Regular use of H_2 blockers reduces the efficacy of roxatidine to control gastric pH and volume

[L'usage régulier des H_2bloquants réduit l'efficacité de la roxatidine à contrôler le pH et le volume gastriques]

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Purpose: H_2 antagonist premedication is common in surgical patients to control gastric pH and volume. However, several reports suggest that long-term medication may produce tolerance. Therefore, we studied the efficacy of a preanesthetic H_2 antagonist (oral roxatidine) in patients on regular H_2 antagonist therapy.

Methods: Forty-eight patients undergoing elective surgery were studied and grouped according to medication: those on no medication (control group) and those receiving H_2-antagonists for less than two weeks (≤ 2 w group), between two and four weeks (2–4 w group) and for longer than four weeks (≥ 4 w group; $n = 12$ each). All patients were given oral roxatidine as anesthetic premedication. Gastric volume and pH were measured after induction of anesthesia. Arterial blood was simultaneously collected for measurement of plasma gastrin levels using an enzyme-linked immunosorbent assay

Results: We observed a significant decrease and increase in, respectively, gastric pH and volume (mL) in the ≤ 2 w group [6.50 ± 0.43 (NS) and 11.6 ± 10.3 (NS)], 2–4 w group [4.77 ± 2.11 ($P < 0.01$) and 14.1 ± 10.8 ($P < 0.05$)], ≥ 4 w group [2.32 ± 1.46 ($P < 0.01$) and 22.2 ± 14.2 ($P < 0.01$)] compared to patients in the control group (6.35 ± 1.32 and 4.9 ± 4.7). Plasma gastrin levels were decreased with increasing time on medication with a significant difference (46%) observed after two weeks' treatment. In addition, there was a significant correlation between gastric pH and plasma gastrin levels ($r = 0.43$, $P < 0.01$).

Conclusion: These data suggest that regular H_2 antagonist treatment for longer than two weeks may produce tolerance to preanesthetic H_2 antagonist administration.

Objectif : *La prémédication avec un antagoniste H_2 est fréquente en chirurgie pour contrôler le pH et le volume gastriques. Mais certains articles montrent que la médication à long terme peut entraîner une tolérance. Nous avons donc vérifié l'efficacité d'un antagoniste H_2 préanesthésique (roxatidine orale) chez des patients qui reçoivent un traitement régulier avec un antagoniste H_2 .*

Méthode : *Des patients de chirurgie réglée (48) ont été regroupés selon la médication : sans médication (groupe témoin), puis ceux qui reçoivent des antagonistes H_2 pour moins de deux semaines (groupe ≤ 2 w), pour deux à quatre semaines (groupe 2-4 w) et pour plus de quatre semaines (groupe ≥ 4 w ; n = 12 chacun). Tous ont reçu de la roxatidine orale comme prémédication anesthésique. Le volume et le pH gastriques ont été mesurés après l'induction de l'anesthésie. Du sang artériel a été prélevé simultanément pour la mesure de la concentration plasmatique de gastrine par dosage immuno-enzymatique.*

Résultats : *Nous avons observé une baisse du pH et une hausse du volume gastriques (mL) significatives chez les patients des groupes ≤ 2 w [6,50 ± 0,43 (NS) et 11,6 ± 10,3 (NS)], 2–4 w [4,77 ± 2,11 ($P < 0,01$) et 14,1 ± 10,8 ($P < 0,05$)], ≥ 4 w [2,32 ± 1,46 ($P < 0,01$) et 22,2 ± 14,2 ($P < 0,01$)] comparés aux patients témoins (6,35 ± 1,32 et 4,9 ± 4,7). Les concentrations plasmatiques de gastrine ont diminué avec le temps de médication et une différence significative (46 %) a été observée après un traitement de deux semaines. De plus, il y avait une corrélation significative entre le pH gastrique et les concentrations plasmatiques de gastrine ($r = 0,43$, $P < 0,01$).*

Conclusion : *Ces données suggèrent qu'un traitement régulier avec un antagoniste H_2 pendant plus de deux semaines puisse produire une tolérance à l'administration préanesthésique d'antagoniste H_2.*

