

# Ondansetron Inhibits the Analgesic Effects of Tramadol: A Possible 5-HT<sub>3</sub> Spinal Receptor Involvement in Acute Pain in Humans

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To investigate a possible antinociceptive role of serotonin receptor subtype 3 (5-HT<sub>3</sub>), we evaluated the effects of a coadministration of ondansetron, a 5-HT<sub>3</sub> selective antagonist, and tramadol, a central analgesic dependent on enhanced serotonergic transmission. Fifty-nine patients undergoing ear, throat, and nose surgery, using tramadol for 24-h postoperative patient-controlled analgesia (bolus = 30 mg; lockout interval = 10 min) were randomly allocated either to a group receiving ondansetron continuous infusion (1 mg · mL<sup>-1</sup> · h<sup>-1</sup>) for postoperative nausea and vomiting (Group O) or to a control group receiving saline (Group T). Pain and

vomiting scores and tramadol consumption were evaluated at 4, 8, 12, and 24 h. Pain scores were never >4, according to a 0–10 numerical rating scale, in both groups. Group O required significantly larger doses of tramadol at 4 h (213 versus 71 mg, *P* < 0.001), 8 h (285 versus 128 mg, *P* < 0.002), and 12 h (406 versus 190 mg, *P* < 0.002). Vomiting scores were higher in Group O at 4 h (*P* < 0.05) and 8 h (*P* = 0.05). We conclude that ondansetron reduced the overall analgesic effect of tramadol, probably blocking spinal 5-HT<sub>3</sub> receptors.

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Ondansetron is an antiemetic for which indication is extended to the prophylaxis and treatment of postoperative nausea and vomiting. Tramadol is a central analgesic effective for the management of postoperative pain. Tramadol is safe, particularly regarding the minimal incidence of respiratory depression (1,2). The concomitant use of these drugs postoperatively is therefore a concrete possibility, even more so because vomiting is tramadol's adverse effect.

Ondansetron is a potent and selective competitive antagonist at serotonin (5-hydroxytryptamine, 5-HT) subtype 3 (5-HT<sub>3</sub>) receptors, whereas tramadol, initially considered a pure opioid, subsequently proved to be a reuptake inhibitor and a release enhancer of norepinephrine and 5-HT (3–5). Hence, we hypothesized that this drug combination could induce mutually contrasting modifications on the 5-HT<sub>3</sub> receptor-mediated serotonergic transmission, and particularly that ondansetron-induced receptor antagonism could enhance or weaken tramadol-induced analgesia. In fact, animal testing suggests both a pro- and an antinociceptive role for 5-HT<sub>3</sub>

neural receptors, depending on their peripheral or central expression. Given tramadol's central action, we wanted to verify whether postoperatively administered ondansetron would increase tramadol demand during patient-controlled analgesia (PCA).

## Methods

The study was approved by our institutional ethics committee, and all patients provided written informed consent. Excluded from the study were: pregnant or lactating women; patients <18 yr old; those with ASA physical status IV or above; patients unable to operate PCA; those with a known allergy to tramadol or ondansetron; those with a known history of motion sickness, epilepsy, or substance/alcohol abuse; and patients who received treatment with antiemetic drugs in the month before surgery. Antidepressants can interfere with serotonergic and adrenergic neurotransmission with tramadol-like actions, and the combined administration of monoamine oxidase inhibitors and tramadol represents one of the few cases of potentially lethal pharmacological interaction known for this analgesic (6). Therefore, the presence of antidepressants in the pharmacological anamnesis has been regarded

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as an absolute exclusion criterion for methodological and clinical safeguard.

Patients scheduled to undergo neck dissection or mastoidectomy were eligible for the study. The choice of these surgical interventions relies on the high demolitive component, granting a complete triggering of nociceptive mechanisms, and on the availability of preexisting references on the assessment of the related postoperative pain intensity (7).

During each of the 2 preoperative days, all patients were given instructions on the use of PCA and the 11-point verbal numerical rating scale (NRS) (0 = no pain, 10 = maximal pain ever suffered) to assess pain intensity.

General anesthesia was induced with IV propofol (1.9–2.8 mg/kg), a single bolus of remifentanyl (0.75  $\mu$ g/kg), and vecuronium bromide (0.1 mg/kg). Endotracheal intubation was performed, and intermittent positive ventilation provided to achieve an  $\text{EtCO}_2$  = 30–35 mm Hg. Anesthesia was maintained with  $\text{N}_2\text{O}$  (60% in  $\text{O}_2$ ) plus sevoflurane; continuous-infusion remifentanyl (0.25  $\mu$ g/kg) was used for intraoperative analgesia and vecuronium (2-mg boluses as needed) for muscle paralysis. All patients had an oral gastric tube placed intraoperatively and maintained during the 24-h study period.

