Does ranitidine provide protection against acid gastroesophageal reflux?

Daisy Verbessem MD, Frederic Camu MD,
Anne Van de Velde MD

Continuous gastroesophageal pH monitoring was used to evaluate the effect of ranitidine on gastroesophageal reflux (GOR) in 60 patients scheduled for elective non-gastrointestinal abdominal or gynaecological surgery. The patients were randomly assigned to receive a single dose of ranitidine 50 mg either iv (RANIV group) or im (RANIM group) or a placebo iv (PLAC group) 90 min before surgery. The pH was measured continuously for six hours in the lower oesophagus using a flexible calibrated glass electrode. A pH < 4.0 was chosen as the boundary for defining occurrence of acid GOR. Both ranitidine treatments reduced the total number of acid reflux episodes and the global reflux index ($P < 0.05$). The duration of the acid reflux episodes (sum of refluxes) and the number of acid reflux episodes longer than five minutes were markedly decreased by ranitidine but the mean duration of the reflux episodes was unaffected. The pH values at induction, intubation, surgical incision and extubation were similar in the PLAC and RANIV groups but more acid than in the RANIM group. The mean pH of reflux episodes was less acid in both ranitidine groups than in the PLAC group ($P < 0.05$). Also the number of very acid refluxes (pH < 2.5) decreased with ranitidine ($P < 0.05$). Intramuscular and intravenous administration of ranitidine provide protection against gastroesophageal reflux, with shorter duration of reflux episodes occurring in the intramuscular group. Regardless of the administration of ranitidine, protection against gastroesophageal reflux is incomplete; the frequency of reflux episodes is reduced but not eliminated.

Key words

COMPLICATIONS: acid gastroesophageal reflux;
GASTROINTESTINAL TRACT: antacids, oesophagus, reflux;
HISTAMINE: ranitidine.

From the Department of Anaesthesiology, Flemish Free University of Brussels Medical Center, Laarbeeklaan 101, B-1090 Brussels, Belgium

Address correspondence to: Dr. F. Camu, Professor of Anaesthesiology, Department of Anaesthesiology, Flemish Free University of Brussels Medical Center, Laarbeeklaan 101, B-1090 Brussels, Belgium.

Accepted for publication 4th September, 1992.

Dans le but d'évaluer les effets de la ranitidine sur le reflux gastro-oesophagien (GOR), on utilise un monitoring continu du pH chez 60 patients programmés pour chirurgie gynécologique et non digestive. Les patients sont assignés au hasard à recevoir une seule dose de ranitidine 50 mg soit intraveineuse (groupe RANIV) soit intramusculaire (groupe RANIM) ou un placebo intraveineux (groupe PLAC) 90 min avant la chirurgie. Le pH est mesuré de façon continue pendant six heures dans l'oesophage inférieur à l'aide d'une électrode flexible de verre calibrée. Un pH < 4,0 est choisi comme la limite d'apparition d'un GOR acide. Les deux traitements à la ranitidine diminuent le nombre total d'épisodes de reflux acide et l'index de reflux global ($P < 0,05$). La durée des épisodes de reflux acide (somme des réflexes) et le nombre des épisodes de reflux acide de plus de cinq minutes sont considérablement diminués par la ranitidine mais la durée moyenne des épisodes n'est pas modifiée. Les valeurs du pH à l'induction, l'intubation, l'incision et l'extubation sont identiques dans le groupe PLAC et RANIV mais plus acides que dans le groupe RANIM. Le pH moyen des épisodes de reflux est moins acide dans les groupes ranitidine que dans le groupe PLAC ($P < 0,05$). De plus, le nombre des reflux très acides (pH < 2,5) diminue avec la ranitidine ($P < 0,05$). L'administration intramusculaire ou intraveineuse de ranitidine protège contre le reflux gastro-oesophagien et la durée des épisodes de reflux dans le groupe intramusculaire est moindre. Même après l'administration de ranitidine, la protection est incomplète; la présence des épisodes de reflux est réduite mais non éliminée.