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AS described in our recent editorial,[1] it has been suggested that long-term H_2 antagonist medication produces a reduction in antisecretory efficacy or tolerance. In particular, *iv*, frequent and/or high dose oral administration rapidly produces tolerance. However, in the anesthetic setting there are no reports of preanesthetic H_2 antagonist efficacy in patients receiving regular H_2 antagonist medication. Thus, in the present study, we examined the effects of preanesthetic H_2 antagonists on both gastric fluid acidity and volume in patients receiving regular H_2 antagonist medication. In addition, we attempted to determine the time frame over which tolerance develops. While the mechanisms of tolerance remain to be determined, previous reports[2,3] suggest that, as gastrin stimulates enterochromaffin-like (ECL) cells to secrete histamine, and thereby increase acid production, H_2 antagonist-induced hypergastrinemia may be involved. We also measured plasma gastrin and attempted to correlate this with the pH of gastric contents.

Methods

With University Ethical Committee approval and informed consent, 48 adult surgical patients without (control group, n = 12) and with regular oral H_2 antagonist medication (H_2 antagonist medication group, n = 36) were studied. The medication group patients were subgrouped to three groups by duration of H_2 antagonist medication: less than two weeks medication ($\leq$ 2 w group: n = 12), between two and four weeks medication (2–4 w group: n = 12) and more than four weeks medication ($\geq$ 4 w group: n = 12). Patients scheduled for gastrointestinal tract surgery were excluded from this study.

All patients were premedicated orally with triazolam 0.25 mg and roxatidine 75 mg at 21:00 the night before surgery and with diazepam 10 mg and roxatidine 75 mg 90 min before induction of anesthesia as only roxatidine has been approved as an oral preanesthetic H_2 antagonist by our Ministry of Health, Labour and Welfare in Japan. All patients were hospitalized at least the night before surgery and were fasted from the first anesthetic premedication.

Anesthesia was induced with propofol 1.0 to 1.5 $mg \cdot kg^{-1}$, ketamine 0.5 $mg \cdot kg^{-1}$ and fentanyl 2 $\mu g \cdot kg^{-1}$, and maintained with propofol 5 to 8 $mg \cdot kg^{-1} \cdot hr^{-1}$, ketamine 0 to 0.5 $mg \cdot kg^{-1} \cdot hr^{-1}$ and fentanyl 4 to 8 $\mu g \cdot kg^{-1}$. The trachea was intubated after muscle relaxation was induced by succinylcholine 0.8 $mg \cdot kg^{-1}$ *iv*. Muscle relaxation was maintained with an *iv* bolus of vecuronium 0.08 $mg \cdot kg^{-1}$ and then a further 1 mg given *iv* every 30 min. Following induction of anesthesia (tracheal intubation) a gastric tube (Argyle® Salem Sump Tube, Japan Sherwood, Tokyo, Japan) was inserted into the stomach and its position was verified by auscultation of the epigastrium during insufflation of air.

Gastric fluid was obtained by aspiration with a 10-mL or 50-mL syringe under changing patient positions (supine, Trendelenburg and reverse Trendelenburg position, and right and left 20° semilateral position) and with insufflation of 50-mL of air plus upper-abdominal massage. The volume of gastric fluid was measured using the scale of a 10-mL or 50-mL syringe. Gastric pH was determined using a pH metre, with 0.01 pH unit precision over the entire pH range (Ecoscan pH5 pH6, Iuchi Seieido Co, Ltd., Osaka, Japan) that was calibrated each morning.

Arterial blood was simultaneously collected and centrifuged at 3000 rpm for ten minutes at -10°C in order to separate the plasma, which was kept frozen at -70°C until assay. Plasma gastrin levels were analyzed using a commercially available enzyme-linked immunosorbent assay (Peninsula Laboratories Inc., San Carlos, CA, USA) with a minimum sensitivity, inter and intra assay coefficient of variation of 7.27 $pg \cdot mL^{-1}$, 6.5% and 3.7% respectively.

