Anesthesiology
59:86–90, 1983

Comparison of Cimetidine (Tagamet®) with Antacid for Safety and Effectiveness in Reducing Gastric Acidity before Elective Cesarean Section

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One hundred twenty-six parturients for elective cesarean section under general anesthesia were allocated to either a cimetidine or an antacid group in a randomized, double-blind, multicenter trial. The cimetidine-treated group received 300 mg cimetidine orally the evening before the operation and 300 mg intramuscularly between 1 and 3 h preoperatively. The antacid-treated group received 30 ml of Mylanta-II® orally on both occasions. Gastric volume, 30 min after induction of anesthesia and 30 min before response to oral commands, was less in the cimetidine-treated group. Gastric *p*H 30 min after induction was greater in the cimetidine-treated group. The maternal serum level of cimetidine at birth was 1.31 ± 0.12 μg/ml and the umbilical venous level was 0.78 ± 0.05 μg/ml. The neonatal gastric acidity, Apgar scores, and Early Neonatal Neurobehavioral Scale (ENNS) scores were similar in both groups. No maternal or neonatal complication was attributed to treatment. (Key words: Anesthesia: obstetrics. Gastrointestinal tract: stomach. Histamine: cimetidine. Pregnancy: cesarean section

OF THE 196 DEATHS resulting from obstetric anesthesia between 1961 and 1975 in England and Wales, 93 (47%) resulted from aspiration of stomach contents.[1–5] Between 1973 and 1975 there were 13 aspiration deaths, of which nine were diagnosed as Mendelson's syndrome. All but one of these nine parturients had received adequate antacid therapy during labor and immediately before anesthesia. It was concluded that "antacid therapy cannot always protect against Mendelson's syndrome and it must be regarded as only one of several preventative measures."[5] The objective of this trial was to evaluate whether cimetidine, an H_2 antagonist, was effective in reducing gastric acidity and was safe for the mother and neonate.

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Methods

Informed consent was obtained from the 126 parturients participating in this study. All were expected to deliver a single normal fetus, were between 17 and 40 years of age, and had not received anticholinergic drugs in the previous 24 h.

The patients were allocated in a random, double-blind manner to either a cimetidine or an antacid treatment group. The antacid used was Mylanta-II® which contains 400 mg of both aluminum hydroxide and magnesium hydroxide with 30 mg of simethicone in 5 ml. It will neutralize 12.7 Eq of acid. On the evening before elective cesarean section, they received either one 300-mg tablet of cimetidine with 30 ml of a placebo mixture that was identical in appearance to Mylanta-II® or one placebo tablet and 30 ml Mylanta-II®. One to three hours before induction of anesthesia, 300 mg of cimetidine im with 30 ml of the placebo mixture or 30 ml Mylanta-II® and an im injection of placebo was given.

Significant medical disease consisted of diabetes mellitus in seven patients in the cimetidine-treated group and six in the antacid-treated group; asthma, bronchitis, or hay fever in three patients in each group; hypertension in five patients in the cimetidine-treated group and three in the antacid-treated group; and renal disease in three patients in the cimetidine-treated group (unilateral kidney, renal transplant, or urinary tract infection). A history of allergy was reported by three parturients in the cimetidine-treated group and 10 in the antacid-treated group, and a history of drug abuse was obtained from one patient in the antacid-treated group.

A rapid sequence anesthetic technique was used involving preoxygenation, intravenous induction with thiopental, and muscle relaxation followed by intubation of the trachea. Halothane 0.5% with 50% nitrous oxide and oxygen was employed until the infant was delivered, after which narcotics were used. The mean dose of thiopental was 3.5 ± 0.1 mg/kg in the cimetidine-treated group and 3.4 ± 0.2 mg/kg in the antacid-treated group. A 100 mg dose of succinylcholine was used for all parturients. The induction to delivery time was 12.8 ± 0.2 min in the cimetidine-treated group and 11.8 ± 0.2 min in the antacid-treated group. Excessive positive pressure ventilation was avoided, and the rate

0003-3022/83/0800/0086 $01.05

and volume was such that, in the judgment of the anesthesiologist, normocarbia would result.

