The Effects of Tramadol and Morphine on Immune Responses and Pain After Surgery in Cancer Patients

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There has been growing interest in determining the possible immune consequences of opioid administration for the management of postoperative pain. We studied the effects of morphine and tramadol on pain and immune function during the postoperative period in 30 patients undergoing abdominal surgery for uterine carcinoma. Phytohemoagglutinin-induced T lymphocyte proliferation and natural killer cell activity were evaluated immediately before and after surgery, and 2 h after the acute administration of either 10 mg of morphine IM or 100 mg tramadol IM for pain. In all patients, phytohemagglutinin-induced lymphoproliferation was significantly depressed by surgical stress. However, in the morphine-treated group, proliferative values remained lower than basal levels for 2 h after treatment, whereas in tramadol-administered patients proliferative values returned to basal levels. Natural killer cell activity was not significantly affected by surgery nor by morphine administration, whereas tramadol significantly enhanced the activity of natural killer cells. Both drugs produced a comparable reduction in postoperative pain. We conclude that, as previously observed in the experimental animal, tramadol and morphine, when administered in analgesic doses, induce different immune effects.

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Several studies conducted in animals and humans have shown that opioids can exert immunosuppressive effects (1–3). In particular, acute, as well as chronic administration of morphine decreases lymphoproliferation, natural killer (NK) activity, macrophage functions, and the production of interferon-γ and interleukin-2 in the rodent (2). Consistent with these observations, opioid administration has been associated with increased susceptibility of animals to bacterial and viral infections (4), and with decreased survival in tumor-bearing animals (5). Similar effects have been shown in humans, in which most studies have been performed in IV-opioid abusers (4) and relatively few in subjects exposed to opioids for therapeutic reasons (6,7).

It is well known that the activation of endocrine and sympathetic nervous systems during surgery leads to a transient period of immunosuppression (8–10). The therapeutic use of morphine might, therefore, be relatively contraindicated in the postoperative period, in which the functionality of the immune system is already compromised by stress exposure. Tramadol is a centrally acting, analgesic drug, with a double mechanism of action; it binds with low affinity to μ-opioid receptors, and activates central monoaminergic pathways inhibiting the neuronal uptake of serotonin and noradrenaline (11,12). We previously showed that, in mice, in contrast to morphine, tramadol did not suppress cellular immune functions, whereas it increased NK activity, lymphocyte proliferation, and interleukin-2 production (13).

For all of these reasons, we wanted to study, in humans, the effects on immune responses of tramadol and morphine administered for acute treatment of postoperative pain in cancer patients. We evaluated the impact of surgical stress and drug administration on two typical immune functions, proliferation of T lymphocyte and NK activity. Proliferation of T lymphocyte is a reliable index of the ability of these cells to undergo clonal expansion after antigen stimulation, and NK cells are a population of lymphocytes important in tumor surveillance and in defense against viral infections (14).

Methods

A total of 30 patients undergoing abdominal surgery for uterine carcinoma entered the study. These patients had never received radiotherapy, chemotherapy, nor immunosuppressive drugs. After informed

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consent, and approval of the ethical committee of the Department of Pharmacology, University of Milano, Italy, patients were randomized into one of the two study groups according to a computer-generated, randomized list.

In all patients, after the IV induction with fentanyl 1 μg/kg, thiopental 5 mg/kg, and succinylcholine 1 mg/kg, anesthesia was maintained with isoflurane 1.5–1.7 minimum alveolar anesthetic concentration (% inspiration 1.6:1.2 and % expiration 1.2:1.0), 66% nitrous oxide in oxygen and pancuronium 0.07 mg/kg. Immediately after the end of surgery, patients were given an IM injection of either 10 mg of morphine HCl or 100 mg of tramadol. At 2 h after the administration of morphine or tramadol, pain was assessed by using visual analog scale (VAS) (scores 0–100), and the degree of sedation was evaluated by clinicians with scores from 0 to 4, where 0 = awake, 1 = easily aroused, 2 = awakens after tactile stimulation, 3 = awakens after verbal stimulation, and 4 = not arousable. Both evaluations were performed by clinicians unaware of patient treatment group.

Blood was withdrawn before the beginning of surgery, before drug administration, and 2 h after drug administration. Blood was collected into tubes containing EDTA. Peripheral blood mononuclear cells were separated by gradient centrifugation over Ficoll-Paque (Amersham Pharmacia Biotech, Milano, Italy) as described by Manfredi et al. (15). Microcultures of fresh peripheral blood mononuclear cells were set up in triplicate for each sample (10^6 cells/mL) in RPMI 1640, 10% fetal calf serum with or without Phytohemoagglutinin (4, 1, and 0.25 μg/mL) (15).

