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Anesthesia: Essays and Researches

Original Article

Effects of varying doses of tramadol on gastric pH

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Abstract

Background: Tramadol is licensed primarily as an analgesic, but has additional properties, one of which is the ability to increase gastric pH. However, it has not been established if this action is dose related, hence we set out to provide further evidence about this action of tramadol.

Patients and Methods: Fifty-five female adult patients presenting for gynecological surgery were randomized into three groups. After induction, 2.5 ml of gastric juice was aspirated to determine baseline pH, after which groups 1, 2, and 3 received 50 mg, 75 mg, and 100 mg of IV tramadol, respectively. Gastric pH was subsequently assessed every 30 min for as long as the surgery lasted.

Results: There was no significant difference in the pH of the three groups before anesthesia (3.88 ± 0.75, 3.54 ± 0.73, and 3.75 ± 0.70; $P = 0.393$). Similarly, no significant statistical difference was observed in the pH of the three tramadol groups during the subsequent three readings (pH1: 4.21 ± 0.93, 4.27 ± 0.95, 4.07 ± 0.82; pH2: 4.75 ± 1.00, 4.68 ± 0.94, 4.59 ± 0.78; pH3: 5.33 ± 0.86, 5.13 ± 0.95, 4.97 ± 0.78; $P = 0.793, 0.876$, and 0.490). There were statistically significant increases in the pH of each group when the baseline pH was compared with the subsequent three readings, with P values of 0.002, 0.0001, 0.001 in the 50 mg group, 0.0001, 0.0001, 0.0001 in the 75 mg group, and 0.008, 0.0001, 0.001 in the 100 mg group.

Conclusion: Our result further confirms that tramadol elevates gastric pH. However, the degree of elevation was not found to be dose dependent.

Key words: Dose, gastric pH, tramadol

INTRODUCTION

Tramadol is a centrally acting analgesic drug in clinical use worldwide. Its mechanism of action was realized after prolonged clinical use did not conform to the described pharmacology.[1] Sagata *et al*. reported that (14C)-tramadol bound to adrenal medullary cells is replaced by atropine, indicating that tramadol competitively affects muscarinic receptors.[2] In addition, tramadol inhibits M_3 receptor function via quinuclidinyl benzilate (QNB)-binding sites at clinically relevant concentrations[3] and M_1 receptor function via QNB-binding sites.[4] The inhibitory effect of tramadol on muscarinic receptor is presently being suggested as the reason for its elevation of gastric pH. We set out to determine the effect of varying doses of tramadol on the pH of gastric juice during anesthesia.

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PATIENTS AND METHODS

Following approval of the hospital/university ethics committee and informed consent obtained from the subjects, a double-blind randomized study was conducted.

Fifty-five female patients with American Society of Anesthesiologists' (ASA) physical status I or II, of age 18–65 years, who have had at least 6 h of preoperative fast presenting for gynecological procedures under general anesthesia, participated in the study. Excluded were the patients with previous history of allergy to tramadol or any opioid in the past, recent ingestion of antacids/H2-receptor blocker, upper gastrointestinal bleeding, history of seizure disorder, and patients with liver or kidney disease. Also excluded were patients with history suggestive of acid-peptic disease or gastroesophageal reflux disease, patients receiving analgesics like non-steroidal anti-inflammatory agents, and morbidly obese patients.

All patients received 5 mg of diazepam on the night before and morning of surgery. Following institution of baseline monitoring, general anesthesia was induced using thiopentone 4 mg/kg, pancuronium bromide 0.1 mg/kg, and pentazocine 0.5 mg/kg, and maintenance was with 1.0–1.5% halothane in oxygen. A size 18 nasogastric tube was passed by the duty anesthetist after endotracheal intubation. Patients were randomly assigned to receive intravenous tramadol 50 mg (n = 18), tramadol 75 mg (n = 18), or tramadol 100 mg (n = 19). The study drug was administered by the attending anesthetist who was blinded to the group allotment.