Evaluation of the effect of the two treatments on gastric volume and acidity was made by continuously emptying the stomach and collecting in 15-min aliquots from immediately after induction until the patient responded to oral commands and was extubated. The gastric contents were pooled for 30 min after induction and 30 min before extubation. The effect of the two treatments on the mother was assessed by recording all intraoperative and postpartum complications and by performing hematologic tests (RBC, Hct, Hb, total and differential WCC, and platelet counts), hepatic function tests (serum bilirubin, alkaline phosphatase, and SGOT), renal function tests (BUN and serum creatinine), and urinalysis (specific gravity, sugar, protein, and microscopy) 24 h before operation and on postpartum days 2 and 4. The effects of the two treatments on the neonate were assessed by the Apgar score at 1, 5, and 15 min after birth, the early neonatal neurobehavioral scale (ENNS) at 2–4 h after birth and again on the third day of life. Maternal and umbilical cimetidine levels at birth and the acidity of the neonates' gastric contents at birth and at 48 h of age were measured.

The volume and *p*H of the gastric contents were compared for the two groups by Student's *t* test and the number of patients having a zero volume, a volume less than 10 ml and a *p*H greater than 2.5 in the two groups were compared by chi-square analysis. Because the Apgar score is on a ranking scale, the frequency of Apgar scores below 7 was analyzed by chi-square. The neurobehavioral scores, also on a ranking scale, were analyzed by chi-square and Fisher's Exact Test. Because the numbers in the cells of the contingency table were not large enough to test alone, the cells were combined to give high and low scores providing a four-fold contingency table. The division of scores into high and low was made so that the score data for the combined groups nearly fell into two equal halves. The percentages of high scores are given in table 1, and the percentage of low scores can be obtained by subtracting from 100.

TABLE 1. Percentage of Neonates with High Scores on Neurobehavioral Testing on the First and Third Day after Delivery*

Response	Cimetidine (n = 31)	Antacid (n = 31)
Overall:		
Day 1	69	69
Day 3	83	90
Pinprick:		
Day 1	62	53
Day 3	67	61
Tone:		
Day 1	40	53
Day 3	32	51
Rooting:		
Day 1	44	37
Day 3	26	26
Sucking:		
Day 1	42	28
Day 3	32	29
Moro:		
Day 1	35	51
Day 3	40	60
Sound:		
Day 1	51	37
Day 3	75	53
Placing:		
Day 1	37	44
Day 3	47	57
Alertness:		
Day 1	47	44
Day 3	42	48
Decrement scores		
Sound:		
Day 1	51	55
Day 3	42	45
Pinprick:		
Day 1	51	48
Day 3	48	40
Light:		
Day 1	49	44
Day 3	52	48
Moro:		
Day 1	51	58
Day 3	48	48
State changes:		
Day 1	59	36
Day 3	63	40

* No statistically significant difference between groups for any score on day 1 and 3.

Results

A physician unaware of the treatment administered excluded 37 of the 126 case records from the analysis of gastric secretion because of protocol violations but included them in the safety assessments. Thirteen of the 37 had been entered by one investigator in an unblinded study as required by his Institutional Review Board. The remainder were excluded because general anesthesia was not induced between 1 and 3 h of the morning administration of the appropriate medication. The excluded data did not provide sufficient information to state whether or not antacid and cimetidine were effective when administered more than 3 h before operation.

The maternal gastric volume and acidity, 30 min after induction and 30 min before response to verbal commands, are shown in table 2. The mean volume of the gastric contents after induction in the cimetidine-treated group was only one-third of that measured in the antacid-treated group ($P < 0.01$). The mean gastric *p*H and the percentage of patients having a volume less than 10 ml were greater in the cimetidine-treated group. The gastric volume was smaller in the cimetidine-treated

TABLE 2. Gastric Volume and Acidity in the 30 Minutes after Induction and 30 Minutes before Response to Verbal Commands

	30 Minutes after Induction		30 Minutes before Response to Verbal Commands	
	Cimetidine (n = 48)	Antacid (n = 41)	Cimetidine (n = 26)	Antacid (n = 29)
Gastric volume (mean ± SE) ml	11 ± 2*	33.4 ± 5.2	3.2 ± 0.6*	11.9 ± 4.2
Gastric *p*H (mean ± SE)	6.3 ± 0.2†	5.5 ± 0.3	6.6 ± 0.4	6.2 ± 0.4
Zero volume %	12	0	31	17
Volume < 10 ml %	67*	27	96	76
*p*H > 2.5%	100	88	92	92

* $P < 0.01$. † $P < 0.05$.

group in the 30 min prior to response to verbal commands.