Where appropriate data are expressed as mean ± SD. Statistical analysis was performed by one way ANOVA followed by a Student-Neuman-Keuls test, paired t test or Chi-square test as appropriate with $P < 0.05$ considered significant. The correlation between gastric pH and plasma gastrin levels was assessed by Pearson's correlation coefficient, and a least squares linear regression line was fitted using GraphPad Prism V3 (GraphPad Software Inc., CA, USA).

Results

Two of 48 patients (1 each in $\leq$ 2 w and 2–4 w groups) were excluded from the study, as the aspirated gastric contents were green, suggesting the presence of bile. Thus, data from the remaining 46 patients were included for analysis. There were no differences between these three groups for sex, age, height and weight. Except for the control group 79%, 12% and 9% of patients were receiving famotidine, cimetidine and roxatidine, respectively. These data are summarized in Table I.

There was a decrease in gastric pH such that a significant reduction was observed after two to four weeks and greater or equal to four weeks treatment. In addition there was a significant increase in the number of patients with a pH < 2.5 such that in the greater or equal to four weeks group the proportion amounted to approximately 67%, Table II.

TABLE I Patient demographics

		Duration of H_2 antagonist therapy		
	Control (n = 12)	*≤ 2 w (n = 11)*	*2-4 w (n = 11)*	*≥ 4 w (n = 12)*
Sex (M/F)	8/4	6/5	6/5	5/7
Age (yr)	60.8 ± 11.0	65.2 ± 11.6	62.9 ± 12.2	56.3 ± 15.2
Height (cm)	158.1 ± 10.0	154.7 ± 8.6	156.0 ± 7.6	158.9 ± 10.7
Weight (kg)	56.1 ± 10.7	56.2 ± 9.6	57.6 ± 10.9	56.3 ± 9.7
H_2 antagonist				
Famotidine	0	8	8	11
Cimetidine	0	3	1	0
Roxatidine	0	0	2	1

Data are either incidence in numbers or mean ± SD as appropriate. Daily dose of H_2 antagonists before surgery. Famotidine = 40 mg; Cimetidine = 400 mg; Roxatidine =150 mg.

TABLE II Number of patients with pH < 2.5 and volume > 25 mL and hypergastrinemia

		Duration of H_2 antagonist therapy		
	Control	*≤ 2 w*	*2-4 w*	*≥ 4 w*
Gastric pH < 2.5[+]	0/12	0/11	1/11	8/12
Gastric volume > 25 mL	0/12	1/11	2/11	5/12
Plasma gastrin > 200 pg·mL^{-1}	9/12	9/11	4/11	4/12

Number/total, [+]$P < 0.01$ significant increase in number with pH < 2.5, gastric volume > 25 mL and plasma gastrin level > 200 pg·mL^{-1} (normal range).

There was a significant increase in the volume of gastric contents. With treatment greater or equal to four weeks, there were five patients who had gastric volumes in excess of 25 mL (Table II). Plasma gastrin levels decreased with increasing time on medication with a significant difference (46%) observed after two to four weeks medication (Table II). In addition, there was a significant correlation between gastric pH and plasma gastrin levels (Figure 2, r = 0.43, $P < 0.01$).

No patient with a high gastric volume (> 25 mL) and low gastric pH (< 2.5) presented acid aspiration pneumonia.

Discussion

In the present study, gastric pH and volume in patients receiving H_2-antagonists regularly for two to four weeks and ≥ four weeks were significantly lower and higher, respectively, than those in the control group. In addition a large proportion of patients treated for longer periods had a gastric pH of < 2.5.

Haavik and colleagues[4] reported in 246 patients that the mean gastric pH and volume without preanesthetic H_2 antagonist use was 2.2 ± 1.2 and 20 ± 18 mL, respectively. In addition, the proportion of patients with more than 25 mL of gastric fluid and a pH of less than 2.5 was 26%. These data are similar to those (gastric pH = 2.32 ± 1.46, volume = 22.2 ± 14.2 mL, and % of gastric pH > 2.5 and volume > 25 mL = 33%) in ≥ 4 w group. Therefore, preanesthetic roxatidine no longer prevents acidic gastric contents in those patients receiving this antagonist for ≥ four weeks. Moreover, our data also suggest that tolerance may be fully established as early as one month after starting regular medication.

