Anesthesiology
52:321-323, 1980

Effect of Domperidone on Lower Esophageal Sphincter Tone in Late Pregnancy

J. G. Brock-Utne, M.B., B.Ch., J. W. Downing, M.B., B.Ch. (Rand),† G. E. Dimopoulos, Ch.M. (L'pool),‡ J. Rubin, M.B., B.Ch.,§ M. G. Moshal, M.R.C.P.¶*

Increasing the resting lower esophageal sphincter (LES) tone is a useful method of preventing gastroesophageal reflux. The effects of a new antiemetic, domperidone, on LES were studied in 28 subjects. Group I included eight normal nonpregnant control subjects. The remaining 20 pregnant women were divided into two groups, Groups II and III—ten parturients without and ten with symptoms of heartburn. Domperidone increased LES pressure by 19, 11 and 10 cm H_2O in Groups I, II and III, respectively ($P < 0.05$). Domperidone may be a valuable premedicant in some patients to decrease the chance of gastroesophageal reflux. (Key words: Anesthesia, obstetric. Complications: aspiration. Gastrointestinal tract, esophagus. Lung: aspiration. Vomiting, antiemetics, domperidone.)

MENDELSON'S SYNDROME remains a major cause of death and morbidity in obstetric anesthesia. According to a confidential inquiry in the United Kingdom, there was no significant decrease in maternal mortality from aspiration during the years 1973–1975 (13 deaths) compared with the years 1970–1972 (14 deaths).[1] This disappointing finding may have many explanations. In medical literature, however, little emphasis has been placed on the importance of the lower esophageal sphincter (LES). Anesthetic drugs may decrease LES tone[2-5] and thereby increase the incidence of gastroesophageal reflux.[3-6] Regurgitation or vomiting and subsequent tracheobronchial aspiration, atelectasis, and hypoxia are recognized complications occurring in the perioperative period.[7]

Gastroesophageal relaxation with reflux is obviously the forerunner of overt aspiration. Silent regurgitation of gastric contents has been reported to occur in 25 to 70 per cent of patients receiving general anesthesia,[8-10] with tracheal aspiration occurring in 76 per cent.[11] Theoretically, regurgitation of acidic gastric content into the esophagus may result from one of three causes[12]: decreased LES tone; intragastric pressure increased to above levels normally withstood by the resting LES; and mechanical factors, now thought to be of little importance.[13] Most current evidence supports the theory that the LES is the major barrier preventing gastroesophageal reflux.[14]

Domperidone, a benzimidazol derivative, is a potent antiemetic[15,16] with gastrointestinal stimulatory properties.** Its chemical structure and pharmacokinetics has been recently described.[16] The drug has been shown to increase LES tone in dogs and baboons.[17] Hence, domperidone, by increasing LES tone, could have a prophylactic action in the prevention of the acid-aspiration syndrome. This paper concerns our investigation into the effects of domperidone on the LES in both normal and pregnant human subjects.

Materials and Methods

Three groups of subjects were studied. All subjects gave informed consent. The study was approved by the Ethical Committee of the Faculty of Medicine, University of Natal. The drug was cleared by the South African Medicines Control Council for full distribution with no restriction to pregnant patients, except in the first trimester. The first group (Group I) of eight nonpregnant volunteers, ranging in age from 18 to 55 years (mean 35 ± 4 SEM), acted as a control group. Group II consisted of ten normal pregnant women, without symptoms of heartburn, between 18 and 36 years of age (mean 26 ± 2); Group III included ten parturients between 17 and 29 years of age (mean 23 ± 2), all of whom complained of heartburn during their current pregnancy. Patients who had histories of gastrointestinal symptoms or surgical operations involving the gastrointestinal tract, with the exception of those with heartburn in Group III, were excluded from the study. All pregnant patients were between the thirty-sixth and fortieth weeks of gestation and were comparable in weight. Esophageal motility studies were performed with subjects resting quietly in the supine or left lateral position, after a fast of at least ten hours. Methods previously described were used.[6,18]

In brief, a motility tube consisting of three No. 54 polyethylene tubes attached together at the distal

* Principal Anesthetist and Senior Lecturer.
† Professor and Head (Anesthetics).
‡ Senior Lecturer, Department of Surgery.
§ Specialist Anesthetist.
¶ Professor and Head of Department of Gastroenterology.