The maternal intraoperative and postpartum complications in the cimetidine-treated and antacid-treated groups are listed in table 3. An evaluation by the investigator, while the investigator was still unaware of the treatment administered, did not associate any complication with treatment. Bigeminy occurred during operation in a 22-year-old patient who had diabetes and was dependent on insulin who had received cimetidine. It was noted again on the fifth postoperative day. One patient in the antacid-treated group developed tachycardia intraoperatively, which responded to propranolol.

Abnormalities in laboratory tests were reported in a small proportion of the parturients in both treatment groups. The values for the red and platelet cell counts, serum creatinine, and blood urea nitrogen were within the normal range for pregnancy in both groups, both before surgery and on postoperative days 2 and 4. One WCC was over 19,000 on day 2 in a patient who had received antacid. One patient with severe preeclampsia had a SGOT of 110 preoperatively. Six patients in the cimetidine-treated group and five in the antacid-treated group had high SGOT values after surgery, but this did not exceed 80 U/l and there was no evidence of hepatic dysfunction. One patient in the cimetidine-treated group had a bilirubin level of 1.9 mg/dl postpartum, and two in the antacid-treated group had a level of 1.5 mg/dl. Two patients in the group receiving cimetidine and four in the group receiving antacids had 2+ protein in the urine postoperatively. This was attributed to contamination of the lochia and rated of no clinical significance by the investigators. Two patients in the group receiving antacids had glycosurea postoperatively; one suffered from diabetes and the other from preeclampsia.

TABLE 3. Maternal Intraoperative or Postpartum Complications in the Cimetidine-treated and Antacid-treated Groups

	Cimetidine group (n = 63)	Antacid group (n = 63)
Pulmonary embolism	0	1
Intraoperative arrhythmia	1	0
Intraoperative tachycardia	0	1
Postpartum hemorrhage	3	3
Headache/insomnia	2	2
Cough	1	0
Constipation	13	17
Flatulence, indigestion, nausea	3	5
Metritis	4	4
Urinary tract or incisional infection	1	1
Temp > 37.8°C on day 2	12	10
Temp > 37.8°C on day 4	3	2
WBC > 19,000 on day 2	0	1
WBC > 19,000 on day 4	0	0

A major objective of the study was the evaluation of possible effects of the investigational treatments on the neonate. At birth, the serum level of cimetidine in 41 mothers was 1.31 ± 0.12 μg/ml, while the umbilical venous level was 0.78 ± 0.05 μg/ml. The Apgar score at 1, 5, and 15 min after birth was measured for 63 neonates in the cimetidine-treated group and 65 neonates (twins occurred twice) in the group receiving antacids (table 4). The ENNS was administered to 31 neonates in the cimetidine-treated group and 31 neonates in the antacid-treated group on days 1 and 3 of life (table 1). Neither the Apgar scores nor the ENNS scores in the two groups exhibited a statistically significant difference at $P < 0.05$ at any time. The neonatal gastric *p*H at birth was 7.6 ± 0.6 for the cimetidine-treated group and 7.4 ± 0.7 for the antacid-treated group. At 3 days, the *p*H was 6.2 ± 0.6 and 6.1 ± 0.8, respectively.

A number of neonatal complications occurred in both antacid-treated and cimetidine-treated groups (table 5), but none were attributed to the test medications by the investigator while the investigator was still unaware of the investigation treatment administered. Some could be explained by maternal complications and their treatment or by prematurity or postmaturity. In the cimetidine-treated group, one case of birth asphyxia was resulted from anoxia secondary to extreme difficulty in intubating the mother's trachea and the other was associated with lethargy and was related to severe maternal preeclampsia treated with magnesium sulfate, methyldopa, and meperidine. One lethargic baby was pre-

TABLE 4. The Frequency of Low Apgar Scores in Infants Whose Mothers Were Given Cimetidine and Antacid before Surgery

	1 Minute			5 Minutes			15 Minutes		
	0–3	4–6	7+	0–3	4–6	7+	0–3	4–6	7+
Cimetidine	1	7	55 (n = 63)	0	0	62 (n = 62)*	0	0	58 (n = 58)*
Antacid	7	5	53 (n = 65)	0	1	64 (n = 65)	0	0	60 (n = 60)*

* Not all infants were evaluated.

mature. In the antacid-treated group, three cases of respiratory distress resulted from prematurity, an irritable and hypotonic neonate was born to a patient who had diabetes, and one lethargic baby was large for gestational age.