Tradyl® (I nterbat) was employed in this study for all patients. For all the patients, 5 ml of gastric juice was aspirated for baseline pH assessment immediately after induction of anesthesia, and subsequently the study drug was administered after induction of general anesthesia and before the commencement of surgery. Gastric juice was aspirated every 30 min after administration of tramadol for as long as the surgery lasted; however, for uniformity, only the first three readings were employed for analysis because some of the procedures ended before 120 min and as such only three other samples were obtained after the baseline sample. The analysis of the pH and postoperative pain assessment using the verbal response scale (VRS) were done by a laboratory technician and an anesthetist respectively, both blinded to the study objectives.

pH analysis

The gastric samples collected in the universal bottle were capped properly and transported to the laboratory in a cold pack for pH measurement. The pH measurement of samples was done using Jenway Model 3305 pH/mV meter with optional Automatic Temperature Compensation (ATC) probe,[5] which enables the user to perform temperature measurements within the range of 0–100°C. Commercially available buffer solutions, 025 037, pH 4.00 buffer, and 025 038, pH 7.00 buffer, were used to calibrate the pH meter machine. The electrode and ATC probe were immersed in the pH 7 buffer solution and allowed sufficient time for the pH reading to stabilize. The display was set to read the temperature-compensated value of the buffer solution using the buffer control. The electrode and ATC probe were rinsed in deionized water and subsequently immersed in the second pH 4 buffer solution, and allowed sufficient time for the pH reading to stabilize. The display was also set to read the temperature-compensated value of the buffer solution using the SLOPE control. The above procedure was repeated until no further adjustments were necessary. Care was taken when making adjustments as the controls are slightly interdependent. The electrode and ATC probe were then rinsed with deionized water and subsequently immersed in the unknown sample solution. The reading was allowed to stabilize; the display value indicated the pH of the sample solution.

Both the electrode and ATC probe when in use were rinsed in deionized water and blotted with clean tissue prior to immersing in the next sample. This will minimize carry over and contamination.

Statistics

Data were entered into SPSS version 17.0 for analysis. Results are presented in tables and figures and expressed as mean (± SD). After data editing and cleaning, statistical association was determined using Chi-square test for categorical variables and analysis of variance (ANOVA) for the continuous variables. P values less than 0.05 were considered significant.

RESULTS

Fifty-five patients were involved in the study. We had 18, 18, and 19 patients in the 50 mg, 75 mg, and 100 mg groups, respectively. All the tramadol groups were comparable in age, height, body weight, body mass index (BMI), and duration of anesthesia [Table 1 and Figure 1]. There was no significant difference in the pH of the three groups before anesthesia (3.88 ± 0.75, 3.54 ± 0.73, and 3.75 ± 0.70; P = 0.393). Also, there were no significant statistical differences in the pH of the three tramadol groups during the subsequent three readings (pH 1: 4.21 ± 0.93,

Table 1: Patient characteristics

	Group 1 n=18	Group 2 N=18	Group 3 n=19	P-value
Age (years)	34.11±7.15	36.94±9.64	33.74±9.36	0.489
Weight (kg)	62.44±8.89	63.78±5.56	61.74±8.90	0.312
Height (cm)	158.24±9.70	157.17±8.44	154.89±7.58	0.492
BMI (kg/m^2)	24.68±2.92	25.87±2.07	25.71±2.82	0.353
Surgery duration	94.83±19.34	103.28±15.03	95.89±20.69	0.353

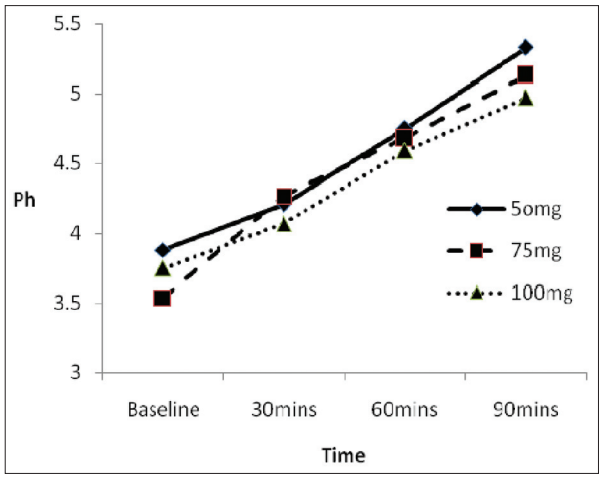

Figure 1: Mean pH change over time

Table 2: Mean pH values over time in the tramadol groups

	50 mg	75 mg	100 mg	*P*-value
Baseline	3.88±0.75	3.54±0.73	3.75±0.70	0.393
pH1	4.21±0.93	4.27±0.95	4.07±0.82	0.793
pH2	4.75±1.00	4.68±0.94	4.59±0.78	0.876
pH2	5.33±0.86	5.13±0.95	4.99±0.78	0.490