Received from the Departments of Anaesthetics and Surgery and the Gastrointestinal Unit, University of Natal and King Edward VIII Hospital, Durban, South Africa. Accepted for publication October 15, 1979. Presented at the Biannual South African Congress of Anaesthesiology, Cape Town, September 1978.

Address reprint requests to Dr. Brock-Utne: Department of Anaesthetics, University of Natal, P.O. Box 17039, Congella 4013, Durban, South Africa.

** Unpublished research reports supplied by Janssen R & D, Inc., Johannesburg, South Africa.

TABLE 1. Esophageal, Lower Esophageal Sphincter, Gastric and Barrier Pressure (cm H_2O) before and after Domperidone (Mean ± SEM)

	Group I Non-pregnant, Control		Group II Pregnant, No Heartburn		Group III Pregnant, Heartburn	
	Basal	After Domperidone	Basal	After Domperidone	Basal	After Domperidone
Gastric pressure	21 ± 2	25 ± 2	31 ± 1	32 ± 1	27 ± 1	27 ± 1
Sphincter pressure	55 ± 3	74 ± 3	51 ± 2	62 ± 3	45 ± 3	55 ± 4
Esophageal pressure	2 ± 1	3 ± 1	1 ± 1	1 ± 0.2	1 ± 0.4	1 ± 0.5
Barrier pressure	34 ± 4	49 ± 4	20 ± 2	30 ± 3	18 ± 2	28 ± 4

end was assembled. Each tube had a single lateral orifice situated 5, 10, and 15 cm, respectively, from the distal tip. The catheter was swallowed orally until all the recording orifices lay in the stomach. Throughout the entire procedure, each tube was continuously perfused with water at a rate of 0.19 ml/min, using a Harvard constant-infusion pump. Each tube was connected to a Beckman Instrument® physiologic transducer Model 215071 linked to an eight-channel Beckman R411 Dynograph® amplifier and recorder. The tube was then slowly withdrawn, 0.5 cm at a time, until the pressure recordings, and their alterations in response to swallowing, indicated that all three orifices lay in the esophagus above the LES. Normally, the lower esophageal sphincter relaxes and then contracts during swallowing, producing fluctuations in the pressure profile of the sphincter. These latter fluctuations result in an abnormally low reading at first, then a substantially higher reading. Pressure changes recorded during swallowing were therefore excluded, and time was allowed for the pressure profile to settle to preswallowing levels before continuing with tube withdrawal. Basal levels of gastric (GP), LES (SP), and esophageal pressures (EP) were determined initially for each subject. The difference between SP and GP was termed the barrier pressure. Each patient then received domperidone, 0.2 mg/kg (to as much as 10 mg maximum), intravenously. All pressures were expressed in cm H_2O above atmospheric pressure. Respiration was monitored using a tubular pneumograph placed around the subject's chest, and connected to the Dynograph amplification and recorder system.

All sphincter-profile recordings were analyzed independently by one experienced person (G.E.D.), whose sole function was to determine mean pressure values from the profiles. Unsatisfactory recordings were rejected and the subjects excluded from the study. Statistical analyses were performed using the Student *t* tests for paired and unpaired data. A P value < 0.05 was regarded as significant.

Results

In Group I (control) mean pressures in the stomach, LES, and esophagus were 21, 55, and 2 cm H_2O, respectively (table 1). After the administration of domperidone, there were significant increases in both LES pressure and barrier pressure of 19 and 15 cm H_2O, respectively. Mean esophageal pressure did not change. The onset of drug effect on the LES was evident within 10 min and peaked within 30 min.

