are not present, thus even with extreme care, gastric fluid aspiration remains a risk. In the past, 26% of documented cases of gastric fluid aspiration could be attributed to general anaesthesia, resulting in a mortality as high as 62%.^{10,11} Recent investigations^{12,13} and editorials^{14,15} have emphasized the importance of re-evaluating fasting guidelines. One consideration is to use an H₂ blocker such as ranitidine hydrochloride⁴ to improve the gastric environment prior to induction of anaesthesia.

Orally administered ranitidine hydrochloride has previously been demonstrated⁴ to increase the pH of gastric aspirate in children when given as a single dose prior to the induction of anaesthesia. Although not recommended for routine use in preparation of patients for surgery, its use has been advocated in a variety of situations for patients who are at increased risk of intraoperative aspiration of gastric contents. Previous studies have been undertaken using an intravenous preparation of ranitidine hydrochloride administered by the oral route. The recently developed peppermint-flavoured preparation of the drug was evaluated in this randomized comparative

trial. At the time of initiation of the study, unanswered questions related to the suitability of the oral preparation of ranitidine hydrochloride, its effectiveness in increasing the pH and reducing the measured volume of gastric aspirate, and its duration of effect on pH. Previous studies^{1,4} of orally administered ranitidine hydrochloride indicated that a number of subjects receiving the drug failed to respond – there was no demonstrable effect on the pH after administration of a single dose. This study was therefore also designed to determine whether failure of the medication was secondary to decreased absorption or to lack of pharmacological effect. Serum ranitidine concentrations were measured with the assumption that measurable levels of the medication would reflect the adequacy of absorption of the medication.

Suitability of the oral preparation and effects of a single dose on pH and volume

The oral preparation used in this study was administered to children aged one to six years, prior to their surgery, but only two of the three centres identified patient response to the medication. Based on records from these two centres, palatability was not high. Seventy five percent of subjects spontaneously indicated they did not approve of the taste and/or aroma, and eight subjects gagged and spat out or vomited the treatment agents. All treatment agents contained bromosulphthalein which has a bitter taste, and therefore the evaluation for palatability was biased. If this product is to be used for routine administration to children, an aroma and taste more attractive than the preparation used in this investigation is desirable. Palatability should therefore be assessed without the presence of the bromosulphthalein.

When mean values between study groups were compared, the oral preparation was effective in increasing the pH of gastric aspirate. Although the differences in mean values between treatment and placebo groups were significant, 33% of the subjects who had received ranitidine failed to demonstrate a gastric aspirate pH value greater than 2.5. The results of the serum analysis in this study indicate that those failures were not the result of failure of absorption of the drug, as 28 of 32 subjects with lack of response demonstrated therapeutic serum levels. The lack of change in gastric pH is a lack of demonstrable response to the drug as measured by a single sample of gastric aspirate. We were unable to identify an indicator of which subjects would fail to respond to oral ranitidine.

In comparing the results of this study with results obtained by others, the oral ranitidine liquid is less effective in reducing the frequency of high-risk classification. Using oral administration of the intravenous preparation, Sandhar *et al.*⁴ demonstrated an incidence of 5.5% (cf 11%) frequency of children in the high-risk category who

received 5 ml · kg⁻¹ of orange juice and ranitidine 2 mg · kg⁻¹; and 0.0% (cf 15%) frequency of children in the high-risk category who received water 5 ml and ranitidine 2 mg · kg⁻¹. Similarly, Sutherland *et al.*¹⁶ were able to reduce successfully the frequency of adult subjects in the high-risk category to 0% and 4% in subjects receiving similar (although not identical) doses of fluids and a ranitidine tablet. The intravenous preparation of ranitidine administered intravenously has been shown to be very effective in reducing the proportion of patients in a similar high-risk category to 0% when given in doses of 1.5 mg · kg⁻¹ intravenously to adults.¹⁷ Using the oral liquid preparation in this study does not appear to have been as effective in reducing the number of subjects in the category of high risk; oral tablets, the intravenous preparation of ranitidine administered orally, and intravenous administration of ranitidine all have been more effective in achieving this objective.

Goudsouzian,¹⁸ in a study evaluating the prophylactic value of ranitidine hydrochloride in children, stated that ranitidine at a dose of 2.5 mg · kg⁻¹ given orally at least an hour before the induction of anaesthesia can provide a safe pH level in the gastric contents in patients who are at risk of acid aspiration. In this study we have demonstrated that a single dose of ranitidine hydrochloride 2 mg · kg⁻¹ will be effective in increasing the pH of gastric aspirate in the majority of children aged one to six years; it should be expected, however, for those children receiving ranitidine, that no measurable response to the medication will occur in a large proportion of patients (33% of subjects in this study). Our measurements were made on a single gastric aspirate, and Goudsouzian carried out two measurements, one hour apart. Although we have demonstrated that the pH of gastric aspirate was low in subjects who had measurable blood levels of ranitidine, it is possible that a later measurement of gastric contents would demonstrate an increase in pH as a result of the ranitidine. Using the oral liquid preparation in children, we have been unable to demonstrate effects as reliable as those previously described.

Of the 120 patients receiving ranitidine, there were no major adverse events associated with the use of the drug, and this would imply a reasonable degree of safety associated with a single dose of ranitidine used in children. For major events of an infrequent nature, experience with a much larger number of patients is required.

Timing of fluids and ranitidine administration and duration of effect

In all groups, the minimal recovery of dye indicates that the stomach is completely emptying of ingested fluids before the obtaining of the gastric aspirate.

As demonstrated in previous studies using ranitidine

hydrochloride we have shown that the most reliable time interval for achieving elevated intragastric pH is two to four hours after administration of ranitidine. In situations where a longer duration of effect is required, either an adjustment in the initial dose or a second dose would be required.

Summary

A single dose of ranitidine hydrochloride 2 mg · kg⁻¹ is effective in increasing the pH of gastric aspirate in children aged one to six years in the majority of patients. It should be expected, however, that no measurable response to the medication will occur in some patients (33% of subjects in this study).

The frequency of patients in the placebo groups with gastric aspirate pH less than 2.5 and volumes greater than 0.4 ml · kg⁻¹ was 31–39%. These results are similar to those found in fasting children by Splinter *et al.*¹⁰ (32–33%), and Schreiner *et al.*¹¹ (46–48%). With the administration of ranitidine hydrochloride 2 mg · kg⁻¹, it is possible to reduce this percentage to 11% to 15% of patients.

The expected duration of effect of oral ranitidine 2 mg · kg⁻¹ would be for three to four hours after administration, a factor which should be taken into consideration where surgery is prolonged and control of gastric pH is desired at the completion of surgery.

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