Effect of single oral dose of tramadol on gastric secretions pH

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ABSTRACT

Background: Tramadol is an atypical analgesic agent. It has been shown that intramuscular or intravenous injection tramadol is able to inhibit M3 muscarinic receptors. Tramadol is able to mediate smooth muscles contraction and glandular secretions. We have evaluated the effects of single oral dose of tramadol given preoperatively on gastric juices pH in patients electively scheduled for laparoscopic cholecystectomy.

Materials and Methods: Sixty adult, American Society of Anesthesiologist I and II patients scheduled for laparoscopic cholecystectomy were included in the study. Patients were randomly assigned to receive either placebo (n = 30) or oral tramadol 50 mg (n = 30). General anesthesia was induced using propofol, fentanyl and cisatracurium. After induction of anesthesia 5 ml of gastric fluid was aspirated through orogastric tube. The gastric fluid pH was measured using pH meter.

Result: There was no significant difference in the pH between the groups. Gastric pH of the placebo and tramadol groups was 1.97 versus 1.98 (P = 0.092) respectively.

Conclusion: Preoperatively single oral dose of tramadol was unable to elevate the desired level of gastric acid secretions pH (>2.5). This may be due to pharmacokinetic disparity between the analgesic and pH elevating properties of tramadol.

Key words: Gastric pH, M3 muscrinic receptors, tramadol

INTRODUCTION

Tramadol is an atypical centrally acting analgesic agent. It has approximately 100 times less affinity than morphine for μ-opioid receptors. Tramadol inhibits M3 type receptors, gastric gland secretions and mediates smooth muscle contraction. Some emerging role of tramadol in reducing gastric acid secretions has been studied. Recently, it is reported that intraoperatively intramuscular (IM) and intravenous (IV) injection of tramadol reduces the gastric secretions and acidity. The aim of our study is to assess the antacid effect of single oral dose of tramadol given 3h preoperatively for elective laparoscopic cholecystectomy under general anesthesia.

MATERIALS AND METHODS

This study was approved by our University Ethics Committee. Sixty adult patients, of either sex, age between 18 and 50 years. Sixty adult patients, of either sex, age between 18 and 50 years, American Society of Anesthesiologist (ASA) physical status I or II presenting for laparoscopic cholecystectomy surgery were included in the study. Patients taking any sedative, tranquillizers, history of acid peptic, obesity body weight more than 20% of ideal body weight and any contraindication to tramadol were excluded. Informed consent was obtained from all patients. Randomization and drug delivery was done through hospital pharmacy. Patients were randomly assigned to receive either tramadol (Group-T, n = 30), or placebo (Group-C, n = 30). Patients in Group-C received empty capsule and Group-T received tramadol 50 mg orally 3 h before calling the patient to the operating room. General anesthesia was induced with IV propofol 1.5-2 mg/kg and fentanyl 2 μg/kg. The lungs were ventilated with 100% oxygen and sevoflurane using circle breathing circuit with care to avoid inflation of the stomach. Tracheal intubation was facilitated after 3 min of administration of cisatracurium 0.2 mg/kg. Ventilation was adjusted to maintain the PaCO2 at 35-40 mmHg. General anesthesia was maintained with 2.0-2.5% sevoflurane in combination with...
50% oxygen in the air. All patients were monitored according to the ASA standard. A new a 16-Fr orogastric catheter was inserted into the stomach. Placement of the orogastric tube within the stomach was verified by auscultation over the epigastrium during introduction of 10 ml air. Five milliliters of gastric fluid samples were obtained by gentle aspiration with a 50 ml syringe by an investigator who was unaware of the patient’s preanesthetic medication. Aspirations were attempted with the patient held in supine and reverse trendelenburg position. The pH of the gastric fluid was determined immediately using a pH meter (Horiba F-8 L; Horiba, Kyoto, Japan) that was already calibrated using standard buffers at pH values of 2, 4, and 7. The pH meter had 0.01 pH units precision over the entire pH range.

The results are presented as the mean standard deviation and percentage where as appropriate. The data were analyzed using independent t-test. P < 0.05 was accepted as statistically significant.