The protocol began at awakening, reached when the patient correctly identified his birthdate among three written alternatives. An anesthesiologist asked each subject to indicate his pain level at that time; if the NRS pain score was  $>4$ , tramadol 50 mg IV was administered. Evaluations were performed after 5 min for 4 times total. Patients with an NRS  $>4$  after the fourth assessment (i.e., 4 boluses of tramadol 50 mg administered) were excluded from further study and received morphine.

According to random selection of sealed envelopes, eligible patients were allocated to one of two treatment groups: Group T (tramadol and saline) or Group O (ondansetron and tramadol).

In the recovery room, all subjects were connected to a PCA device (Rythmic PCAP; Alaris Medical System, San Diego, CA) and a balloon infuser (Nipro Surefuser, 1 mL/h; Nissho Corp., Osaka, Japan). PCA pumps were filled with tramadol 10 mg/mL in saline solution and set with a bolus of 3 mL (corresponding with tramadol 30-mg demand dose), a lockout interval of 10 min, and a daily maximal dose of 900 mg.

In Group O, the balloon devices were filled with ondansetron 1 mg/mL in saline (total volume = 24 mL), with a drug infusion rate of 1 mg/h. In Group T, the elastomer contained 24 mL of saline. According to the manufacturer's guarantee on the balloon infuser, it operates reliably with diluted solutions and with an attested deviation between the effective and the declared flow always  $\leq 10\%$ . All nurses and physicians in the recovery room and wards were blinded

to the infuser contents, prepared by the hospital pharmacist.

At 4-h intervals during the following 12 h and at 24 h after pump connection, the same two anesthesiologists always recorded the following data: blood pressure, heart rate, respiratory rate, and oxygen saturation; tramadol consumption through the number of boluses released by the PCA pump; NRS; and degree of nausea, vomiting, and sedation by using 3 separate 4-point scoring scales (Table 1). Patient evaluation of the overall analgesic technique as good, fair, and bad (needing a discontinuation of the PCA pump) was also recorded.

The primary outcome variable was tramadol consumption between the groups, establishing as clinically relevant the one-third increase in Group O. However, previous studies that could be used as references for the standard deviation calculation were not found. Therefore, for the determination of the sample dimension ( $n$ ), and the requirement of a power of 0.8 and a bilateral significance level of 0.05, we hypothesized a critical ratio between estimated standard deviation ( $s$ ) and average difference between the two groups ( $\delta$ ), such that  $s/\delta = 1.33$ . Then, the power analysis estimated as necessary  $n > 28$  and we aimed for 30 patients in each group to prevent patient dropout.

Statistical analysis was performed by using the Mann-Whitney  $U$ -test for nonparametric data, such as nausea and vomiting scores, pain scores, and patient demographics; parametric data were compared by using the two-tailed independent  $t$ -test. Significance level was set at  $P < 0.05$ , and data were presented as mean (SD).

Tramadol was provided by Farmaceutici Formenti S.p.A. (Italy) as Contramal<sup>®</sup> 100-mg vials; ondansetron was provided by Glaxo Wellcome S.p.A (Italy) as Zofran<sup>™</sup> 8-mg vials.

## Results

Fifty-nine patients were studied, 30 in Group T and 29 in Group O. One subject in Group O was excluded from the study because of repeated problems with the infusion line. Patient demographic data, duration of anesthesia, and the number requesting rescue tramadol were similar between the groups (Table 2).

No difference was observed in pain scores, at any interval, between the two treatment groups throughout the study period (Fig. 1). No patient was excluded because of inadequate analgesia.

Group O requested significantly larger amounts of tramadol in the initial 4 h (213 mg [101] versus 71 mg [54],  $P < 0.001$ ), as well as 8 h (285 mg [132] versus 128 mg [85],  $P < 0.002$ ) and 12 h (406 mg [188] versus 190 mg [126]  $P < 0.002$ ) after the operation. During the

**Table 1.** Scoring for Nausea, Vomiting, and Sedation

Condition	Scoring criteria
Nausea	0 = No nausea
	1 = Mild nausea, not requesting pharmacological rescue
	2 = Nausea, requesting pharmacological rescue
	3 = Nausea resistant to pharmacological treatment
Vomiting	0 = No vomiting
	1 = Vomiting, single event
	2 = Vomiting, repeated events requesting pharmacological rescue
	3 = Vomiting resistant to pharmacological treatment
Sedation	0 = Patient fully awake
	1 = Patient slightly drowsy
	2 = Patient sleeping but easily arousable
	3 = Patient unconscious, not arousable

last interval (12–24 h), there was no difference (484 mg [230] versus 314 mg [212]) (Fig. 2).