Pulmonary aspiration of gastric contents remains a major risk of perioperative morbidity and mortality in anaesthesia.¹⁻³ The major aetiological factors in the development of aspiration pneumonitis involve acidity of the aspirate (pH < 2.5) combined with a regurgitation volume greater than 25 ml.⁴ These factors have been extrapolated from animal experiments and their validity for humans has been disputed.^{5,6} Silent gastro-pharyngeal regurgitation has been reported to occur in 5% of patients admitted for elective surgery. This incidence increased to 20% in patients admitted for emergency laparoscopy.⁷ Gastroesophageal sphincter competence prevents all oc-

currences of gastroesophageal acid reflux (GOR) from progressing to regurgitation. Indeed, the oesophagus can retain large volumes of fluid in the presence of an incompetent cardiac sphincter.⁸ The prevalence of troublesome GOR in adults is 5–8%.^{9,10} Vomiting occurs only rarely considering the incidence of GOR although 7 to 36% of the adult population have, at least occasionally, symptoms that can be related to GOR.¹¹

Ranitidine inhibits basal and nocturnal gastric acid secretion. It is four to nine times more potent than cimetidine with a longer duration of action and fewer side effects.^{12–16} These H₂-receptor antagonists are reported to increase gastric pH above 2.5 and decrease the volume of gastric aspirate.^{17–21} Whether they modify the incidence and characteristics of GOR has, surprisingly, not been studied in detail. This study aimed to assess the effects of a single dose of ranitidine, given preoperatively by either the *iv* or *im* route, on GOR compared with placebo, using oesophageal pH monitoring to quantitate the efficacy of treatment with this H₂-receptor blocker, in patients without clinical history of GOR.

Methods

The protocol was approved by the Committee of Medical Ethics of the University and oral informed consent was obtained from all patients on the evening before surgery. Sixty healthy patients aged 21 to 65 yr, ASA physical status I or II, were admitted to the study. All patients required general anaesthesia with tracheal intubation for elective non gastro-intestinal abdominal or gynaecological procedures. Excluded from the trial were patients weighing < 50 kg or > 90 kg, patients with a history of hiatus hernia, dyspepsia, peptic ulcer or gastro-intestinal diseases.

The patients were fasted for at least eight hours before starting the study and were brought unpremedicated to a waiting area next to the surgical theatre. Under *iv* sedation with lorazepam, 3 mg, or midazolam, 7.5 mg, and after local anaesthesia of the nose, a pH electrode was introduced via the nose into the stomach. Gastric pH was measured and then the electrode was gently withdrawn to the gastroesophageal junction identified by a rapid pH change. The electrode was further withdrawn 3 cm and taped to the skin. The patients were randomly allocated to each treatment according to a table of random numbers. Twenty patients each received 50 mg ranitidine either *iv* (RANIV) or *im* (RANIM), or a similar volume of saline *iv* (placebo group, PLAC). Vital signs and side effects were noted every 15 min for 90 min at which time the patients were transferred to the operating room.

Anaesthesia was induced with fentanyl 50–100 µg and thiopentone 4–6 mg · kg⁻¹ *iv*. Tracheal intubation was per-

FIGURE Examples of GOR using continuous lower oesophageal pH monitoring. The broken line (pH = 4) represents the boundary level for quantification of GOR. pH units as ordinate, time as abscissa.

formed after a bolus of succinylcholine 1 mg · kg⁻¹. For maintenance of anaesthesia enflurane was administered in a mixture of nitrous oxide and oxygen (70:30) with incremental doses of fentanyl and pancuronium bromide as required by surgical needs. At the end of surgery, the patients were allowed to regain spontaneous breathing, reflexes and consciousness, and following extubation of the trachea were transferred to the postanaesthesia care unit where they remained in semi-recumbent position for six hours after the ranitidine or placebo administration.

For pH measurements we used a GK 2801C flexible glass electrode (Radiometer, Copenhagen) with a maximum outer body diameter of 4.5 mm, a pH range between 0 to 12 and a temperature range between 0 and 60° C. Its response time (98%) varied from 5 to 15 sec at 37° C. The noise level was 0.03 pH units. Calibration of the electrode using two buffer solutions (pH = 1.0 and pH = 7.0) was performed before and after each study. A Memolog 600 system collected the registered pH values measured every 7.5 sec into memory. At the end of the test, the data were read by computer with graphical representation of the pH curve obtained (Figure). A pH of 4.0 was chosen as the boundary level because it is unequivocally different from the usual oesophageal pH which is close to 7. A pH < 4 for 30 sec was assumed to indicate GOR. The variables calculated included the mean ambient pH in the lower oesophagus, the percentage of investigation time with pH < 4 (reflux index),