Several clinical investigations[2,3,5,6] indicate that repeated oral and *iv* administration of H_2 antagonists leads to the development of tolerance. This is especially true for *iv*, frequent and high dose oral administration. Netzer *et al.*[5] reported that repeated *iv* injection or continuous infusion of ranitidine (100 mg every six hours and 50 mg bolus *iv* + 0.25 mg·kg^{-1}·hr^{-1}, respectively) produced a rapid diminution of anti-acid effects within only three days. Gastric pH on day two and three, in more than 95% volunteers, was less than 4. In addition, high dose oral ranitidine (600 mg·day^{-1}) has also been reported to produce a rapid "fade-out" of acid inhibition within one week.[3,6] However, the data reported by Nwokolo *et al.*[2] suggest that conventional doses of H_2 antagonists (cimetidine, nizatidine, famotidine and ranitidine) may produce tolerance by 29 days although tolerance develops slowly. Similarly, the present study suggests that less than two weeks' medication with a conventional dose of H_2 antagonists does not produce tolerance but longer than two weeks medication may.

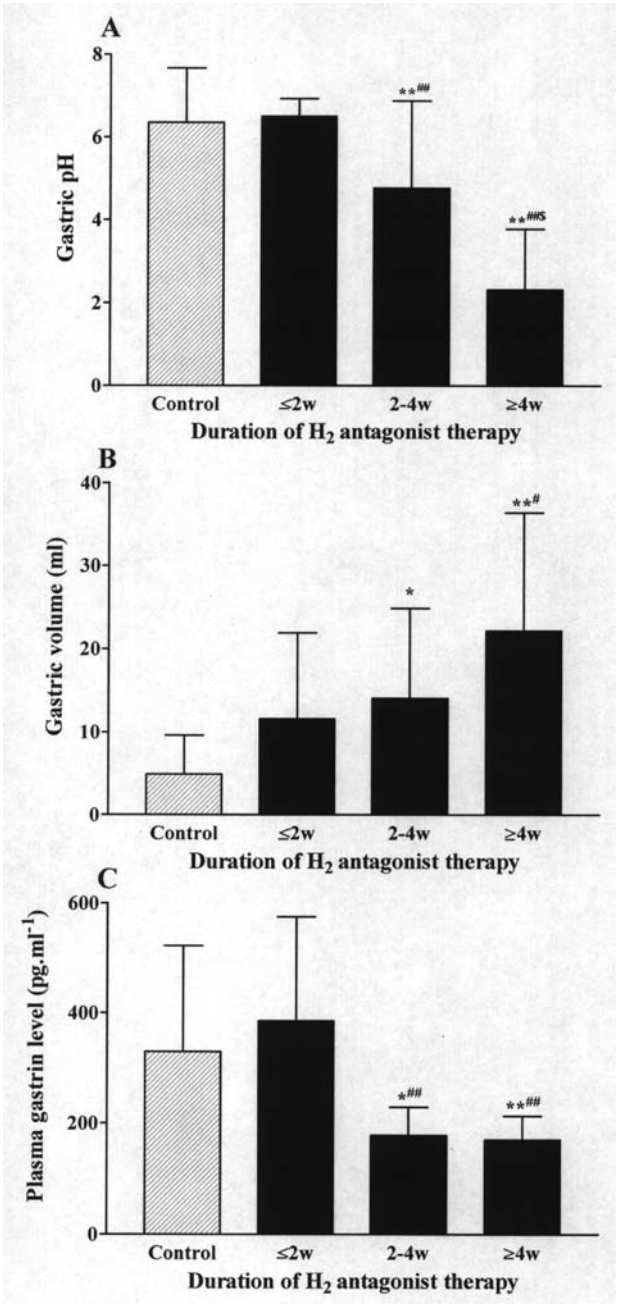

FIGURE 1 Effect of duration of H_2 antagonist medication on gastric pH (A), gastric fluid volume (B) and plasma gastrin level (C). Mean ± SD. *$P < 0.05$, **$P < 0.01$ *vs* control, #$P < 0.05$, ##$P < 0.01$ *vs* ≤ 2 w, \$$P < 0.01$ *vs* 2-4 w.

