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The Dose-Response Effects of Oral Cimetidine on Gastric pH and Volume in Children

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The effects of preanesthetic oral cimetidine on gastric fluid *p*H and volume were studied in 97 infants and children. A dose-response curve was constructed using doses of 2.5, 5.0, 7.5, and 10 mg/kg. The ED_{50} of cimetidine that produces *p*H values higher than 2.5 was 3.0 mg/kg, and the ED_{95} was 7.5 mg/kg. Cimetidine exponentially reduced the volume of gastric fluid. Cimetidine was most effective between one and four hours after oral administration. In children who are at high risk of pulmonary aspiration, we recommend that oral cimetidine, 7.5 mg/kg, be given 1–3 hours preoperatively in order to protect the lungs from the accidental aspiration of acidic gastric secretions. (Key words: Pharmacology: cimetidine, dose response. Gastrointestinal tract: gastric *p*H and volume. Complications: aspiration. Anesthesia: pediatric.)

PULMONARY ASPIRATION of acidic gastric contents is a major hazard for the anesthetized patient. In adults it is estimated that 12–24 per cent of anesthetic deaths are due to inhalation of gastric contents.[1,2] In pediatric patients, 26 per cent of anesthesia-related mortality has been attributed to aspiration of vomitus or blood.[3] In a more recent report, two of 73 cardiac arrests associated with anesthesia in infants and children were due to aspiration of stomach contents.[4]

Both the hydrogen ion concentration and the volume of aspirated fluid are important factors in the development of the pulmonary acid aspiration syndrome.[5,6] In pediatric patients, the critical *p*H and volume of gastric contents that make the child at risk for this syndrome are unknown. We can reasonably assume that, like adults,[5] children are at greater risk if they aspirate a volume of 0.4 ml/kg or greater with a *p*H of less than 2.5.

Cimetidine is a specific histamine (H_2 receptor) antagonist that reduces gastric acid secretion but has little effect on the tone of the lower esophageal sphincter or the rate of gastric emptying. As a premedicant in adults, it can effectively reduce gastric hydrogen ion concentration.[7–9] Its effectiveness as a premedicant in children for reducing gastric acidity has not been studied despite the frequent use of cimetidine in neonates and children to treat hyperacidity syndromes.[10]

For these reasons we undertook the present prospective study of oral cimetidine in children to determine the optimal dose that raises the *p*H of gastric aspirate > 2.5 and reduces the volume < 0.4 ml/kg.

Methods

The protocol was approved by the Subcommittee on Human Studies of the Committee on Research of the Massachusetts General Hospital; parental consent was obtained for each child.

One hundred and five patients, 4 months to 14 years of age, were studied. All children were of ASA I status and none had any history of ulcer disease or manifestation of hyperacidity. All had fasted for a minimum of five hours prior to induction of anesthesia.

Infants less than one year of age received no premedication. Children 1–5 years of age were not premedicated on the ward but received rectal methohexital (20–25 mg/kg), administered by a physician in the presence of a parent in an induction area. They were asleep before transport to the operating suite. Older children received no premedication, or were given diazepam 0.1–0.3 mg/kg, po, with a maximum of 30 ml of water one to two hours prior to induction of anesthesia. None of the children received anticholinergic preoperative medication.

Liquid cimetidine, which was prepared in the pharmacy by suspending the soaked tablets in a cherry-flavored sorbitol solution, was given with a sip of water (maximum 30 ml) 1.5 hours prior to the scheduled time of surgery. Changes in the operative schedule resulted in variability in the interval of time from premedication to the induction of anesthesia.

The infants and children were divided into five groups according to the dose of cimetidine. The groups were similar in age distribution. Group I, the control group, received no cimetidine. Group II received 2.5 mg/kg cimetidine; Group III, 5 mg/kg; Group IV, 7.5 mg/kg; Group V, 10 mg/kg. For ease of administration, the total dose of cimetidine was approximated to the nearest increment of 30 mg.