Background values, (<1000 cpm), i.e., thymidine incorporation by unstimulated cells, were subtracted from values of mitogen-induced proliferation. NK cell activity was evaluated by using a standard 4-h ^{51}Cr-release assay, with K562 cells as target cells (16,17). ^{51}Cr-labeled K562 (target cells) were incubated with splenocytes (effector cells) at effector/target cell ratios of 100:1.

Specific ^{51}Cr release was calculated according to the formula:

$$100 \times [(\textit{experimental release} - \textit{spontaneous release})/$$
$$(\textit{maximal release} - \textit{spontaneous release})]$$

All of the immunological analysis were performed in a blinded fashion by researchers unaware of patient treatments. A sample size of 15 patients in each group has 80% power to detect a difference of 1 SD between the means of Group 1 and Group 2, assuming that the common SD is 1 by using a two-tailed *t*-test with a 0.05 two-sided significance level. Demographic data of patients and VAS values were analyzed by using one-way analysis of variance and the degree of sedation measured by Mann-Whitney *U*-test. Lymphocyte proliferation and NK activity were analyzed by using mean of one-way analysis of variance for repeated measures.

Results

Patient characteristics were homogeneous in the two groups. Indeed, no statistical differences were observed considering age (50 ± 14 vs 51 ± 15 yr), weight (66 ± 13 vs 65 ± 13 kg), and the duration of surgery (126 ± 33 vs 122 ± 35 min). No patient needed blood transfusion during or after surgery.

The analgesic effects of acute tramadol and morphine were similar; in fact, the VAS values 2 h after the drug administration were not significantly different (tramadol 44 ± 19 mm; morphine 31 ± 20 mm). There was a comparable degree of sedation in the two treatment groups (scores, 1.3 ± 0.9 vs 1.6 ± 0.8).

As shown in Figure 1, immediately after the end of surgery, T lymphocyte proliferation was significantly lower than basal proliferative levels in all patients. At 2 h after the injection of the analgesic drugs, a different pattern of responses was observed in the two groups of patients. In the morphine-treated patients (Figure 1, left panel) lymphocyte proliferation was still significantly lower than in basal conditions. In contrast, the Phytohemoagglutinin-induced proliferation in the group of patients treated with tramadol was not significantly different from that observed before the beginning of surgery, whereas a significant difference was present in comparison with postsurgery values (Figure 1, right panel).

NK cell activity was not impaired after the end of surgery (Figure 2). However, morphine and tramadol induced different effects on this immune variable. Whereas a nonsignificant decrease of NK activity was observed 2 h after morphine administration (Figure 2, left), a significant increase of NK activity was present in the group of patients treated with tramadol (Figure 2, right).

Discussion

We previously showed, in mice, that morphine and tramadol exerted different effects on immune responses. Indeed, although morphine decreased lymphocyte proliferation and NK activity (2), the same variables were significantly enhanced by tramadol (13).

The current study was undertaken to evaluate whether similar effects could be described in humans. The postoperative period represents an interesting opportunity to address this problem, because it is known that surgical stress results in activation of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system, leading to an alteration of immune responses (8–10). Indeed, we observed a clear-cut

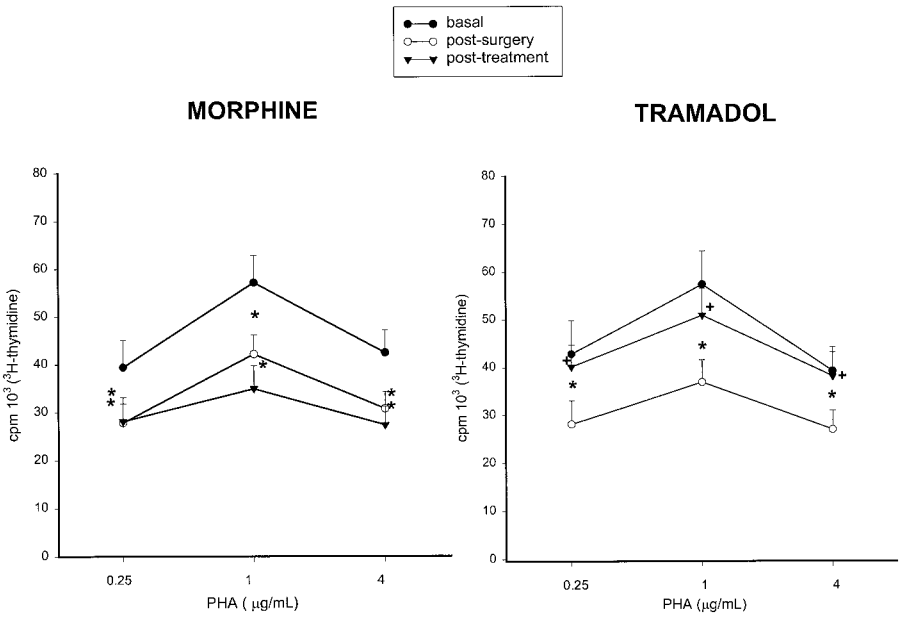

Figure 1. Phytohemoagglutinin (PHA) (0.25, 1.0, 4.0 μg/mL) induced proliferation of lymphocytes obtained from patients before the beginning of surgery (basal), immediately after surgery and predrug (postsurgery), and 2 h after treatment with 10 mg of morphine IM (left panel) or 100 mg of tramadol IM (right panel). Values are mean ± SD. *$P < 0.01$ versus basal. +$P < 0.01$ versus postsurgery.

