

The Analgesic Efficacy of Tramadol is Impaired by Concurrent Administration of Ondansetron

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Tramadol has weak opioid properties, and an analgesic effect that is mediated mainly by inhibition of the reuptake of norepinephrine and serotonin (5-hydroxytryptamine [5-HT]) and facilitation of 5-HT release (1,2) at the spinal cord.

Because 5-HT₃ receptors play a key role in pain transmission at the spinal level (3), the 5-HT₃ antagonist ondansetron may decrease the efficacy of tramadol, as suggested in an abstract by Maroof et al.¹

In that study, a small dose of 1 mg/kg tramadol was administered along with ondansetron 0.1 mg/kg or placebo, 15 min before the induction of anesthesia. Early postoperative pain scores differed significantly between the treatment groups. We therefore tested the hypothesis that the tramadol requirement by patient-controlled analgesia (PCA) may be increased when ondansetron is administered for antiemetic prophylaxis.

Methods

With ethics committee approval, written, informed consent was obtained from 40 adult patients undergoing lumbar laminectomy. Criteria for exclusion were a history of alcohol or drug abuse or seizures, age more than 70 yr, and intake of monoamine oxidase inhibitors. Patients were randomly assigned to receive 4 mg of ondansetron (Zofran®; Glaxo Wellcome, Parma, Italy) or saline 0.9%. Both solutions were given 1 min before the induction of anesthesia. Patients and investigators were blinded to the study drug.

At induction of anesthesia, remifentanyl 1 µg/kg was injected, followed by an infusion of 0.25 µg/kg/min until skin closure. A Diprifusor™ (AstraZeneca,

Södertälje, Sweden) pharmacokinetic model (Fresenius Vial S. A., Brézius, France) was used for propofol infusion to a target plasma concentration of 4 µg/mL for intubation, which was adjusted thereafter to between 2 and 4 µg/mL. Atracurium was administered to facilitate endotracheal intubation. Tramadol, 2 mg/kg for 10 min, was given at discontinuation of remifentanyl. A PCA pump (Pain Management Provider; Abbott Laboratories, North Chicago, IL) was programmed as follows: tramadol, 24 mg IV bolus; lockout time, 5 min; 4-h dose limit, 384 mg. The PCA system automatically recorded the doses.

Patients who required supplemental medication for analgesia could receive a single 100-mg tramadol top-up dose, or 5 mg piritramid, a synthetic opioid (Dipidolor®; Janssen Pharmaceutica, Beerse, Belgium). Simultaneous use of the PCA pump was always permitted. Nausea or vomiting was treated with alizapride 50–100 mg IV. Patients in both study groups were given 2 g IV propacetamol (Prodafalgan®; Upsamedica s.a., Brussels, Belgium) at 6-h intervals after discharge from the recovery unit. Other analgesic or sedative drugs than those mentioned above, were prohibited.

Patients were observed for 4 h in the recovery unit by study nurses. Pain was evaluated at rest with a 100-mm long visual analog scale, where 0 mm represented no pain and 100 mm represented the worst imaginable pain. The degree of sedation was rated on a 4-point scale, and the presence of postoperative nausea and vomiting (PONV) was registered. A verbal retrospective pain score (4) was obtained 24 h after discharge from the recovery unit by using a 5-point scale. Overall satisfaction with pain relief was recorded.

Differences between the two groups were compared by using two-tailed unpaired *t* tests, χ^2 analysis, and Mann-Whitney ranked sum tests. The cumulative incidence of PONV was compared by using the log rank

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Address correspondence to Jan De Witte, MD, Department of Anesthesia and Intensive Care, OLV-Hospital, Aalst, Belgium. Address e-mail to jan.de.witte@olvz-aalst.be. ¹Maroof M, Moied AS, Bano S, Khan RM. Ondansetron inhibits the analgesic effect of tramadol hydrochloride [abstract]. *Anesth Analg* 1996;82:S296.