There was no significant difference in control gastric and barrier pressures between Groups II and III. After domperidone administration, there was no change in mean gastric pressure in either group. However, LES pressure increased significantly by 11 cm H_2O in Group II and 10 cm H_2O in Group III. Barrier pressure increased significantly in both groups after domperidone, 10 cm H_2O in each group. No change in esophageal pressure was observed.

Under basal conditions, mean gastric pressures were significantly higher in the pregnant patients than in the control group. After domperidone, the control group had a significantly higher mean barrier pressure than both pregnant groups.

Except for mild pain on injection of domperidone, which was experienced by three patients, no adverse side effect or serious complication was encountered in this investigation.

Discussion

This study confirms previous observations[6,19] that intragastric pressure increases with pregnancy; presumably, this is caused by the presence of the enlarging uterus within the abdominal cavity. Normally, with the increase in gastric pressure, LES pressure also increases. In some patients, however, LES pressure is not seen to increase, and heartburn may result from acid regurgitation through a "weak" sphincter.[6,18]

The mean barrier pressures of both the pregnant groups were significantly lower than control and virtually identical. This finding was not unexpected, since correlation between a decreased LES pressure and symptomatic gastroesophageal reflux and esophagitis[20] is not absolute. Also, some of our patients without heartburn may have had "weak" sphincters, even though they had been symptom-free at the time of study. The statistical significant difference in ages between the nonpregnant control and the pregnant heartburn group is probably of little consequence, since LES pressure is not age-dependent in this age range.[21]

Increasing the resting tone of the lower esophageal sphincter is currently believed to be the best method of obtunding gastroesophageal reflux.[5,14] Hence, domperidone could be used as an antiemetic in patients at risk before operations and general anesthesia to help prevent aspiration of gastric content. The mechanism of action of domperidone on the LES remains to be elucidated. However, it is claimed that the action of domperidone is based on its dopamine-receptor blocking properties.[17] Dopamine has been shown to cause a decrease in LES pressure in the opossum.[22]

Domperidone does not belong to one of the well-known classes of antiemetics. Pharmacologically, it antagonizes apomorphine-induced vomiting in dogs, but it has no effect on the central nervous system, which indicates an inability to cross the blood–brain barrier.[23] Therefore, the drug does not affect the dopaminergic receptors in either the chemoreceptor trigger zone or the basal ganglia of the brain. The antiemetic action of domperidone is due solely to its peripheral dopamine blocking effect.**

Domperidone is rapidly redistributed to all body tissues after both oral and parenteral administration, and is effectively metabolized by the liver. Fecal excretion of metabolites is the main route of elimination after the drug's biodegradation. Domperidone has thus been claimed to be an effective antiemetic[16] with a wide margin of safety.** Initial results comparing domperidone with metoclopramide, which does cross the blood–brain barrier, in patients undergoing elective cesarean section have shown no differences in fetal blood–gas values and Apgar scores (Brock-Utne *et al.*, unpublished observations). The drug has little effect on gastric acid secretion but does increase the rate of gastric emptying,** an obvious added advantage. Pharmacokinetic studies** have shown that the duration of antiemetic effect after intravenous injection of domperidone should last for at least two and possibly four hours. The drug's effect on the LES persisted for at least 60 min, but further studies may prove the duration of this action to be longer.

The intravenous injection of domperidone increases lower esophageal sphincter tone in both normal and pregnant patients without associated undesirable side effects. Domperidone's beneficial effect on the LES appears comparable to that of metoclopramide.[18] Thus, the drug may prove useful in preventing regurgitation of acidic gastric contents in patients having elective or emergency anesthesia.