TABLE I Demographic and surgical data

	PLAC	RANIM	RANIV
<i>n</i>	18	20	20
Sex M/F	2/16	2/18	2/18
Age (yr)	34.6 ± 1.3	33.8 ± 1.7	36.8 ± 2.1
Weight (kg)	62.8 ± 2.0	63.8 ± 2.5	65.0 ± 2.2
Height (cm)	165 ± 2	162 ± 2	164 ± 1
Asa I	16	18	18
II	2	2	2
Duration of surgery (min)	55 ± 4	86 ± 10*	77 ± 9*
Anaesthetic agents (vol %)	0.82 ± 0.04	0.89 ± 0.03	0.80 ± 0.03
Fentanyl amount (µg)	167 ± 11	213 ± 27	185 ± 14
<i>Type of surgery</i>			
Laparoscopic salpingolysis	15	14	14
Inguinal hernia	2	2	2
Retroperitoneal abscess	1	—	—
Abdominal hysterectomy	—	4	3
Cholecystectomy	—	—	1

(mean data ± SEM; * $P < 0.05$ vs placebo).

the total duration of episodes with pH < 4 (sum of refluxes, min), the average oesophageal acid clearing time (duration of reflux episodes, min), the number of episodes with pH < 4, the number of episodes of more than five minutes with pH < 4 and the incidence of very acid GOR with pH < 2.5.

Statistical evaluation included Kruskal-Wallis analysis of variance for comparison of data. Differences among treatment groups with respect to drug efficacy were analyzed by Mann-Whitney's U test. Tables of frequencies classified according to two factors were analyzed using chi-square statistic or the G test to assess the hypothesis of independency between factors. $P < 0.05$ was accepted as the limit of significance for rejection of the null hypothesis.

Results

Two patients from the placebo group were excluded from the analysis of data because of pregnancy. The three groups of patients were similar with respect to distribution of age, weight, height and sex ratio (Table I). Also no differences were found among groups in the type of surgery, nor in the amounts of anaesthetic agents or opiates administered. The duration of surgery was longer in both ranitidine groups than with placebo. Starting from similar initial pH values before drug administration, the pH values at selected anaesthetic events (induction, intubation, incision) were not different in the PLAC and RANIV groups but were higher in the RANIM group (Table II). Both ranitidine treatments reduced the number of total acid reflux episodes and the reflux index (Table III) but there were no important differences among

TABLE II Lower oesophageal pH values at selected anaesthetic events

Group	PLAC	RANIM	RANIV
Baseline	6.28 ± 0.13 (5.20–7.37)	6.37 ± 0.13 (5.31–7.48)	6.24 ± 0.10 (5.12–6.90)
Induction	5.73 ± 0.26 (2.96–7.25)	6.35 ± 0.10* (5.50–7.29)	6.10 ± 0.27 (1.42–7.38)
Intubation	5.56 ± 0.32 (1.05–6.82)	6.26 ± 0.11* (5.44–7.07)	5.98 ± 0.29 (1.33–7.36)
Incision	5.88 ± 0.19 (4.30–7.25)	6.25 ± 0.15* (5.47–7.58)	5.86 ± 0.29 (1.49–7.51)
Extubation	4.29 ± 0.46 (1.06–7.23)	6.62 ± 0.15* (5.00–7.75)	5.93 ± 0.34* (1.82–7.51)

The mean values represent the average of a single pH measure made at the specific event in each individual for each group. Mean values ± SEM with range in parenthesis. * $P < 0.05$ vs placebo)

groups for the first 90 min of the investigation (i.e., the time between drug administration and anaesthesia induction). The total duration of the reflux episodes with pH < 4 (sum of refluxes) was shorter in both ranitidine than in the placebo treatment groups ($P < 0.05$) although the mean duration of these reflux episodes was similar in all groups. The number of patients with acid reflux episodes longer than five minutes was reduced by ranitidine ($P < 0.05$). During reflux episodes the mean pH value remained higher in both ranitidine groups ($P < 0.05$). The mean values for the ambient pH in the lower oesophagus during the six hours observation period were higher in both ranitidine groups than in placebo.

Also the number of very acid refluxes (pH < 2.5) was reduced by ranitidine ($P < 0.05$) as shown in Table IV. Fewer patients showed episodes of very acid GOR before and during anaesthesia in each ranitidine treatment group in comparison with placebo, but the incidence of such episodes in all these patients was similar. Pairwise comparisons between treatment groups revealed no differences between the effects of the *im* and *iv* administration of ranitidine.