Table 3: Pain management in the different groups

Tramadol group (n)	VRS	Analgesic given (%)
50 mg (18)	Mild (10)	1 (10)
75 mg (18)	Mild (12) Moderate (5)	3 (60)
100 mg (19)	Mild (17) Moderate (2)	

P-value = 0.27; VRS: Verbal rating scale

4.27 ± 0.95, 4.07 ± 0.82; pH 2: 4.75 ± 1.00, 4.68 ± 0.94, 4.59 ± 0.78; pH 3: 5.33 ± 0.86, 5.13 ± 0.95, 4.99 ± 0.78; *P* = 0.793, 0.876, and 0.490) [Table 2]. There were statistically significant increases in the pH of each group when the baseline pH was compared with the subsequent three readings, with *P* values of 0.002, 0.0001, 0.001 in the 50 mg group, 0.0001, 0.0001, 0.0001 in the 75 mg group, and 0.008, 0.0001, 0.001 in the 100 mg group. The maximum increase from baseline after the third reading was observed in the tramadol 50 mg group, though it was not statistically significant when compared with those of other groups. There was no difference in the incidence of mild/moderate pain and analgesic requirement in the three tramadol groups (*P* = 0.27) [Table 3].

DISCUSSION

Our result showed that tramadol elevates gastric pH; this is consistent with other reports[6,7] on the gastric pH elevating effect of tramadol. However, the degree of elevation of the gastric pH was not found to be dose dependent. Minami *et al*.,[6] in a study of 30 ASA physical status I or II adult patients presenting for major elective orthopedic surgery of the upper extremities or mastectomy under general anesthesia, observed that gastric pH was increased in the tramadol group by the same amount as it was in the famotidine group. Similarly, Elhakim *et al*.,[7] in a study involving 60 ASA I parturients undergoing elective cesarean section in a randomized double-blind study, confirmed the result of Minami *et al*. and concluded that a single IM dose of tramadol is useful pre-treatment to minimize the risk of acid aspiration during operation. Tramadol has been reported to inhibit muscarinic type 3 receptor function, which causes smooth muscle contraction and glandular secretion.[3,8]

Gastric content may reach the pharynx and be available for aspiration via two mechanisms, frank vomiting, which is usually obvious, and regurgitation, which can be very subtle and is often unrecognized. Aspiration increases perioperative morbidity and mortality. Patients with gastrointestinal obstruction or dysfunction, abnormalities of esophageal function, and, perhaps, obesity have increased potential for regurgitation. Because of the proper emphasis on the danger of aspiration, anesthetists use extreme caution to prevent its occurrence, including fasting patients; aspiration of stomach contents before inducing anesthesia, a marked head up, or conversely, down position; and firm pressure over the cricoid cartilage until the endotracheal cuff has been inflated. In spite of all these efforts, substantial complications may still occur. The acidity of aspirated liquid appears critical. Teabeaut,[9] studying rabbits, found that hydrochloric acid and human gastric juice with a pH of 2.5 or greater was not much worse than saline, whereas a pH below 1.5 caused a severe inflammatory reaction. A number of medicines have been used, including anticholinergics such as atropine and glycopyrrolate. Others include antacids, histamine-2 receptor blockers, and metoclopramide to prevent or reduce the consequence of aspiration. Tramadol may also find a place in this clinical armamentarium.

In contrast to other studies,[6,7] we commenced the measurement of gastric pH earlier in our study because of the intravenous route employed for the tramadol. The maximum plasma concentration after 50 mg of intramuscular tramadol has been put at 166 ng/ml 45 min after injection and the corresponding value for intravenous dose is 293 ng/ml 30 min after injection.[10] When compared to baseline, we observed significant elevation in the pH values. However, it is not unlikely that higher values could have been obtained if we had waited much longer before measuring the gastric pH. We also observed that the degree of elevation of gastric pH in the 75 mg and 100 mg groups did not significantly differ from that recorded in the 50 mg group.

Unlike the non-steroidal anti-inflammatory drugs (NSAIDs) and as a pure agonist at mu-opioid receptor, tramadol had been shown not to have a ceiling effect regarding the analgesic property. Moore and McQuay[11] reviewed 18 studies which demonstrated that all doses of tramadol were superior to placebo in relieving post-surgical and dental pain and showed a dose–response effect. We are suggesting the possibility of a pharmacokinetic disparity between the analgesic and pH elevating properties of tramadol, which may not be unrelated to the varying pharmacokinetic profile of the parent tramadol compound and its main metabolite mono-*O*-desmethyl tramadol (M1),[12] though further work is needed to elucidate on this suggested disparity.