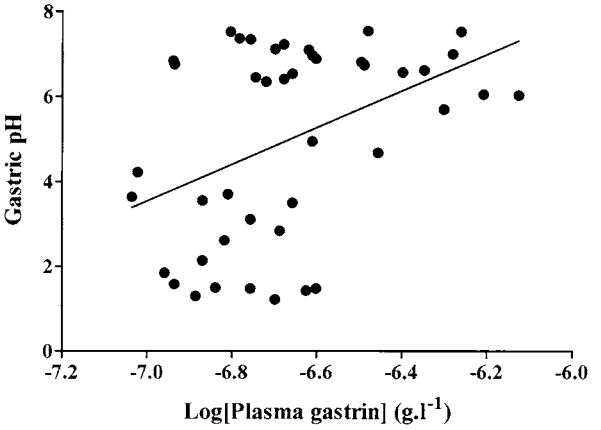

FIGURE 2 Correlation between plasma gastrin levels and pH of gastric fluid (r = 0.43; $P < 0.01$).

In the present study correlation between gastric pH and plasma gastrin was significant but weak (Figure 2: $P < 0.01$, r = 0.43). Gastric acid secretion is regulated by both neural (vagal) and endocrine reflexes (Figure 3). The endocrine systems of the antrum and corpus of the stomach contribute to control gastric acid secretion in different ways.[7] In the antrum, gastrin released from G-cells in response to the presence of luminal protein and amino acid stimulates ECL cells by activating cholecystokinin receptor subtype 2 to secrete histamine. Then, histamine stimulates parietal cells by excitation of H_2 receptors to increase acid secretion. In contrast, somatostatin, released from antral D-cells that respond to a luminal pH below 3.5, suppresses G-cell function.[7] Thus, these complete a negative feedback loop regulating acid secretion. Recently, pituitary adenylate cyclase-activating peptide has also been considered to regulate gastric acid secretion.[8] Therefore, the various mechanisms involved explain why the correlation between gastric pH and plasma gastrin is weak (but significant).

Several reports[2,3] suggest that prolonged hypergastrinemia caused by H_2 antagonists induces tolerance. Gastrin induces ECL cell hyperactivity to hyperplasia (an increase in histamine release).[9] Thus, tolerance may be due to upregulation of histamine synthesis by hypergastrinemia, which competes with the H_2 antagonist. This implies that hypergastrinemia would be a likely finding in tolerant patients with low gastric pH, as upregulation of histamine synthesis should be maintained by high gastrin levels. However, there is no evidence that long-term maintenance therapy with H_2 antagonists causes clinically significant hypergastrinemia.[10] Indeed, in the present study, plasma gastrin levels in patients with low gastric pH (i.e., tolerance) were close to the normal range (37–172 pg·mL^{-1}:

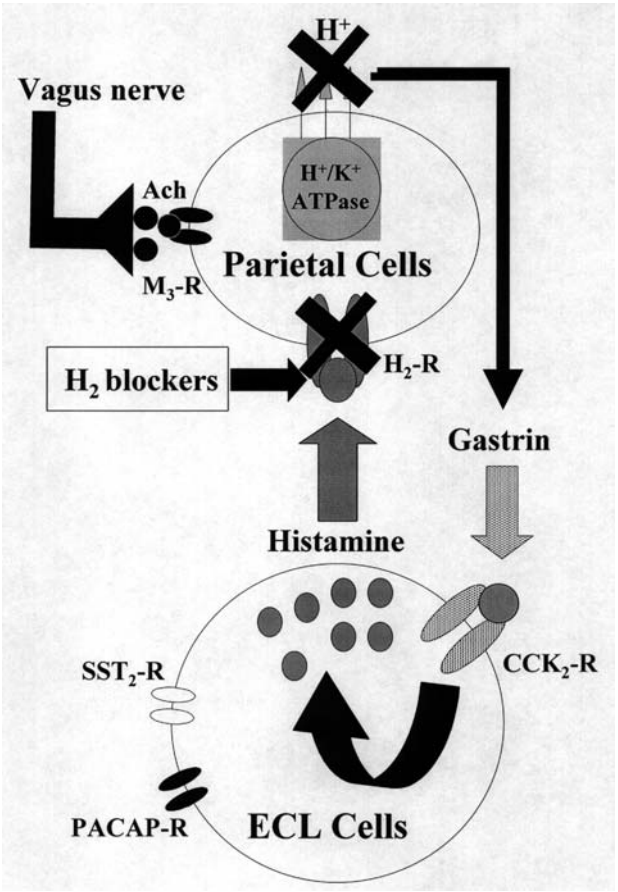

FIGURE 3 Schematic representation of the mechanism(s) of H_2 antagonist-induced gastrin release. H_2-R = histamine (H) receptor subtype 2; M_3-R = muscarinic (M) receptor subtype 3; Ach = acetylcholine; CCK_2-R = cholecystokinin (CCK) receptor subtype 2; SST_2-R = somatostatin (SST) receptor subtype 2; PACAP-R = pituitary adenylate cyclase-activating peptide (PACAP) receptor; ECL cells = enterochromaffin-like (ECL) cells.

Gastrin RIA Kit II, Dinabot Co Ltd., Tokyo, Japan, < 200 pg·mL^{-1}: RIA PEG, SRL Co Ltd., Tokyo, Japan). Therefore, hypergastrinemia may not be involved in the maintenance of tolerance.

Smit and colleagues[11] reported a further interesting mechanism of tolerance where H_2 receptor upregulation occurs in response to several H_2 antagonists displaying inverse agonism. In their report, H_2 receptors transfected into Chinese hamster ovary cells are upregulated in a time- and concentration-dependent manner by exposure to cimetidine and ranitidine. These upregulated H_2 receptors (increased density) displayed agonist-independent basal activity for which cimetidine and ranitidine displayed inverse agonism that is negative intrinsic activity. In contrast, burimamide, a neutral H_2 antagonist with no inverse agonist action did not induce H_2 receptor upregulation. Therefore, we feel that H_2 receptor upregulation may be an important cause of the tolerance as this does not have to be accompanied by hypergastrinemia.

Four patients in the control group had a gastric pH less than 5. Oral roxatidine 75 mg was given twice, once at 21:00 on the night before surgery and again 90 min before induction of anesthesia in the present study. Jacobs *et al.*[12] reported that oral ranitidine 300 mg (equivalent to roxatidine 150 mg) consistently prevents acid production when given more than 90 min before induction. However, the data reported by Atanassoff *et al.*[13] suggest that oral ranitidine 150 and 300 mg produce peak gastric elevation of pH (~ 7) at eight and 12 hr following administration. Therefore pH after induction of anesthesia may not have reached its maximal elevation.

In the present study no patient had acid aspiration pneumonia although nine and eight of 46 patients had low gastric pH and high volume. The issue of prophylaxis of acid aspiration pneumonia in anesthesia patients remains controversial. However, this complication has a high morbidity and mortality. Rosenstock and colleagues[14] reported complaints related to adverse respiratory events in anesthesia and intensive care medicine from 1994 to 1998 in Denmark. In their report, six of the seven patients suffering from pulmonary aspiration of gastric contents were in anesthesia and intensive care, in poor general condition and died following the events. Therefore, preanesthetic prophylaxis may be warranted in some patients, to reduce the risk of this adverse event.

If patients develop a tolerance to H_2 antagonists, their preanesthetic administration would be, essentially, useless. Several reports[3,5] suggest that proton pump inhibitors may be a suitable alternative to control gastric acidity preoperatively. These clinical reports show that proton pump inhibitors produce a similar or more potent inhibitory effect on gastric acid secretion when compared with H_2 antagonists. In addition, tolerance to proton pump inhibitors does not seem to develop.[3,5] As proton pump inhibitors inhibit H^+/K^+-adenosine triphosphatase, the final step in gastric acid secretion,[7] long-term use is unlikely to produce tolerance. Therefore we suggest that, in patients undergoing anesthesia, proton pump inhibitors may be more reliable than H_2 antagonists, especially in those who have received long-term medication.

In summary, the present study suggests that full tolerance to the effect of H_2 antagonists may occur in patients who have received H_2 antagonists for more than one month and adequate control of gastric acidity must be questioned.

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