Discussion

In the present study, the placebo patients showed a high incidence of acid GOR, 58% of these had a pH < 2.5 and 37% lasted longer than five minutes. The considerable reduction of these very acid refluxes during the 90 min preceding anaesthesia in the ranitidine treated patients suggests a rapid onset of effect of ranitidine on gastric pH. Ranitidine seemed more potent following the *im* route as the differences in effect with regard to the placebo group were more pronounced than in the *iv* group. However, the total number of acid reflux episodes during the six hour investigation was similar in

TABLE III Gastroesophageal reflux data

Group	PLAC	RANIM	RANIV
Number of reflux episodes (pH < 4)			
- Before anaesthesia	25	9	6
- During anaesthesia	28	4	5
- After anaesthesia	23	2	7
- Total	76	15*	18*
Reflux index (%)			
- 0-90 min	8.0 ± 3.4	3.1 ± 1.5	2.2 ± 1.3
- 90 min-6h	9.9 ± 4.2	0.8 ± 0.5§	4.3 ± 2.1
Sum of refluxes (min)	36.1 ± 14.0	5.3 ± 2.6§	13.8 ± 6.5*
Duration of episodes (min)	8.7 ± 1.7 (0.5-74)	4.8 ± 1.1 (0.5-15)	8.9 ± 3.5 (0.5-59)
Refluxes episodes ≥ 5 min (n)	28	7*	7*
Mean pH of reflux episodes	1.69 ± 0.12 (0.50-3.94)	2.41 ± 0.20§ (1.49-3.91)	2.18 ± 0.21* (1.13-3.93)
Mean ambient pH over 6h	5.68 ± 0.23 (2.82-7.53)	6.31 ± 0.12* (5.45-7.52)	6.10 ± 0.12* (4.92-7.15)
Patients without GOR	4	14†	12†

(Mean ± SEM, range in parentheses * $P < 0.05$ vs placebo. † $P < 0.01$ vs placebo).

TABLE IV Incidence of very acid GOR (pH < 2.5)

	PLAC	RANIM	RANIV	P
Before anaesthesia	9 (1-4)	3 (1-3)	2 (1)	<0.01
During anaesthesia	10 (1-3)	1 (1)	4 (1-3)	<0.01
After anaesthesia	4 (4-7)	0 (0)	4 (1-2)	NS
Total incidence of very acid GOR (n)	44	9	14	<0.05

(Data represent the number of patients with their range of episodes in parenthesis, P indicates probability of differences vs placebo)

both ranitidine groups, but the number of acid reflux events after 90 min was reduced by half in the *im* group. Similarly the mean pH values during these episodes remained somewhat higher than in the *iv* group. The sum of refluxes was the lowest in the *im* group. Oesophageal acid clearing was more efficient in this group as the duration of the reflux episodes decreased while the total number of long lasting reflux events (> five minutes) was similar to the *iv* group.

Some GOR is physiological in normal healthy persons. These episodes are asymptomatic and characterized by their short duration with rapid elimination of refluxed gastric acid fluid from the oesophagus.²² It is also commonly agreed that the barrier pressure (difference between gastric and lower oesophageal sphincter pressures) is the

main determinant for creating gastric reflux.²³ Although the gastroesophageal junction is more competent in the supine than in upright position and sleep does not affect this competence, many anaesthetic agents may influence its barrier function. The incidence of GOR in non-emergency asymptomatic surgical patients is usually overlooked and largely unknown. Pharyngeal regurgitation of acidic contents was not evaluated in this study, but our data indicate that a substantial number of healthy surgical patients may present a considerable oesophageal acid exposure during anaesthesia requiring prolonged periods to clear the oesophagus of gastric fluid. "Silent" regurgitation of gastric contents has been shown to occur in 5 to 20% of patients with incidences up to 30% during upper abdominal procedures.^{7,24,25} Factors which may elicit GOR included the type of surgery and hormonal concentrations of progesterone and oestrogens.²³ But no relationships existed between GOR and age, sex, alcohol use,⁶ nor type of inhalation anaesthetic agent²⁵ or muscle relaxant,⁷ nor position with the exception of the prone position. There is no evidence that GOR occurs during laparoscopy.²⁵ Hardy *et al.*⁶ suggested recently that the risk of GOR on induction of anaesthesia was negligible despite gastric fluid volumes of 30 ml. However, Martin *et al.*²⁷ found a five percent incidence of acid reflux into the oesophagus during anaesthesia in patients without clinical history of GOR. The discrepancy between these studies is probably related to differences in methodology, but they cast some doubt on the validity of using a gastric

fluid volume of 25 ml as a critical factor for the development of regurgitation pneumonia.