References

1. Scott DB: Mendelson's syndrome (editorial). Br J Anaesth 50:977–978, 1978
2. Lind JF, Crispin JS, McIver DK, et al: The effect of atropine on the gastroesophageal sphincter. Can J Physiol Pharmacol 46:233–238, 1968
3. Hall AW, Moossa AR, Clark J, et al: The effects of premedication drugs on the lower esophageal high pressure zone and reflux status of rhesus monkeys and man. GUT 16:347–352, 1975
4. Bettarello A, Tuttle SG, Morton I: Effect of autonomic drugs on gastroesophageal reflux. Gastroenterology 30:340–345, 1960
5. Brock-Utne JG, Rubin J, Welman S, et al: The action of commonly used antiemetics on the lower oesophageal sphincter. Br J Anaesth 50:295–298, 1978
6. Dow TGB, Brock-Utne JG, Rubin J, et al: The effect of atropine on the lower esophageal sphincter in late pregnancy. Am J Obstet Gynecol 51:426–430, 1978
7. Stewardson RH, Nyhus LM: Pulmonary aspiration. Arch Surg 112:1192–1197, 1977
8. Culver GA, Makel HP, Beecher HK: Frequency of aspiration of gastric contents by lungs during anesthesia and surgery. Am Surg 133:289–292, 1951
9. Benson W, Adriani J: "Silent" regurgitation and aspiration during anesthesia. ANESTHESIOLOGY 15:644–649, 1954
10. Blitt CD, Gutman HL, Cohen DD, et al: Silent regurgitation and aspiration with general anesthesia. Anesth Analg (Cleve) 49:707–713, 1970
11. Weiss WA: Regurgitation aspiration of gastric contents during inhalation anesthesia. ANESTHESIOLOGY 11:102–109, 1950
12. Marchand P: The gastro-oesophageal "sphincter" and the mechanism of regurgitation. Br J Surg 42:504–513, 1955
13. Mann CB, Greenwood RK, Ellis FH: The esophagogastric junction. Surg Gynecol Obstet 118:853–862, 1964
14. Behar J: Reflux esophagitis: Pathogenesis, diagnosis and management. Arch Intern Med 136:560–566, 1976
15. Zegveld C, Knape H, Smits J, et al: Domperidone in the treatment of post-operative vomiting. A double-blind multicenter study. Anesth Analg (Cleve) 57:700–703, 1978
16. Fragen RJ, Caldwell N: A new benzimidazole antiemetic, Domperidone, for the treatment of post-operative nausea and vomiting. ANESTHESIOLOGY 49:289–290, 1978
17. Bremner CG, Kessler E, Bremner CH: The effect of intravenous domperidone on the resting oesophageal sphincter pressure in dogs and baboons (abstr). S Afr J Surg 16: 217–218, 1978
18. Brock-Utne JG, Dow TGB, Welman S, et al: The effect of metoclopramide on the lower oesophageal sphincter in late pregnancy. Anaesth Intensive Care 6:26–29, 1978
19. Lind JF, Smith AM, McIver DK, et al: Heartburn in pregnancy—a manometric study. Can Med Assoc J 98:571–574, 1975
20. Winans CS, Harris LD: Quantitation of lower esophageal sphincter competence. Gastroenterology 52:773–778, 1967
21. Ali Khan T, Shragge BW, Crispin JS, et al: Effect of aging in the motor function of esophagus and lower esophageal sphincter. *In* Proceedings of the 5th International Symposium on Gastrointestinal Motility. Edited by G. Vantrappen. Ebelstraat 136, B2410 Herentals, Belgium, Typoff Press, 1975, p 400
22. Rattan S, Goyal RK: Effect of dopamine on the esophageal smooth muscle *in vivo*. Gastroenterology 70:377–381, 1976
23. Laduron PM, Leysen JE: Domperidone, a specific *in vitro* dopamine antagonist, devoid of *in vivo* central dopaminergic activity. Biochem Pharmacol 28:2161–2165, 1979