In infants and children who received rectal methohexital, anesthesia was induced with N_2O/O_2 and halothane, and an intravenous infusion was started. When a satisfactory level of anesthesia was reached, an appro-

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priate-sized endotracheal tube was inserted under direct laryngoscopy. Precordial heart sounds, blood pressure, temperature, and the electrocardiogram were monitored in all patients. Intravenous sodium thiopental was employed to induce older children, followed by an anesthetic technique similar to the preceding.

When the endotracheal tube was secured in place and the general condition of the child stabilized, an appropriate-sized Salem sump® tube (#12, 14, or 16) was inserted orally. The nasal route was only used when the surgical procedure required postoperative nasogastric suctioning. The position of the sump tube was ascertained by epigastric auscultation during air insufflation. Multiple attempts were made to empty the stomach contents with a large bore syringe. The color and volume of gastric contents were recorded. The *p*H was measured by a Corning® digital *p*H meter 125 (#475-150) with a standard combination semi-microelectrode (#476-050) which was calibrated against known reagents before every measurement. The *p*H was also evaluated with pHydrion paper® (Micro Essential Lab). Besides using the standard *p*H paper 1–12, we used intermediate range pHydrion paper® (*p*H 1–1.5, *p*H 3–5.5, *p*H 6.0–8.0). The pHydrion paper® readings were made prior to *p*H meter determinations.

The five groups of patients were compared with respect to *p*H values and volume of gastric contents by one-way analysis of variance and the noncorrelated Student *t* test. Because of the controversy in statistical analysis of *p*H data,[11,12] in addition to grouping the *p*H values, we converted each individual *p*H reading to absolute values of H^+ concentration, then grouped them and redid the statistical analysis. For comparison of readings between the *p*H meter and the readings of intermediate range pHydrion paper®, a correlation coefficient analysis was performed. The chi-square analysis was used for comparison of the number of patients who had *p*H < 2.5 and volume of >0.4 ml/kg. Data were considered significant when P values were less than 0.05. The method of Litchfield and Wilcoxon[13] for quantal data was used to establish the ED_{50} and ED_{95} of cimetidine that resulted in gastric *p*H values greater than 2.5.

Results

Of the 97 infants and children from whom a gastric sample could be obtained the mean age was 5.6 ± 0.5 yr. (range 4 months–14 years) and mean weight was 20.1 ± 1.2 kg (range 5–41 kg). The age and weight ranges of the patients in all groups were similar and there was no signficant difference between their mean values. The average fasting period was eight hours in all five groups. We could not obtain gastric contents from two control and six treated children who were therefore excluded from the study.

Twenty-six infants and children were unpremedicated. Ten children received oral diazepam (0.1–0.3 mg/kg) with the preoperative cimetidine. The remaining 69 patients received rectal methohexital prior to induction of anesthesia. Premedication had no effect on the volume and acidity of gastric secretion.

Because of unexpected changes in the surgical schedule, anesthesia was started in four children within an hour after the administration of cimetidine. In five other children, more than four hours had elapsed after cimetidine was administered and anesthesia was induced. These nine children had *p*H values less than 2.5 and a mean (±SE) volume of 0.4 ± 0.1 ml/kg. In the first four children we considered that cimetidine was not absorbed satisfactorily and in the latter five, we felt that the effect of the drug had worn off. Therefore, we classified their data separately in table 1.

Administration of cimetidine 1–4 hours preoperatively was assumed to be the optimum time range and these children were analyzed together. A dose-response relationship was found between the *p*H and the dose of cimetidine in the range of 2.5–7.5 mg/kg with little further effect at a dose of 10 mg/kg (table 1). There were highly significant differences between the mean *p*H values of the control group of patients and each of the four groups of patients who received cimetidine ($P < 0.005$). Converting the individual *p*H values to H^+ concentrations and then obtaining the mean value did not change the statistical significance of the results. The ED_{50} for the dose of cimetidine that produced a *p*H of more than 2.4 was 3.0 mg/kg with 95 per cent confidence limits between 2.1–4.3. The ED_{95} was 7.5 mg/kg with confidence limits of 3.8–14.6.