There were a number of unexplained complications. Both groups had one case of cardiac arrhythmia, which was diagnosed as accelerated nodal rhythm alternating with normal sinus rhythm and was untreated. In the cimetidine-treated group one infant suffered from respiratory distress, grunting respiration, and tachypnea, and one baby vomited and fed poorly on the first day of life. Both were treated with antibiotics but culture of the blood and cerebrospinal fluid did not reveal a source of sepsis. One baby, born to a mother who had diabetes and received cimetidine, received oxygen in the first 3 hours of life, ultraviolet light for hyperbilirubinemia, packed cells for anemia, and a glycerine suppository for a meconium plug. The persistent fetal circulation resolved spontaneously on the third day, and the baby was discharged in a healthy state on the fifth day. In the antacid-treated group there was one instance of birth asphyxia. There was one case of respiratory distress that was mild and resolved spontaneously but was associated with x-ray evidence of streaking and fluid in the lung. One episode of congested breathing was noted in another neonate briefly on the third day, and there was one report of hypotonia. Unexplained and brief periods of irritability or tremor occurred in four neonates in the antacid-treated group and one in the cimetidine-treated group.

Discussion

Gastric acidity can be reduced by antacids or H_2 antagonists such as cimetidine. Antacids have the disadvantage that they are not totally effective in preventing Mendelson's syndrome, because eight fatal cases have been reported in parturients who had received adequate antacid therapy during labor and immediately before operation.[5] They also increase gastric volume and the particulate antacids can produce an aspiration pneumonitis in animals.[6] Cimetidine reduces gastric volume and acidity but has the disadvantages that it can only inhibit gastric secretion after effective blood levels have been reached and it does not neutralize acid already in the stomach.

In this trial, cimetidine given orally the previous night and intramuscularly 1–3 h before operation, was completely effective in increasing the gastric *p*H to over 2.5 on induction of anesthesia. This contrasts with the findings that 71% of parturients not in labor had a *p*H of less than 2.6.[7] The gastric volume following cimetidine was only a third of that after the antacid; a finding previously reported by other investigators.[8,9]

Following oral administration of 300 mg cimetidine, peak blood levels are reached after 30 min, whereas following im injection, higher peak levels are reached within 10 min. Effective levels of 0.5 μg/ml are maintained by both routes for over 4 h.[9,10] A plasma concentration of 0.5 μg/ml suppresses gastric secretion of acid by over 80%.[11] A single oral dose of 300 mg of cimetidine will significantly reduce gastric acidity for over 8 h in normal man.[12] It would seem reasonable, therefore, to suppress nocturnal secretion by an oral dose of cimetidine in the evening before elective cesarean section. To obtain an effective blood level rapidly on the morning of operation, cimetidine im is indicated.

No side effects in mother or neonate were attributed to either treatment by the investigator while the investigator was still unaware of which medication had been administered. Cimetidine crosses the placenta, but neo-

TABLE 5. The Frequency of Neonatal Complications in the Cimetidine-treated and Antacid-treated Groups

Neonatal complications	Cimetidine	Antacid
Premature or small for gestational age	2	4
Postmature or large for gestational age	2	3
Birth asphyxia	2 (0)*	1 (1)
Arrhythmia	1 (1)	1 (1)
Respiratory distress	1 (1)	4 (1)
Congested breathing	0	1 (1)
Irritable or tremulous	1 (1)	5 (4)
Lethargic or unresponsive	3 (1)	3 (2)
Vomiting with reluctance to feed	1 (1)	0
Hypotonia	0	2 (1)
Persistant fetal circulation, etc.	1 (1)	0

* In parentheses are the number of complications unexplained by prematurity, postmaturity, or maternal complications.

natal gastric acidity did not differ significantly between the cimetidine-treated and antacid-treated groups. The reason cimetidine has little effect on neonatal gastric acidity may be that neonates delivered by cesarean section have a mean gastric *p*H of 6.79 (range 5.9–7.4), in contrast to vaginally delivered neonates, who have a mean gastric *p*H of 6.00 (range 1.4–7.6).[13] There was also no statistically significant difference in Apgar or neurobehavioral scores between the two groups.

A number of alternatives exist for the use of cimetidine and antacids in an attempt to prevent Mendelson's syndrome. For elective cesarean section, cimetidine can be given orally the previous evening and intramuscularly 1–3 h before surgery. For emergency cesarean section, it would be reasonable to administer cimetidine intramuscularly to inhibit gastric secretion and to combine this with a nonparticulate antacid such as sodium citrate to neutralize acid already secreted. Although cimetidine has been administered intravenously before cesarean section,[14] this is not recommended because bradycardia, hypotension, cardiac arrhythmias, and cardiac arrest have followed its use by this route.[15,16]

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