Table 1. Demographic Characteristics and Anesthetic and Surgical Variables

	Ondansetron	Control
Patients (<i>n</i>)	20	20
Age (yr)	56 ± 9	54 ± 14
Weight (kg)	85 ± 18	76 ± 15
Height (cm)	170 ± 8	168 ± 10
Body mass index (kg/m ²)	29 ± 6	27 ± 5
Sex (M/F)	10/10	9/11
ASA physical status (I/II)	10/10	9/11
Levels of laminectomy (<i>n</i>)	2 ± 0.9	2 ± 0.9
Duration of surgery (min)	52 ± 17	52 ± 14
Duration of anesthesia (min)	82 ± 21	80 ± 18

Data are presented as mean ± SD, or as number of patients.

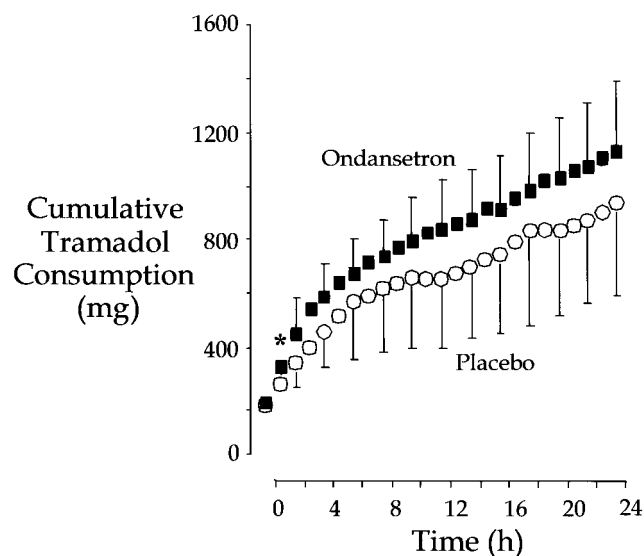


Figure 1. Cumulative tramadol consumption was larger in the Ondansetron than Control group during the first 24 h postoperatively. Tramadol consumption on an hourly basis did not differ significantly between the groups except during the first postoperative hour: 155 ± 83 mg in the Ondansetron group versus 86 ± 54 mg in the Control group. (**P* = 0.003).

Table 2. Postoperative Responses

	Ondansetron	Control
PONV (4-h cumulative incidence) (%)	5%	20%
PONV (24-h cumulative incidence) (%)	40%	50%
Shivering (%)	5%	15%
Sweating (%)	30%	5%
Dizziness (%)	0%	10%
Sedation first postoperative hour (0-3)	0.9 ± 0.6	0.8 ± 0.5
Global VAS pain in recovery unit (mm)	35 ± 16	38 ± 17
VAS pain 8 h postoperatively (mm)	22 ± 18	20 ± 19
VAS pain 12 h postoperatively (mm)	18 ± 19	15 ± 20
VAS pain 24 h postoperatively (mm)	18 ± 20	13 ± 17
Retrospective pain score (0-5)	1.1 ± 0.9	1.4 ± 1.0
Similar future analgesia (no/yes)	2/18	3/17
Global pain relief (insufficient/don't know/sufficient)	1/1/18	1/2/17

Data are presented as mean ± SD, *n*, or proportion (%).
PONV = postoperative nausea and vomiting, VAS = visual analog scale.

test. All results were presented as means ± SD; *P* < 0.05 was considered statistically significant.

Results

The patient groups were comparable with respect to age, weight, height, ASA physical status, and duration of surgery (Table 1).

Cumulative tramadol consumption was larger in the Ondansetron group than in the Control group during the first 24 h (Fig. 1). From 1 to 4 h postoperatively, cumulative tramadol consumption was between 26% and 35% more in the patients given ondansetron (*P* < 0.01), remaining 22%–25% more thereafter (*P* < 0.05). Tramadol consumption on an hourly basis did not differ significantly between the groups, except for the first postoperative hour: 155 ± 83 mg in the Ondansetron group versus 86 ± 54 mg in the Control group (*P* = 0.003). A single rescue dose of tramadol 100 mg, was given to eight patients in each study group. Piritramid was required in four patients given ondansetron and two patients given saline.