Notably, the peak total daily dose demanded by some subjects in Group O (900 mg) exceeded the upper recommended level of tramadol dose (600 mg), referred to as adequate and well tolerated, when administered via PCA for postoperative pain.

Patients in Group O had significantly higher vomiting scores at 4 h ( $P = 0.04$ ) and at 8 h ( $P = 0.05$ ) postoperatively (Fig. 3); there were no differences in the nausea scores.

There were no differences in sedation scores at any interval during the observed period; blood pressure, heart rate, respiratory rate, and oxygen saturation always remained within the range of clinical safety.

Twenty-one patients (70%) judged their PCA experience as good overall, 9 (26.7%) as fair, and 1 (3.3%) as bad in Group T; 17 (58.7%) as good, 11 (37.9%) as fair, and 1 (3.4%) as bad in Group O. The differences were not significant ( $P = 0.47$  in Mann-Whitney  $U$ -test).

## Discussion

Serotonin plays a key role in pain control mechanisms and affects nociception through a variety of specific receptors, including 5-HT<sub>1A-D</sub>, 5-HT<sub>2A-C</sub>, 5-HT<sub>3</sub>, and 5-HT<sub>4</sub> (3,8). Animal studies designed to clarify their role in pain modulation along the spinal serotonergic pathways have been performed using local injection of selective agonists and antagonists at different receptor subtypes. Therefore, the interaction between ondansetron, as antagonist, and tramadol, as agonist release inducer, can be conceived as an emulation of such protocols.

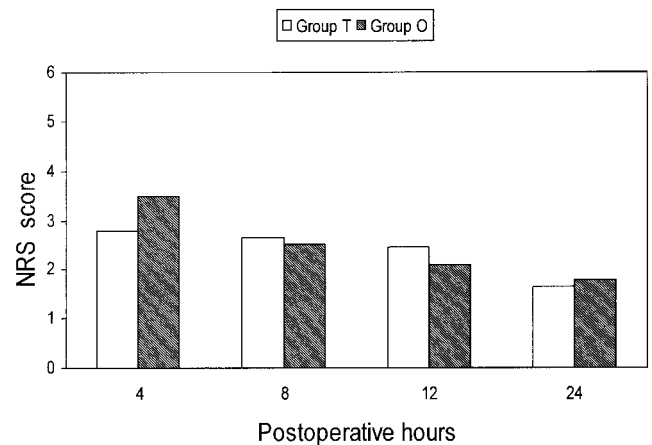
The antiemetic properties of ondansetron are based on the block of the chemoreceptor trigger zone and enteric neuron 5-HT<sub>3</sub> receptors. Identical receptors are expressed by the nociceptive primary afferent fibers (PAF)

**Table 2.** Demographic Data and Operative Details

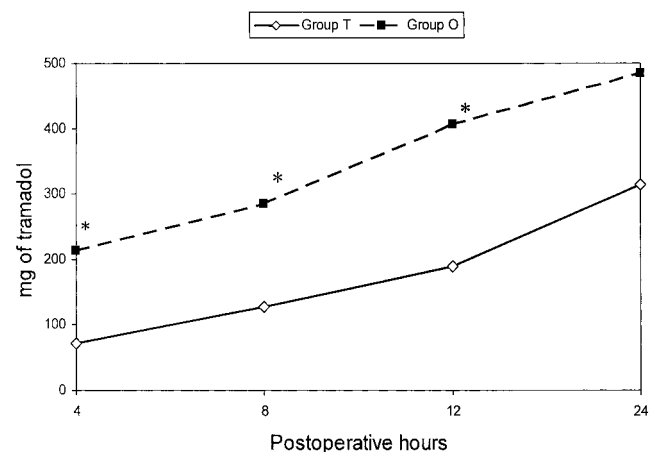
Group	Tramadol (n = 30)	Ondansetron (n = 29)
Age (yr)	62 (11)	63 (6)
Sex (Male/Female)	27/3	25/4
Body weight (kg)	79 (13)	75 (11)
Operation duration (h)	5.9 (2.0)	5.5 (1.3)
Requesting rescue tramadol <sup>a</sup>	6 (50)	5 (50)
	3 (100)	2 (100)
ASA physical status <sup>a</sup> I/II/III	14/12/4	13/11/5

Values are means (sd).

<sup>a</sup> Number (milligrams of tramadol).

