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Does Metoclopramide Decrease the Volume of Gastric Contents in Patients Undergoing Cesarean Section?

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Pulmonary aspiration of gastric contents is responsible for 30–50% of maternal deaths caused by anesthesia.[1] The factors that predispose to this complication during pregnancy include hormonal influences,[2–4] which decrease gastric motility and reduce lower esophageal sphincter (LES) tone, and mechanical changes, which increase intragastric pressure and distort gastric anatomy. As a result, the stomach may not be empty many hours after cessation of oral intake, and regurgitation and aspiration occur more frequently in pregnant than in nonpregnant patients.[5] The severity of pulmonary damage following aspiration of gastric contents is related to the volume and acidity of the aspirate. A volume of 25 ml and a *p*H of 2.5 are said to be hazardous,[6] although these values have not been validated in humans. Food or other particles in the lungs further increases the severity of both the short-term and long-term physiologic and morphologic abnormalities.[7]

To decrease the consequences of aspiration, antacids and, more recently, H_2 receptor antagonists such as cimetidine, have been used to increase the *p*H of gastric contents. However, neither therapy decreases the risk posed by significant volumes of gastric contents already present in the stomach. In that respect, metoclopramide, an antiemetic agent that accelerates gastric emptying and increases LES tone, is of potential benefit to the parturient with a full stomach who requires general anesthesia. In a previous study[8] of surgical outpatients in early pregnancy, metoclopramide, 10 mg, iv, administered shortly before anesthesia significantly decreased the volume of gastric contents. The present study was designed to ascertain the efficacy and safety of similar therapy in term parturients scheduled for elective cesarean section.

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METHODS

The study was approved by the Human Subjects Committee, and informed consent was obtained from 58 healthy parturients who had requested general anesthesia for elective cesarean section. Approximately 15 min before anesthesia, patients received, double-blinded, a 2-ml iv injection of either metoclopramide, 10 mg, (Group 1, n = 30) or saline, (Group 2, n = 28). Treatments were prepared by the drug manufacturer (A. H. Robins) in coded ampules. Anesthesia was induced with ketamine, 1.5–2 mg/kg iv and was maintained until delivery by inhalation of nitrous oxide, 50%, and up to 0.5% enflurane. Following endotracheal intubation, an 18-gauge salem sump nasogastric tube was passed into the stomach, and its position was verified by auscultating over the epigastrium for insufflated air. Gastric contents were aspirated with a syringe for at least a 10-min period, moving the position of the patient and the tube to maximize retrieval¶; volume and *p*H were measured immediately. The times between drug administration and induction of anesthesia, gastric aspiration, uterine incision, and delivery of the infant were recorded. Assessment of the newborn included Apgar scores assigned by the pediatrician at 1 and 5 min, and umbilical arterial and venous blood gas analyses performed on samples obtained from an isolated segment of umbilical cord immediately after delivery. Neurobehavioral examinations using the Neurologic and Adaptive Capacity Score[9] were performed at 30 min, 2 h, and 24 h of age.

Metoclopramide levels at delivery were measured in maternal and umbilical venous blood in eight cases. Blood for drug assays was collected into heparinized tubes, centrifuged, and the supernatant plasma stored at −20° C. All samples were analyzed together using a technique employing high-pressure liquid chromatography and a spectophotometric detector.[10]

Data were analyzed using Student's *t* test for unpaired data and chi-square analysis. $P < 0.05$ was considered significant. A gastric volume in excess of 25 ml in combination with a *p*H of less than 2.5 was considered a risk with respect to aspiration.

Results

The groups were similar with respect to maternal age, height, weight, gestational age, infant weight (table 1), and anesthetic dosage. There also were no intergroup differences in mean times between study drug administration and: induction of anesthesia (12.5 ± 1 min: combined data from both groups); gastric aspiration (19 ± 1 min); and delivery (35.5 ± 2 min). The rather prolonged interval between induction of anesthesia and delivery resulted from the practice at this institution of performing the surgical preparation, draping, and inserting the urinary catheter after the patient was asleep, rather than before, as is the custom in the United States. The uterine incision–delivery interval (which correlates well with neonatal status) was less than 2 min in all cases. Treatment with metoclopramide did not result in significant differences in mean gastric volume, the number of patients with a volume greater than 25 ml, gastric *p*H, or the number of patients with a *p*H less than 2.5 (table 2). However, when gastric volume > 25 ml and *p*H < 2.5 were considered together, only seven patients (23%) were at risk in the metoclopramide group, compared with 12 (43%) in the placebo group ($P < 0.025$).