Many clinical studies have demonstrated the beneficial effect of H_2 -receptor antagonists on gastric pH and fluid volume.¹³⁻²¹ The results of this investigation confirm previous findings of reduced gastric acidity following ranitidine at times of tracheal intubation and extubation¹⁸⁻²⁰ but, as Durrant *et al.*¹⁷ reported, there remain an important number of very acid GOR episodes (pH < 2.5) despite ranitidine pretreatment. Based on the known pharmacokinetic behaviour of the drug,^{28,29} it was estimated that a single dose of ranitidine 50 mg would be sufficient to reach and maintain the plasma concentration near the inhibitory concentration (IC₅₀) for acid secretion of 200 ng · ml⁻¹ for several hours.³⁰ The differences observed in pharmacodynamic effect of ranitidine following *iv* and *im* administration could possibly be explained by a longer maintenance of ranitidine plasma concentration within a therapeutic window following the *im* route.

Does ranitidine influence the mechanical aspects of GOR or is the observed reduction of GOR the consequence of its neutralizing effect on gastric secretion only? Gastroesophageal pH monitoring alone does not allow this question to be answered. However, Kravitz *et al.* showed that, in humans, histamine exerts a biphasic effect on the lower oesophageal sphincter mediated only by the H_2 -receptor with weak excitation at low doses and reversal of this effect at moderate doses.³¹ Despite being a specific H_2 -receptor antagonist, ranitidine does not affect oesophageal motility.³² When given before atropine, ranitidine was reported to produce a net increase in lower oesophageal sphincter pressure³³ although this has been disclaimed by others.³² Therefore, we do not know at present whether ranitidine influences the real incidence of reflux itself. Possibly a reduction of the gastric residual fluid volume may also influence the incidence of GOR.¹⁷⁻²¹

In conclusion, fewer episodes of acid gastroesophageal reflux were observed following a single parenteral administration of ranitidine. The pH of such episodes was less acid than in placebo treated patients. Both factors reduced the total time of oesophageal exposure to gastric acid. However, protection against GOR was not complete; a considerable number of very acid refluxes occurred in patients in both ranitidine groups.

References

- Mendelson CL. Aspiration of stomach contents into the lungs during obstetric anesthesia. *Am J Obstet Gynecol* 1946; 53: 191-205.
- Kaunitz AM, Hughes JM, Grimes DA, Smith JC, Rochat RW, Kafrissen ME. Causes of maternal mortality in the United States. *Obstet Gynecol* 1985; 65: 605-12.
- Olsson GL, Hallen B, Hambræus-Jonzon K. Aspiration during anaesthesia: a computer-aided study of 185,358 anaesthetics. *Acta Anaesthesiol Scand* 1986; 30: 84-92.
- James CF, Modell JH, Gibbs CP, Kuck EJ, Ruiz BC. Pulmonary aspiration-effects of volume and pH in the rat. *Anesth Analg* 1984; 63: 665-8.
- Hardy JF. Large volume gastroesophageal reflux: a rationale for risk reduction in the perioperative period. *Can J Anaesth* 1988; 35: 162-73.
- Hardy JF, Lepage Y, Bonneville-Chouinard N. Occurrence of gastroesophageal reflux on induction of anaesthesia does not correlate with the volume of gastric contents. *Can J Anaesth* 1990; 37: 502-8.
- Carlsson C, Islander G. Silent gastropharyngeal regurgitation during anesthesia. *Anesth Analg* 1981; 60: 665-7.
- O'Mullane EJ. Vomiting and regurgitation during anaesthesia. *Lancet* 1954; 1: 1209-12.
- Heading RC. Epidemiology of oesophageal reflux disease. *Scand J Gastroenterol* 1989; 24: 33-7 (suppl. 168).
- Wienbeck M, Barnert J. Epidemiology of reflux disease and reflux esophagitis. *Scand J Gastroenterol* 1989; 24: 7-13 (suppl. 156).
- Nebel OT, Fornes MF, Castell DO. Symptomatic gastroesophageal reflux: incidence and precipitating factors. *Dig Dis* 1976; 21: 953-6.
- Daly MJ, Humphray JM, Stables R. Inhibition of gastric acid secretion in the dog by the H_2 -receptor antagonists, ranitidine, cimetidine, and metiamide. *Gut* 1980; 21: 408-12.
- Desechalliers JP, Galmiche JP, Touchais JY, Denis P, Colin R. Ranitidine, cimetidine, antacids and gastro-esophageal reflux: results of a 20-hour oesophageal pH study. *Int J Clin Pharmacol Res* 1984; 4: 217-22.
- Domschke W, Lux G, Domschke S. Furan H_2 -antagonist ranitidine inhibits pentagastrin-stimulated gastric secretion stronger than cimetidine. *Gastroenterology* 1980; 79: 1267-71.
- Dammann HG, Muller P, Simon R. Parenteral ranitidine: onset and duration of action. *Br J Anaesth* 1982; 54: 1235-6.
- Williams JG. H_2 -receptor antagonists and anaesthesia. *Can Anaesth Soc J* 1983; 30: 264-9.
- Durrant JM, Strunin L. Comparative trial of the effect of ranitidine and cimetidine on gastric secretion in fasting patients at induction of anesthesia. *Can Anaesth Soc J* 1982; 29: 446-51.
- Morison DH, Dunn GL, Fargas-Babjak AM, Moudgil GC, Smedstad K, Woo J. A double-blind comparison of cimetidine and ranitidine as prophylaxis against gastric aspiration syndrome. *Anesth Analg* 1982; 61: 988-92.
- Maile CJD, Francis RN. Preoperative ranitidine. Effect of a single intravenous dose on pH and volume of gastric aspirate. *Anaesthesia* 1983; 38: 324-6.