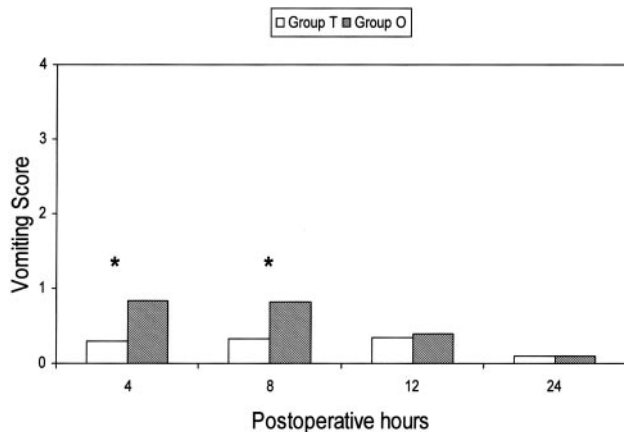


**Figure 1.** Pain score on numerical rating scale (NRS) (0–10) in the postoperative 24 h. There were no differences between groups during the study period. Values are means (Mann-Whitney  $U$ -test for group comparisons). Group T, n = 30, Group O, n = 29.



**Figure 2.** Tramadol (in milligrams) delivered in the postoperative 24 h. In Group O, consumption was significantly larger in the first 12 h. Values are means (unpaired  $t$ -test for group comparisons). \* $P < 0.05$ . Group T, n = 30, Group O, n = 29.

either on the peripheral free terminal and centrally, on their spinal terminal, and by the neurons of the superficial laminae of the dorsal horn (9,10). Intravenous or intradermal 5-HT strengthens (and, physiologically,



**Figure 3.** Vomiting score in the postoperative 24 h. Group O showed significantly higher scores in the first 8 h. Values are means (Mann-Whitney *U*-test for groups comparison). \**P* < 0.05. Group T, *n* = 30, Group O, *n* = 29.

participates in the onset of) the inflammation-associated pain in humans (11,12), but intrathecal administration exerts antinociceptive effects (13). This central effect can be interpreted as equivalent to the inhibition, produced by the nucleus raphe magnus serotonergic neurons, on the nociceptive stimuli conveyed in the dorsal horn by the PAF (14–16). The likely 5-HT<sub>3</sub> receptor involvement in all these events suggests that the same receptors mediate not only multiple, but opposing net results too, depending on different locations in the nociceptive circuit. Whereas the 5-HT<sub>3</sub> receptors on PAF—from the nociceptors up to the dorsal horn—mediate a pronociceptive action, only those postsynaptically located in regard to PAF allow the antinociceptive effect of endogenous (5-HT) or administered agonists (8,17). Accordingly, Peng et al. (18) prevented periaqueductal gray matter electrostimulation-induced analgesia, blocking spinal 5-HT<sub>3</sub> receptors by ondansetron.

However, in the mouse, the tramadol antinociceptive activity on the spinal ascending fibers and that produced by 2-methyl 5-HT (a selective 5-HT<sub>3</sub> agonist) are poorly antagonized by naloxone (19), but the intrathecal tramadol analgesia is reversed by the antiserotonergic ritanserin (20). Thus, it seems that, between the two modes of action of tramadol, the monoaminergic mode seems to be crucial at the dorsal horn level.

Undoubtedly, the 5-HT released upon tramadol action binds all 5-HT receptor subtypes, but, because of selective ondansetron antagonism, we assume that the described inhibition of tramadol analgesia could consist of a reduction of binding 5-HT<sub>3</sub> receptors at the spinal level.

Such a possible interference may have practical consequences. In terms of a theoretical “equipotency,” using ondansetron as antiemetic makes tramadol approximately 50% less potent than when used alone.

The progressive slowing of tramadol consumption in Group O could be only apparently paradoxical.

Increasing doses and concentrations of ondansetron seemingly allow the onset of analgesic effects, acting on peripheral 5-HT<sub>3</sub> receptors and/or blocking the sodium channels (21).

The higher vomiting score in Group O seems to be correlated to the intensity of tramadol use in the first eight hours, induced by ondansetron. Broome et al. (22) had previously reported similar effects on postoperative nausea and vomiting with this drug combination. Tramadol seems to be too weak an opioid to exclusively sustain  $\mu$ -related vomiting, and the ondansetron doses reached at four and eight hours cannot be defined as insufficient for a pure 5-HT<sub>3</sub> receptor-mediated emesis (23). Therefore, we can only hypothesize that tramadol causes emesis, allowing it to keep a high, and not adequately counterbalanced, adrenergic tone, on  $\alpha_1$  and  $\alpha_2$  receptors in *area postrema* (24).

We conclude that the concomitant administration of ondansetron reduces tramadol’s analgesic power on postoperative pain. This suggests 5-HT<sub>3</sub> receptor involvement in antinociception in humans. Finally, a practical implication: with this association, the increased tramadol dose in the first 12 treatment hours provides effective analgesia, but also an emetic stimulation not well controlled by ondansetron itself. Therefore, the postoperative use of tramadol is not recommended with ondansetron as the first choice antiemetic.

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