Apgar scores and neurobehavioral tests were satisfactory and similar in both groups (table 3). Unexpectedly, umbilical blood gas values demonstrated slightly better oxygenation and less acidosis in babies in the metoclopramide group (table 4). These differences were statistically, although perhaps not clinically, significant.

Metoclopramide assays demonstrated wide variations in both maternal (11–152 ng/ml) and umbilical venous levels. In four infants, the level was below the limits of

TABLE 1. Group Characteristics

	Metoclopramide (n = 30)	Placebo (n = 28)
Age (yr)	30 ± 1	30 ± 1
Height (cm)	158 ± 1	160 ± 1
Weight (kg)	68 ± 2	65 ± 2
Gestation (weeks)	39 ± 0	39 ± 0
Infant weight (g)	3,279 ± 88	3,204 ± 88

Values are mean ± SEM. No significant differences.

TABLE 2. Volume of Gastric Contents and *p*H in Study Groups

	Metoclopramide (n = 30)	Placebo (n = 28)
Gastric volume	24 ± 2 ml*	30 ± 5 ml
(range)	(3–60)	(4–155)
Vol > 25 ml	16†	15
	(53%)	(54%)
Gastric *p*H	2.86 ± 0.27*	2.55 ± 0.24
(range)	(1–6)	(1–5.5)
*p*H < 2.5	12†	16
	(40%)	(57%)

Values represent: *Mean ± SEM; †number of patients.
No significant differences between the groups.

¶ The method used to measure the volume of gastric contents in this study, *i.e.*, simple aspiration, may lead to slight underestimation of total volume. Alternative methods also are prone to inaccuracies[8] or, because of the use of radioactive agents, are unsuitable for use in the pregnant patient.

TABLE 3. Newborn Assessment

	Metoclopramide	Placebo
Apgar score	(n = 30)	(n = 28)
Less than 7		
at: 1 min	2	3
5 min	0	0
NACS*	(n = 25)	(n = 23)
30 min	31 ± 1	31 ± 1
2 hr	36 ± 1	36 ± 1
24 hr	39 ± 1	39 ± 1

No significant differences.
* Neurologic and adaptive capacity score[4]—maximum score is 40.

sensitivity of the assay (10 ng/ml). Data from the remaining four infants revealed umbilical vein levels of 35–145 ng/ml, with a fetal/maternal ratio of 0.84.

DISCUSSION

Metoclopramide (methoxy-chloro-procainamide) initially was developed as an antiemetic and subsequently was found to have diverse effects on the gastrointestinal tract. It exerts a "gastrokinetic" effect, consisting of increased muscle tension in the lower esophageal sphincter and gastric fundus, increased gastric and small intestinal motility, and relaxation of the pylorus and duodendum during stomach contraction.[11] These actions result in accelerated esophageal and gastric clearance of liquids and solids and shortened transit time through the small bowel. Because of these properties, metoclopramide has been utilized for gastrointestinal radiologic procedures and to improve gastric hypomotility and esophageal reflux in a variety of digestive disorders.[11] Metoclopramide's actions are mediated centrally via antidopaminergic and prolactin stimulation and peripherally by facilitation of cholinergic stimulation, predominantly on the upper gastrointestinal tract.[11] Vagotomy does not decrease metoclopramide-induced hypermotility, whereas atropine does, indicating that metoclopramide acts on the postganglionic cholinergic nerves intrinsic to the gut wall.

TABLE 4. Neonatal Acid–Base Status

	Metoclopramide		Placebo	
	UA	UV	UA	UV
*p*H	7.23 ± 0.01	7.31 ± 0.01	7.24 ± 0.01	7.27 ± 0.01*
P_{O_2}	22 ± 1	32 ± 2	17 ± 1†	28 ± 2
P_{CO_2}	42 ± 2	39 ± 1	48 ± 2*	40 ± 2
HCO_3	18.8 ± 1.4	18.2 ± 1.7	16.8 ± 2.8	16.0 ± 2.9
BE	−5.7 ± 1.2	−5.5 ± 1.4	−6.3 ± 1.2	−5.8 ± 1.1

UV and UA = umbilical artery and vein. Values are mean ± SEM with comparisons between metoclopramide and placebo.
* $P < 0.05$.
† $P < 0.005$.

