Intramuscular tramadol increases gastric pH during anesthesia

[L'administration intramusculaire du tramadol augmente le pH gastrique pendant l'anesthésie]

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Purpose: Tramadol, [(1RS, 2RS)-2-dimethylamino) methyl-1-(3-methoxyphenyl)-cyclohexanol hydrochloride], is an analgesic in clinical use. It has been reported that tramadol inhibits muscarinic type 3 receptor function, which primarily mediates smooth muscle contraction and glandular secretion. We investigated the effects of tramadol on the pH of gastric juices during anesthesia to determine whether tramadol inhibits secretion from the gastric glands.

Methods: ASA physical status I or II adult patients ($n = 30$) presenting for major elective orthopedic surgery of the upper extremities or mastectomy were enrolled. Patients were randomly assigned to receive treatment with tramadol ($n = 10$), famotidine ($n = 10$), or saline ($n = 10$). General anesthesia was then induced using propofol, vecuronium bromide, and fentanyl. After inducing anesthesia, the gastric pH was measured using pH test paper and, then, 100 mg tramadol, 20 mg famotidine, or saline were injected into the deltoid muscle. Three hours after starting the operation, gastric juice was again aspirated and its gastric pH measured.

Results: There were no differences in the pH before anesthesia between the three groups. By contrast, gastric pH was increased in the tramadol group by the same amount as it was in the famotidine group three hours after administering the drugs. Gastric pH of the saline, famotidine, and tramadol groups was 2.6 ± 2.5 , 6.3 ± 2.0 , and 6.4 ± 0.8 , respectively.

Conclusion: These results suggest that tramadol inhibits the secretion of gastric acid.

Objectif : Le tramadol, [(1RS, 2RS)-2-diméthylamino) méthyl-1-(3-méthoxyphényl)-cyclohexanol hydrochloride], est un analgésique d'usage clinique. On a montré que le tramadol inhibe la fonction des récepteurs muscariniques de type 3 dont le principal rôle est de servir de médiateur à la contraction des muscles lisses et à la sécrétion glandulaire. Nous avons examiné les effets du tramadol sur le pH des sucs gastriques pendant l'anesthésie afin de déterminer si le tramadol inhibe la sécrétion des glandes gastriques.

Méthode : Des patients adultes d'état physique ASA I et II ($n = 30$) admis pour une intervention orthopédique majeure réglée aux membres supérieurs ou pour une mastectomie ont participé à l'étude. Ils ont été randomisés et ont reçu du tramadol ($n = 10$), de la famotidine ($n = 10$) ou une solution saline ($n = 10$). L'anesthésie générale a été induite avec du propofol, du bromure de vécuronium et du fentanyl. Après l'induction, le pH gastrique a été mesuré avec un papier indicateur de pH et, ensuite, 100 mg tramadol, 20 mg de famotidine ou une solution saline ont été injectés dans le muscle deltoïde. Trois heures après le début de l'opération, les sucs gastriques ont été aspirés et leur pH mesuré.

Résultats : Aucune différence de pH n'a été notée avant l'opération et, ce, chez les patients des trois groupes. Par contre, le pH gastrique était plus élevé dans le groupe sous tramadol, de la même quantité qu'il l'a été dans le groupe sous famotidine trois heures après l'administration des médicaments. Le pH gastrique en présence de solution saline, de famotidine et de tramadol a été de $2,6 \pm 2,5$; $6,3 \pm 2,0$ et $6,4 \pm 0,8$ respectivement.

Conclusion : Ces résultats indiquent que le tramadol inhibe la sécrétion d'acide gastrique.

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TRAMADOL [(1RS, 2RS)-2-dimethylamino-methyl-1-(3-methoxyphenyl)-cyclohexanol hydrochloride] is a centrally acting analgesic (Figure). Tramadol binds to μ -opioid receptors with approximately 100 times less affinity than morphine¹ and tramadol causes much less respiratory depression than equianalgesic doses of morphine.² This suggests that the antinociceptive action of tramadol is not due to opioid receptor binding, but may occur via a different mechanism that is not yet understood. Recently, we reported its inhibitory effects on cholinergic receptors.^{3,4} Sagata *et al.* reported that atropine displaces (¹⁴C)-tramadol binding to adrenal medullary cells.³ Shiraishi *et al.* showed that tramadol at clinically relevant concentrations inhibits muscarinic receptor function. More recently, it was also reported that tramadol inhibits type-3 muscarinic receptor (M_3) function at clinically relevant concentrations.⁴ In a clinical setting, tramadol sometimes causes a dry mouth and constipation.¹ Our previous findings may explain the modulation of the anticholinergic effects of tramadol.

Acetylcholine is a neurotransmitter that directly stimulates gastric gland secretion. Smooth muscle contraction and glandular secretion are primarily mediated by the stimulation of M_3 receptors.⁵ Pfeiffer *et al.* reported that M_3 receptors are overexpressed in duodenal ulcers and may play a part in their pathogenesis.⁶ We recently reported that tramadol inhibits M_3 function.⁴ Therefore, tramadol might inhibit secretion from the gastric glands, although there is little information on this.