The volume of gastric aspirate decreased exponentially as the dose of cimetidine was increased. The difference between the mean volumes of gastric aspirate was statistically significant between Group I and Group II ($P < 0.05$), and the level of significance increased with the increase in the dose of cimetidine (table 2).

The values of *p*H read by the intermediate range pHydrion® papers correlated well with the *p*H values determined by the *p*H electrode. The correlation coefficient between the two readings was highly significant ($r = 0.99$, $P < 0.0001$, slope 0.94) and in no instance was there a difference of more than 0.5 *p*H units.

Discussion

The present study clearly demonstrated that preoperative oral cimetidine at a dose of 7.5 mg/kg or more raised the *p*H of the gastric contents above 2.5 in more than 95 per cent of the children. It also effectively reduced the volume of gastric residual. None of the children at this dose of cimetidine had both a *p*H < 2.5 and a volume > 0.4 mg/kg (table 3). However, if less than one hour

TABLE 1. The *p*H and H^+ Concentration of the Gastric Aspirate in Children

	Cimetidine (< 1 h preoperative)		Cimetidine (1–4 preoperative)				Cimetidine (>4 h preoperative)	
	N	*p*H	N	*p*H (mean ± SE)	*p*H Range	H^+ Concentration mmol/l (mean ± SE)	N	*p*H
Group I Control No Cimetidine	——	——	25	1.61 ± 0.06	1.1–2.2	27.6 ± 3.67	——	——
Group II Cimetidine 2.5 mg/kg	——	——	16	3.94 ± 0.61*	1.5–7.0	9.75 ± 3.03†	1	1.5
Group III Cimetidine 5 mg/kg	2	1.7–2.0	12	4.63 ± 0.63†	2.4–8.1	2.12 ± 0.88†	1	2.5
Group IV Cimetidine 7.5 mg/kg	1	1.8	16	6.16 ± 0.38†	2.1–8.3	0.5 ± 0.4†	1	1.88
Group V Cimetidine 10 mg/kg	1	2.0	19	6.36 ± 0.33†	3.5–7.8	0.042 ± 0.025†	2	1.9–2.2

* Level of significance from control: $P < 0.005$.

† Level of significance from control: $P < 0.001$.

or more than four hours elapsed between the administration of the drug and the start of anesthesia, cimetidine had no effect on *p*H or gastric volume.

In comparing the effectiveness of 7.5 mg/kg to 10 mg/kg of cimetidine, we note that 10 mg/kg is slightly more effective in raising the *p*H and decreasing the volume of gastric aspirate than 7.5 mg/kg. The difference was due to one patient in the 7.5 mg/kg group who had a *p*H of gastric aspirate less than 2.5 (table 3). All of the patients who received 10 mg/kg had *p*H values above 2.5.

Values for *p*H read by the intermediate range pHydrion paper® correlated satisfactorily with the results of the more sophisticated but less practical *p*H electrode, indicating that pHydrion papers® can be used satisfactorily in clinical situations to evaluate *p*H values between 1–8. Also, the availability of intermediate *p*H papers between *p*H 1–2.5, *p*H 3.0–5.5, and vivid papers *p*H 6–8 made the readings more distinguishable.

Comparing our results in children with adult studies of cimetidine, we found that oral cimetidine in children at a dose of 7.5 mg/kg was more reliable than the recommended oral adult dose of 300 mg (4.3 mg/kg in a 70-kg man). In adult studies gastric *p*H after cimetidine was between 3.5–5.1[7,14–16] or greater than 2.5 in 70–84 per cent of patients.[7,14,15] These values are similar to the results that we found in children at a dose of 5 mg/kg cimetidine. In adults a 300-mg dose produced no significant changes in gastric fluid volume.[8,15,16] One adult study,[17] using 400 mg cimetidine, po, at bedtime and 400 mg, po, preoperatively (5.7 mg/kg), found both a reduction in volume and *p*H. In our study, a significant diminution of gastric fluid volume was noted even at the 2.5 mg/kg dose; the diminution in gastric fluid volume was more marked at the larger doses. This implies that even at a low dose, cimetidine is capable of reducing the volume of gastric fluid in children. In adults such a response is not seen after an equivalent low dose. It can be argued that the stomach cannot be completely emptied by a gastric tube. However, we standardized our technique. The position of the gastric tube was ascertained in all patients by injecting air through the tube and listening for the air sound in the epigastrium. We then attempted to empty the abdominal contents by gradual, gentle suction.