Though our patients received a single dose of pentazocine in addition to varying doses of tramadol, only about 8% of the patients requested for analgesia postoperatively. Synergism of the two drugs, similarity of surgical procedures, and comparable duration of surgery could have played a role. However, there is no doubt that tramadol has found a veritable place in overall pain management; the analgesic efficacy of tramadol has been demonstrated in different acute and chronic pain syndromes, being comparable with that of various other opioid and non-opioid analgesics. Some emerging roles of tramadol are in obstetrics, where the analgesic effect has been found comparable to that of pethidine without adverse effect on the neonate.[13-15] In view of the desirability for gastric pH elevation as part of the measures to prevent aspiration pneumonitis in the obstetric population, tramadol may offer some advantage. The knowledge of the dose–effects relationship of tramadol and gastric pH may offer an advantage during such clinical setting.

The lack of placebo group may be a limitation. The placebo group was not included because previous studies have established the pH elevating effect of tramadol and insignificant elevation of gastric pH under normal circumstances during major surgery under general anesthesia.[6] In conclusion, tramadol was found to significantly elevate gastric pH; however, this increase was not proved to be dose dependent. Nonetheless, this reduction in gastric acidity by tramadol may offer an advantage in patients prone to aspiration during anesthesia that requires a potent analgesic with minimal risk of postoperative vomiting.

REFERENCES

1. Raffia RB, Riderichs E, Reimann W, Shank RP, Codd EE, Vaught JL. Opioid and non-opioid components independently contribute to the mechanism of action of tramadol, an'atypical' opioid analgesic. J Pharmacol Exp Ther 1992;260:275-85.
2. Sagata K, Minami K, Yanagihara N, Shiraishi M, Toyohira Y, Ueno S, *et al.* Tramadol inhibits norepinephrine transporter function at desipramine-binding sites in cultured bovine adrenal medullary cells. Anesth Analg 2002;94:901-6.
3. Shiga T, Minami K, Shiraisbi M, Uezono Y, Murasaki O, Kaibara M, *et al.* The inhibitory effects of tramadol on muscarinic receptor-induced responses in Xenopus oocytes expressing cloned M3 receptors. Anesth Analg 2002;95:1269-73.
4. Shiraishi 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.
5. Covington AK, Bates RG, Durst RA. Definition of pH scales, standard reference values, measurement of pH and related technology. Pure and Appl Chem 1985;57:531-42.
6. Minami K, Ogata J, Horishita T, Shiraishi M, Okamota T, Sata T, *et al.* Intramuscular tramadol increases gastric pH during anesthesia. Can J Anaesth 2004;51:545-8.
7. Elhakim M, Abd El-Megid W, Metry A, El-hennawy A, El-Queseny K. Analgesic and antacid properties of i.m. tramadol given before Caesarean section under general anaesthesia. Br J Anaesth 2005;95:811-5.
8. Minami K, Uezono Y, Ueta Y. Pharmacological aspects of the effects of tramadol on G-protein coupled receptors. J Pharmacol Sci 2007;103:253-60.
9. Teabeaut JR 2nd. Aspiration of gastric contents: An experimental study. Am J Pathol 1952;28:51-67.
10. Lintz W, Beier H, Gertoff J. Bioavailability of tramadol after i.m. injection in comparison to i.v. infusion. Int J Clin Pharmacol Ther 1999;37:175-83.
11. Moore RA, McQuay HJ. Single-patient data meta-analysis of 3453 postoperative patients: Oral tramadol versus placebo. Pain 1997;69:287-94.
12. Grond S, Sablotzki A. Clinical Pharmacology of Tramadol. Clin Pharmacokinet 2004;43:879-923.
13. Elbourne D, Wiseman RA. Types of intra-muscular opioids for maternal pain relief in labour. Cochrane Database Syst Rev 2000;(2):CD001237.
14. Viegas OA, Khaw B, Ratnam SS. Tramadol in labour pain in primiparous patients: A prospective comparative clinical trial. Eur J Obstet Gynecol Reprod Biol 1993;49:131-5.
15. Fieni S, Angeri F, Kaihura CT, Ricci L, Bedocchi L, Galanti B, *et al.* Evaluation of the peripartum effects of 2 analgesics: Meperidine and tramadol, used in labour. Acta Biomed Ateneo Parmense 2000;71:397-400.

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