We investigated the effects of tramadol on the pH of gastric juice during anesthesia to determine whether tramadol inhibits secretion from the gastric glands.

Methods

This study was approved by our University Ethics Committee. Thirty adult patients, ASA physical status I or II presenting for major elective orthopedic surgery of the upper extremities or mastectomy were enrolled. Patients who were less than 20 yr old or who had a history of gastric ulcer, duodenal ulcer, or gastritis were excluded. Informed consent was obtained from all patients. Patients were randomly assigned to receive treatment with tramadol (tramadol group, $n = 10$), famotidine (famotidine group, $n = 10$), or saline (control group, $n = 10$). Randomization was done using a computer-generated table of random numbers.

General anesthesia was induced using propofol 1.5 mg·kg⁻¹, vecuronium bromide 0.1 mg·kg⁻¹, and fentanyl 1.2 μ g·kg⁻¹. An orogastric tube (15-Fr; JF-

TABLE I Comparison of the control, famotidine, and tramadol treatment groups

<i>n</i>	Control 10	Famotidine 10	Tramadol 10
Age (yr)	40.5 $\pm$ 21.6	48.2 $\pm$ 17.9	39.4 $\pm$ 13.7
Gender (M/F)	3/7	4/6	4/6
Weight (kg)	56.0 $\pm$ 3.9	59.8 $\pm$ 11.7	60.6 $\pm$ 15.0
Height (cm)	156.9 $\pm$ 10.6	156.5 $\pm$ 5.9	157.3 $\pm$ 8.8
Duration of anesthesia (min)	240 $\pm$ 63	251 $\pm$ 40	260 $\pm$ 54

TABLE II Gastric pH in the control, famotidine, and tramadol treatment groups

	Control (<i>n</i> = 10)	Famotidine (<i>n</i> = 10)	Tramadol (<i>n</i> = 10)
Before administration	2.3 $\pm$ 2.5	1.7 $\pm$ 2.1	2.0 $\pm$ 2.3
After administration	2.6 $\pm$ 2.5	6.3 $\pm$ 2.0***, #	6.4 $\pm$ 0.8***, #

*** $P < 0.001$ vs before administration; # $P < 0.05$ vs control.

CI5120C, JMS, Hiroshima, Japan) was inserted by the same anesthesia resident in all patients, who aspirated the gastric juice and measured gastric pH using pH test paper (pH-Fix 0-14 and pH-Fix 4.5-10, Macherey-Nagel GmbH, Drüen, Germany). The resident was blinded to group assignment. A patient was eliminated from the study if more than two attempts were required to pass the gastric tube. After induction, 100 mg tramadol, 20 mg famotidine, or saline in an equal volume (2 mL) were injected into the deltoid muscle. Ventilation was adjusted to maintain the PaCO₂ at 35 to 40 mmHg. Anesthesia was maintained with 1.0 to 1.5% isoflurane in combination with 67% nitrous oxide in oxygen. Three hours after starting the operation, a new orogastric tube (15-Fr) was inserted and gastric juice was aspirated and the pH measured again.

The results are presented as the mean $\pm$ SD. The data were analyzed using analysis of variance, and a post hoc test (Scheffe test). A P value < 0.05 was accepted as statistically significant.

Results

Of the 30 patients studied, ten patients each received saline, famotidine, or tramadol. There were no significant differences among the groups in age or body weight (Table I). No patient was eliminated from the study because of difficulty with the insertion of the orogastric tube. There was no difference in the pH before anesthesia among the three groups ($P = 0.8282$, power 0.08; Table II). The pH of the gastric juice did not change in the control group three hours after adminis-

FIGURE Comparison of the chemical structure of tramadol, codeine, and atropine.

tering saline ($P = 0.77$, power 0.06). By contrast, gastric pH was elevated in the tramadol ($P = 0.0002$, power 0.98) and famotidine ($P < 0.0001$, power 0.999) groups. There were no significant differences among the groups in postoperative outcomes.

Discussion

In this study, we measured the gastric pH under anesthesia incorporating nitrous oxide, isoflurane and fentanyl. In the control group, gastric pH was about 2 suggesting these anesthetics would have weak effects on gastric pH. However, gastric pH was higher in the tramadol group than in the control group. These results suggest that tramadol would inhibit the secretion of gastric acid during anesthesia. Tramadol causes a dry mouth and constipation, suggesting that tramadol has anticholinergic effects,¹ and our results are consistent with this.

Lintz *et al.* reported that the minimal effective serum concentration was reached within a few minutes.⁷ The maximum plasma concentration peaked at $193 \mu\text{g}\cdot\text{mL}^{-1}$ 0.75 hr after 50 mg tramadol *im* and terminal elimination half-life was 5.5 hr in 12 healthy male subjects.⁷ Noguchi *et al.*, previously reported that the effect of *im* famotidine reached a peak 120 min after injection.⁸ Therefore, we measured the gastric pH three hours after administration. It has also been reported that tramadol concentrations are considerably higher in saliva and urine than in serum and that minimal effective serum concentrations are maintained for nine to ten hours on average.⁷ The concentration/time relationship of tramadol in the gastric mucosa remains unknown.