Investigation into the effect of premedicant drugs on gastric secretions of pediatric patients showed that glycopyrrolate, 7.5–10 μg/kg, reduces the volume of gastric secretions to 0.18 ml/kg (control 0.6 ml/kg) and increases the number of patients with *p*H values above 2.5 to 44 per cent (control 7 per cent).[18] In our study, cimetidine proved to be superior to glycopyrrolate in this latter respect.

Other techniques used to reduce the acidity of gastric contents, such as the administration of antacids, have not been systematically examined in children; however, even if they prove to be beneficial, the risk of fatal aspiration would probably still be present.[19] Children judge antacids

TABLE 2. Volume of Gastric Aspirate in the Five Groups of Children Studied

	Volume of Gastric Aspirate (ml/kg)	
	Mean ± SE	Range
Group I Control No Cimetidine	0.53 ± 0.1	0.11–2.4
Group II Cimetidine 2.5 mg/kg	0.24 ± 0.04*	0.05–0.45
Group III Cimetidine 5 mg/kg	0.18 ± 0.04†	0.03–0.39
Group IV Cimetidine 7.5 mg/kg	0.15 ± 0.04‡	0.01–0.42
Group V Cimetidine 10 mg/kg	0.13 ± 0.03‡	0.01–0.45

* Level of significance from control: $P < 0.05$.
† Level of significance from control: $P < 0.01$.
‡ Level of significance from control: $P < 0.001$.

TABLE 3. The Distribution of Patients with a *p*H < 2.5 and a Volume of Gastric Aspirate > 0.4 mg/kg

	N	*p*H < 2.5	Volume > 0.4 ml/kg	*p*H < 2.5 and Volume > 0.4 ml/kg
Group I Control	25	25 (100 per cent)	14 (64 per cent)	14 (64 per cent)
Group II Cimetidine 2.5 mg/kg	16	8 (50 per cent)*	3 (19 per cent)*	2 (12 per cent)*
Group III Cimetidine 5 mg/kg	12	4 (33 per cent)†	1 (8 per cent)†	1 (8 per cent)†
Group IV Cimetidine 7.5 mg/kg	16	1 (6 per cent)†	1 (6 per cent)†	0 (0 per cent)†
Group V Cimetidine 10 mg/kg	19	0†	1 (5 per cent)†	0 (0 per cent)†

* Level of significance from control: $\chi^2 < 0.01$.

† Level of significance from control: $\chi^2 < 0.001$.

to be unpalatable and probably would reject them if offered voluntarily.

Gastroesophageal reflux is the most important clinical situation in which cimetidine would be indicated. Cimetidine may also be useful if a difficult endotracheal intubation is anticipated. Here distention of the stomach with anesthetic gases with resultant regurgitation and aspiration is a good possibility. Another indication would be for the child who has a tendency to vomit, such as patients with pyloric stenosis and patients operated on for ophthalmic surgery.[20] In children with pyloric stenosis, intramuscular cimetidine would be a more logical choice.

In conclusion, we have found oral cimetidine to be a safe and effective premedicant in children between the ages of 4 months and 14 years. It markedly reduces both gastric acidity and volume. Since there has not been reported, nor have we observed, any complications after a single oral dose of cimetidine, we recommend that children at high risk of pulmonary aspiration receive 7.5 mg/kg cimetidine orally at least one hour but not later than four hours prior to induction of anesthesia.

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