- 20 *Manchikanti L, Colliver JA, Grow JB, Demeyer RG, Hadley CH, Roush JR.* Dose-response effects of intravenous ranitidine on gastric pH and volume in outpatients. *Anesthesiology* 1986; 65: 180–5.
- 21 *Williams JG, Strunin L.* Preoperative intramuscular ranitidine and cimetidine. Double-blind comparative trial, effect on gastric pH and volume. *Anaesthesia* 1985; 40: 242–5.
- 22 *Demeester TR, Johnson LF, Joseph GJ, Toscano MS, Hall AW, Skinner DB.* Patterns of gastroesophageal reflux in health and disease. *Ann Surg* 1976; 184: 459–70.
- 23 *Cotton BR, Smith G.* The lower oesophageal sphincter and anaesthesia. *Br J Anaesth* 1984; 56: 37–46.
- 24 *Turndorf H, Rodis ID, Clark TS.* “Silent” regurgitation during general anesthesia. *Anesth Analg* 1974; 53: 700–3.
- 25 *Blitt CD, Gutman HL, Cohen DD, Weisman H, Dillon JB.* “Silent” regurgitation and aspiration during general anesthesia. *Anesth Analg* 1970; 49: 707–13.
- 26 *Roberts CJ, Goodman NW.* Gastroesophageal reflux during elective laparoscopy. *Anaesthesia* 1990; 45: 1009–11.
- 27 *Martin C, Auffray J, Ragni J, Guillen J, Auge A, Lambert D, Gouin F.* Measurement of lower oesophageal pH during induction of anaesthesia: use of oesophageal probe. *Acta Anaesthesiol Scand* 1992; 36: 226–9.
- 28 *McNeil JJ, Mihaly GW, Anderson A, Marshall AN, Smallwood RA, Louis WJ.* Pharmacokinetics of the H₂-receptor antagonist ranitidine in man. *Br J Clin Pharmacol* 1981; 12: 411–5.
- 29 *Chau NP, Zech PY, Pozet N, Hadj-Aissa A.* Ranitidine kinetics in normal subjects. *Clin Pharmacol Ther* 1982; 31: 97–101.
- 30 *Brogden RN, Carmine AA, Heel RC, Speight TM, Avery GS.* Ranitidine: a review of its pharmacology and therapeutic use in peptic ulcer disease and other allied diseases. *Drugs* 1982; 24: 267–303.
- 31 *Kravitz JJ, Snape WJ, Cohen S.* Effect of histamine and histamine antagonists on human lower esophageal sphincter function. *Gastroenterology* 1978; 74: 435–40.
- 32 *Denis P, Galmiche JP, Ducrotte P, Colin R, Pasquis P, Lefrançois R.* Effect of ranitidine on resting pressure and pentagastrin response of human lower esophageal sphincter. *Dig Dis* 1981; 26: 999–1002.
- 33 *Brock-Utne JG, Downing JW, Humphrey D.* Effect of ranitidine given before atropine sulphate on lower oesophageal sphincter tone. *Anaesth Intensive Care* 1984; 12: 140–2.