In recent studies, we suggested that tramadol inhibits muscarinic receptor function.^{3,4} Sagata *et al.* reported that (^{14}C)-tramadol bound to adrenal medullary cells is replaced by atropine, indicating that tramadol competitively affects muscarinic receptors.³ Shiraishi *et al.* reported that tramadol at clinically relevant concentrations inhibits M_1 receptor function via quinuclidinyl benzilate (QNB)-binding sites.⁹ In addition, tramadol inhibits M_3 receptor function via QNB-binding sites at clinically relevant concentrations.⁴ These findings suggest that tramadol has anticholinergic effects. The inhibitory effects of tramadol on muscarinic receptor function explain our present results. Both gastrin and histamine strongly stimulate the secretion of acid by parietal cells.¹⁰ In our study, the pH in the tramadol group was similar to that in the famotidine group. It would be relevant to study the effects of tramadol on histamine- and gastrin-induced secretion of acid.

Common non-steroidal anti-inflammatory drug (NSAID) analgesics are used widely. However, they often cause ulcers, possibly via the inhibition of prostaglandin synthesis in the stomach. Patients with underlying gastric ulcer are at particular risk of NSAID-induced gastric ulcer.¹¹ Our results suggest that tramadol might be a suitable analgesic for such patients.

In conclusion, gastric pH was higher in the tramadol group than in the control group, which suggests that tramadol inhibits the secretion of gastric acid. Recently, several groups reported that tramadol has less effects on gastric emptying than morphine.^{12,13} The significance of this finding with regard to clinical outcomes remains to be determined.

References

- 1 Katz WA. Pharmacology and clinical experience with tramadol in osteoarthritis. *Drugs* 1996; 52(Suppl 3): 39–47.
- 2 Wilder-Smith CH, Bettiga A. The analgesic tramadol has minimal effect on gastrointestinal motor function. *Br J Clin Pharmacol* 1997; 43: 71–5.
- 3 Sagata K, Minami K, Yanagihara N, *et al.* Tramadol inhibits norepinephrine transporter function at desipramine-binding sites in cultured bovine adrenal medullary cells. *Anesth Analg* 2002; 94: 901–6.
- 4 Shiga Y, Minami K, Shiraishi M, *et al.* The inhibitory effects of tramadol on muscarinic receptor-induced responses in *Xenopus* oocytes expressing cloned M_3 receptors. *Anesth Analg* 2002; 95: 1269–73.
- 5 Lefkowitz RJ, Hoffman BB, Taylor P. Neurohumoral transmission: the autonomic and somatic motor nervous systems. *In*: Gilman AG, Rall TW, Nies AS,

- Taylor P (Eds). Goodman and Gilman's The pharmacological basis of Therapeutics, 8th ed. New York: Pergamon Press; 1990: 84–121.
- 6 Pfeiffer A, Kromer W, Friemann J, *et al.* Muscarinic receptors in gastric mucosa are increased in peptic ulcer disease. *Gut* 1995; 36: 813–8.
 - 7 Lintz W, Beier H, Gerloff J. Bioavailability of tramadol after i.m. injection in comparison to i.v. infusion. *Int J Clin Pharmacol Ther* 1999; 37: 175–83.
 - 8 Noguchi J, Yamamura H, Inada Y, *et al.* A double-blind evaluation of famotidine for pre-anesthetic intramuscular administration – its effects on volume and pH of gastric juice (Japanese). *Masui* 1987; 36: 592–603.
 - 9 Shiraiishi M, Minami K, Uezono Y, Yanagihara N, Shigematsu A. Inhibition by tramadol of muscarinic receptor-induced responses in cultured adrenal medullary cells and in *Xenopus laevis* oocytes expressing cloned M₁ receptors. *J Pharmacol Exp Ther* 2001; 299: 255–60.
 - 10 Guyton AC. Secretory functions of the alimentary tract. *In:* Guyton AC (Ed.). *Textbook of Medical Physiology*, 8th ed. Philadelphia: W.B. Saunders; 1991: 709–25.
 - 11 Zeidler H. Epidemiology of NSAID-induced gastropathy. *Clin Rheumatol* 1991; 10: 369–73.
 - 12 Wilder-Smith CH, Hill L, Wilkins J, Denny L. Effects of morphine and tramadol on somatic and visceral sensory function and gastrointestinal motility after abdominal surgery. *Anesthesiology* 1999; 91: 639–47.
 - 13 Crighton IM, Martin PH, Hobbs GJ, Cobby TF, Fletcher AJ, Stewart PG. A comparison of the effects of intravenous tramadol, codeine, and morphine on gastric emptying in human volunteers. *Anesth Analg* 1998; 87: 445–9.