Although the use of metoclopramide has been advocated to decrease aspiration risk in surgical patients, in this population of term parturients, a 10-mg iv dose did not decrease the volume of gastric contents. These results differ from those of Howard and Sharp,[12] who found that metoclopramide accelerated gastric emptying of a test meal in laboring women, and those of Wyner and Cohen,[8] who demonstrated decreased gastric volume following its administration to women 12–20 weeks pregnant having general anesthesia for therapeutic abortion. Similarly, others have found it to have a beneficial effect when administered to adult[13] and pediatric[14] trauma patients before anesthesia. Metoclopramide's lack of effect in this study may be due to inadequate dosage or insufficient duration between drug administration and induction of anesthesia. Although some anesthetic studies[13,14] in which metoclopramide enhanced gastric emptying have employed larger doses (20 mg, or equivalent in children), others have demonstrated benefit with a 10 mg dose.[8,12] In this study, maternal blood levels were above 40 ng/ml in 80% of mothers at the time of sampling and thus in the therapeutic range for accelerating gastric motility.[11] Various time intervals between administration of metoclopramide and assessment of its effects have been employed. Bateman *et al.*[15] found that metoclopramide 10 mg, iv, administered to male volunteers increased absorption of orally administered ethanol within 12 min after injection. Wyner and Cohen[8] similarly found decreased gastric volume when the drug was administered only 15 min before anesthesia. In the present study, patients had fasted overnight, were not in labor, and may not have had severely abnormal gastric motility.[16] In contrast, the emergency obstetric patient often has recently eaten, is anxious, and may be in labor; gastric emptying is significantly impaired and gastric volume greater than in the elective situation.[16,17] Several investigations suggest that in such circumstances, metoclopramide might be more effective.[12–14] Unfortunately, emergency obstetric patients are difficult to study, because fetal distress or maternal hemorrhage often dictates extreme urgency.

The finding that metoclopramide decreased the number of patients at risk from the combination of both low *p*H and large gastric volume while affecting neither factor individually is of interest. In a previous study of women in early pregnancy, metoclopramide administration resulted in a decrease from 51 to 13% in the number of patients with a volume of gastric contents in excess of 25 ml.[8] While there was no effect on gastric *p*H, only 6% of patients had both a high volume and a low *p*H. Thus, metoclopramide preferentially may promote gastric emptying in the presence of low *p*H.

Placental transfer of metoclopramide occurred rapidly and, in accordance with the findings of Arvela *et al.*,[18]

wide variations in blood levels were noted in both mother and fetus. Although in some cases levels were in the range that has been associated with drowsiness or restlessness in human volunteers (100 ng/ml),[19] no adverse effects on maternal or neonatal well-being were detected. In general, sedation or other side effects following single-dose administration of metoclopramide have not been described.[8,20] With chronic high-dose therapy, particularly in children, extrapyramidal and other minor side effects occasionally develop.

In our study, metoclopramide treatment resulted in a decreased number of patients with both a high volume of gastric contents and a low *p*H, although the effect on gastric volume and *p*H individually were unremarkable. An undisputed additional advantage of metoclopramide is its effect on the LES. Brock-Utne *et al.*[21] have shown that metoclopramide significantly increases LES tone in pregnant women and recommend its routine use before cesarean section. In view of its absence of adverse effects, metoclopramide probably should be administered to the parturient at high risk from aspiration, *e.g.*, the mother who requires general anesthesia but who has recently eaten, the obese parturient, those suffering from heartburn (indicative of LES dysfunction and gastric hypomotility), or those who are likely to pose particular difficulty with endotracheal intubation. The effect of metoclopramide on the LES is clearly beneficial and in high-risk subjects, even a minor increase in gastric motility should somewhat decrease the risk of aspiration in the perioperative period. Atropine should not be administered with metoclopramide because it counteracts the effect of the latter on the LES.[22] On the basis of our results, we do not, however, recommend routine administration of metoclopramide to patients undergoing elective cesarean section. Before routine drug therapy can be recommended in the pregnant population, an extremely low risk/benefit ratio must be demonstrated. Although pharmacologic prophylaxis against aspiration (*e.g.*, antacids) has decreased the number of patients with arbitrarily designated "risk factors," it has not yet demonstrably decreased maternal mortality.[1]

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