RESULTS

A total of 60 patients were studied, 30 patients in each group received empty capsule or tramadol 50 mg per oral 3 h before taking the gastric fluid sample under general anesthesia. There was no significant difference among the groups in age, gender and body weight [Table 1]. None of the patient was eliminated from the study because of the difficulty in the insertion of an orogastric tube. The aspirated gastric juice pH in control and tramadol group was 1.97 ± 0.188 and 1.98 ± 0.189, respectively. There was no statistical difference (P = 0.092) in the mean pH values of gastric juice between the groups. The pH of gastric juice did not change after giving the preoperative single oral dose of tramadol 3 h before taking the gastric fluid sample.

DISCUSSION

Tramadol is an atypical centrally acting synthetic opioid analgesic agent. Its mode of action is not clearly understood. The suggested antinociceptive mechanisms are binding of parent and M1 metabolite to μ-opioid receptors and weak inhibition of serotonin and reuptake of norepinephrine.[1] The analgesia is dependent upon the plasma concentrations of tramadol and M1 compounds. Tramadol at clinically relevant concentrations is known to inhibits M1 receptor.[3] Tramadol competitively affects muscarinic receptor function,[3,4] and bound to adrenal medullary cells and is replaced by atropine. Tramadol at clinically relevant concentrations via quinuclidinyl benzylate binding sites is known to inhibit the M3 receptor function.[4] These findings suggest that tramadol at clinical relevant concentrations has anticholinergic effects. Lintz et al. reported the maximum plasma concentration after 50 mg of IM injection of tramadol reached up to 166 ng/ml in 45 min and the corresponding value for IV dose was 293 ng/ml in 30 min. The terminal elimination half-life was 5.5 h in 12 healthy male subjects.[9] The minimal effective serum concentrations on average were maintained for 9-10 h.

It has been reported that after per oral administration of 100 mg tramadol in healthy adults, the achieved tramadol and M1 metabolite mean peak plasma concentration was 136 ng/ml and 55 ng/ml respectively. Time to peak hours was 1.6 and 3.0 h and half-life of 5.6 and 6.7 h for tramadol and M1 metabolite respectively.[6] The mean absolute bioavailability of 100 mg oral dose of tramadol ranges in between 68% and 75%.[7]

In this study, we measured the gastric pH under general anesthesia 3 h after single oral dose of placebo or tramadol. In the control group and treatment group the gastric pH remained <2.5. These results suggest that oral single dose of tramadol did not inhibit the secretion of gastric acid during anesthesia. This may be due to the reason oral single dose of tramadol failed to achieve the peak plasma concentration as shown in the previous studies. This may reflect the different invasion kinetics of the IV/IM and oral modes of administration.[8] There is a possibility of pharmacokinetic disparity between the analgesic and pH elevating properties of tramadol.[9] It has also been reported that tramadol concentrations are considerably higher in saliva and urine than in serum. However, the concentration/time relationship of tramadol in the gastric mucosa remains unknown.[10] The achieved serum concentrations after single dose of tramadol may be clinical relevant[4] to provide analgesia for short duration, but not enough to provide antimuscarinic effects at M-3 receptors. A limitation of our study was that we have not evaluated the blood levels after the single oral dose of tramadol. We don’t know whether higher dose or repeated dose of tramadol may be able to provide desirable results.

| Patient characteristics | Group-C (n = 30) (%) | Group-T (n = 30) (%) | P value |
|-------------------------|----------------------|----------------------|---------|
| Age                     | 45.47±10.48          | 45.59±8.31           | 0.721   |
| Weight                  | 69.46±7.89           | 69.37±8.17           | 0.721   |
| Sex                     | 17 (56.66)           | 16 (53.33)           |         |
|                         | 13 (45.33)           | 16 (46.66)           |         |
| pH                      | 1.97±0.185           | 1.98±0.189           | 0.092   |

Table 1: Comparison of control and tramadol treatment group.
CONCLUSION

Preoperatively single oral dose of tramadol was unable to elevate the desired level of gastric acid secretions pH (>2.5). This may be due to pharmacokinetic disparity between the analgesic and pH elevating properties of tramadol. Our finding warrants the need for further work to elucidate on this suggested disparity.

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