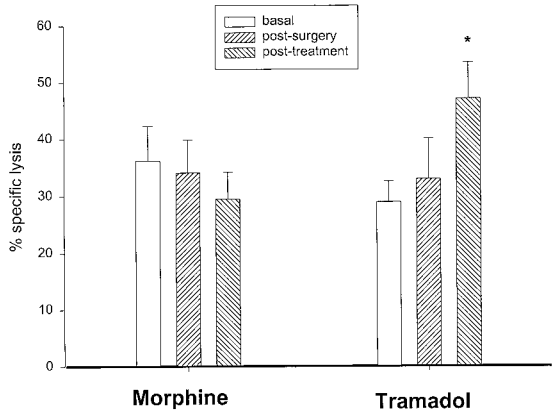

Figure 2. Natural killer cells activity obtained from patients before the beginning of surgery (basal), immediately after surgery and predrug (postsurgery), and 2 h after treatment with 10 mg of morphine IM or 100 mg of tramadol IM. Values are mean ± SD. *$P < 0.01$ versus basal.

decrease in T lymphocyte proliferation immediately after the end of surgery. Cancer patients enrolled in the study were not immunosuppressed, and before the surgical procedure, immune responses were comparable to those described in healthy people (16,17).

The impaired response of T lymphocytes persisted two hours after the administration of morphine, whereby after the administration of tramadol the lymphoproliferation was not different in comparison with presurgery values. Immunosuppression induced by surgical stress has generally been shown to last longer than two hours (18); however, from our study, it is difficult to hypothesize whether the lymphoproliferation levels would have returned to normal values in the absence of treatment with morphine.

We cannot say whether the apparently reestablished levels of lymphoproliferation observed after tramadol administration are caused by the immunostimulant properties of this drug, as was observed in mice (13), or the immune function was slowly returning to basal levels and no interference by tramadol was present. In any case, these findings indicate that tramadol does not exert immunosuppressive actions.

In contrast to what was observed with lymphocyte proliferation, surgery did not affect the cytotoxic activity of NK cells. These two immune variables seem, therefore, to show a different sensitivity to the stress induced by this type of surgical procedure. Although NK activity has generally been observed to be decreased after surgical stress (19,20), increased (21), as well as unchanged (22), NK activity in the perioperative period has also been reported. It is reasonable to suggest that different surgical procedures can produce different modifications of this variable. At two hours after morphine administration, no significant alteration of NK activity was present. Because it has been shown that the immunosuppressive effects of morphine are evident at doses larger than those needed for controlling pain (2), it is likely that doses larger than 10 mg of morphine are required to fully evidentiate the suppression of NK activity in humans. Whereas two hours after morphine administration there was no significant modification of NK activity in the group of patients treated with tramadol, a clear and significant increase of this immune variable was evident. These observations lead us to hypothesize a stimulatory effect of tramadol on NK activity. Taken together, these results confirm the pharmacological properties of tramadol observed in the experimental animal (13).

Morphine and tramadol share the opioid mechanism of action, although the affinity of tramadol for

ANESTHESIA & ANALGESIA

μ-opioid receptors is significantly lower than that of morphine. However, the antinociceptive effects of tramadol are mediated also via a separate, nonopioid mechanism, caused by the inhibition of neuronal uptake of noradrenaline and serotonin (11,12). These differences can account for the diverse pharmacodynamic profile of morphine and tramadol on immune functions.

The involvement of the noradrenergic and serotoninergic systems in neural-immune interactions has been studied by using different experimental models. Although both enhancement and reduction of immune responses have been related to the activation of the noradrenergic system (23), the increase of serotoninergic tone has usually been associated with stimulation of NK activity and lymphocyte proliferation (24,25). Consistent with these observations, drugs which increase serotoninergic tone, such as D-fenfluramine and fluoxetine, stimulate immune function in rodents (24) and our unpublished results. Moreover, in the mouse, we observed that the immune effects of tramadol on lymphoproliferation and NK activity were prevented by the administration of the nonspecific serotoninergic antagonist metergoline (25), indicating an involvement of the serotoninergic system in the immune effects of this drug. Interestingly, we have observed (our unpublished results) that tramadol, when added *in vitro* to splenocyte cultures, was not able to modulate either proliferation or NK activity, thus eliminating a direct effect of the drug on immune cells. Therefore, it can be suggested that activation of the serotoninergic system might be involved in the immune effects of tramadol in experimental and clinical conditions.