Pain scores decreased comparably in both study groups in the recovery unit and on the surgical ward (Table 2). There were no significant differences in frequency or severity of side effects in the two groups (Table 2). No significant differences existed for the cumulative 1-, 2-, 4-, 8-, and 12-h incidence of PONV. Overall, the 24-h incidence of PONV was similar in the two groups: 40% in the patients given ondansetron and 50% in the patients given saline (*P* = 0.47).

Discussion

Cumulative tramadol consumption was significantly increased in the Ondansetron group, thus confirming

our hypothesis. In contrast to the initial large tramadol requirement, subsequent hourly tramadol consumption on the ward was similar in both groups and of a magnitude reported by others (5). This is hardly surprising, because ondansetron was given only once and has a mean plasma half-life of 3.5 hours in young men (20–40 years) and 4.3 hours in elderly patients (60–74 years) (6).

Our results suggest that tramadol will usually be effective when given at a rate near 24 mg/h (i.e., the bolus dose of our PCA system given hourly). The recommended maximum 24-hour dose of 400 mg of tramadol thus seems insufficiently large for treatment of severe acute postoperative pain.

Tramadol administration is associated with a disturbingly frequent incidence of PONV, which often leads to discontinuation of PCA (7). In a recent study, ondansetron failed to reduce the nausea associated with tramadol (8). Our results indicate that ondansetron 4 mg administered at the induction of anesthesia does not reduce the incidence of this complication in the recovery unit and later on. As an alternative for ondansetron, the administration of droperidol (an antiemetic with antidopaminergic activity) might be recommended. Droperidol suppresses PONV effectively in patients who receive tramadol PCA (9).

In conclusion, ondansetron decreases the analgesic effectiveness of tramadol. A single 4-mg dose of ondansetron given at the induction of anesthesia does not reduce the 24-h incidence of PONV.

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References

1. Driessen B, Reimann W. Interaction of the central analgesic tramadol, with the uptake and release of 5-hydroxytryptamine in the rat brain in vitro. *Br J Pharmacol* 1992;105:147–51.
2. Raffa RB, Friderichs E, Reimann W, et al. Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an “atypical” opioid analgesic. *J Pharmacol Exp Ther* 1992;260:275–85.
3. Alhaider AA, Lei SZ, Wilcox GL. Spinal 5-HT₃-mediated antinociception: possible release of GABA. *J Neurosci* 1991;11:1881–8.
4. Lehmann KA, Kratzenberg U, Schroeder-Bark B, Horrichs-Haermeyer G. Postoperative patient-controlled analgesia with tramadol: analgesic efficacy and minimum effective concentrations. *Clin J Pain* 1990;6:212–20.
5. Jellinek H, Haumer H, Grusshofer G, et al. Tramadol zur postoperativen schmerztherapie: patientenkontrollierte analgesie. *Anaesthesist* 1990;39:513–20.
6. Simpson KH, Hicks FM. Clinical pharmacokinetics of ondansetron: a review. *J Pharm Pharmacol* 1996;48:774–81.
7. Silvasti M, Svartling N, Pitkänen M, Rosenberg PH. Comparison of intravenous patient-controlled analgesia with tramadol versus morphine after microvascular breast reconstruction. *Eur J Anaesthesiol* 2000;17:448–55.
8. Broome IJ, Robb HM, Raj N, et al. The use of tramadol following day-case oral surgery. *Anaesthesia* 1999;54:266–96.
9. Ng KF, Tsui SL, Yang JC, Ho ET. Comparison of tramadol and tramadol/droperidol mixture for patient-controlled analgesia. *Can J Anaesth* 1997;44:810–5.