In conclusion, we have confirmed in humans that the immune function is differently affected by morphine and tramadol. Analgesic drugs devoid of immunosuppressive effects might offer a good alternative to morphine for the treatment of postoperative pain.

References

1. Peterson PK, Molitor TW, Chunc CC. Mechanism of morphine-induced immunomodulation. Biochem Pharmacol 1993;46:343–8.
2. Sacerdote P, Manfredi B, Mantegazza P, Panerai AE. Antinociceptive and immunosuppressive effects of opiate drugs: a structure-related activity study. Br J Pharmacol 1997;121:834–40.
3. Eisenstein TK, Hilburger ME. Opioid modulation of immune responses: effects on phagocyte and lymphoid cell populations. J Neuroimmunol 1998;83:36–44.
4. Risdahl JM, Khanna KV, Peterson KW, Molitor TW. Opiates and infections. J Neuroimmunol 1998;83:4–18.
5. Yeager MP, Colacchio TA. Effect of morphine on growth of metastatic colon cancer *in vivo*. Arch Surg 1991;126:454–6.
6. Provinciali M, Di Stefano G, Raffaeli W, et al. Evaluation of NK and LAK cell activities in neoplastic patients during treatment with morphine. Int J Neurosci 1991;59:127–33.
7. Yeager MP, Colacchio TA, Yu CT, et al. Morphine inhibits spontaneous and cytokine enhanced natural killer cell cytotoxicity in volunteers. Anesthesiology 1995;83:500–8.
8. Udelsman R, Blake MJ, Holbrook NJ. Molecular response to surgical stress. Surgery 1991;110:1125–31.
9. Saito T, Kinoshita T, Shigemitsu Y, et al. Impaired humoral immunity is associated with development of methicillin-resistant *Staphylococcus aureus* infections after esophageal surgery. J Infect Dis 1992;166:1459–60.
10. Colacchio TA, Yeager MP, Hildebrandt LW. Perioperative immunomodulation in cancer surgery. Am J Surg 1994;167:174–9.
11. 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.
12. Driessen B, Reimann W, Giertz H. Effects of the central analgesic tramadol on the uptake and release of noradrenaline and dopamine *in vitro*. Br J Pharmacol 1993;108:806–11.
13. Sacerdote P, Bianchi M, Manfredi B, Panerai AE. Effects of tramadol on immune responses and nociceptive thresholds in mice. Pain 1997;72:325–30.
14. Herberman RB, Hortaldo JR. Natural killer cells: their role in defenses against disease. Science 1981;214:24–30.
15. Manfredi B, Sacerdote P, Bianchi M, et al. Evidence for an opioid inhibitory effect on T cell proliferation. J Neuroimmunol 1993;44:43–8.
16. Nagy Z, Sipka R, Ocsovszki I, et al. Suppressive effect of pentoxifylline on natural killer activity: experimental and clinical studies. Naunyn-Schmiedebergs Arch Pharmacol 1999;359:228–34.
17. Robertson MH, Ritz J. Biology and clinical relevance of human natural killer cells. Blood 1990;76:2421–38.
18. Hammer JH, Nielsen HJ, Moesgaard F, Kehlet H. Duration of postoperative immunosuppression assessed by repeated delayed type hypersensitivity skin test. Eur Surg Res 1992;24:133–7.
19. Pollock RE, Lotzova E, Stanford SD. Mechanism of surgical stress impairment of human perioperative natural killer cell cytotoxicity. Arch Surg 1991;126:338–42.
20. Nichols PH, Ramsden CW, Ward U, et al. Perioperative modulation of cellular immunity in patients with colorectal cancer. Clin Exp Immunol 1993;94:4–10.
21. Griffith C, Rees RC, Platts AD, et al. The nature of enhanced natural killer lymphocyte cytotoxicity during anesthesia and surgery in patients with benign disease and cancer. Ann Surgery 1984;200:753–8.
22. Tonnesen E, Mickley H, Grunnet N. Natural killer cell activity during premedication, anaesthesia and surgery. Acta Anaesthesiol Scand 1983;27:238–41.
23. Livnat S, Felten SY, Carlson SL, et al. Involvement of peripheral and central catecholamine systems in neural-immune interactions. J Neuroimmunol 1985;10:5–30.
24. Mossner R, Lesch KP. Role of serotonin in the immune system and in neuroimmune interaction. Brain Behav Immun 1998;12:249–71.
25. Sacerdote P, Bianchi M, Gaspani L, Panerai AE. Effects of tramadol and its enantiomers on concanavalin-A induced proliferation and NK activity of mouse splenocytes: involvement of serotonin. Int J Immunopharmacol 1999;21:727–34.