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Effects of Perioperative Oral Amantadine on Postoperative Pain and Morphine Consumption in Patients after Radical Prostatectomy

Results of a Preliminary Study

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Background: **Amantadine is known to be a noncompetitive *N*-methyl-D-aspartate receptor antagonist and may be useful in preventing postoperative central sensitization, acute opioid tolerance, and opioid-induced hyperalgesia, thereby decreasing pain and analgesic requirements. The aim of this pilot study was to evaluate the effects of perioperative oral amantadine on postoperative pain and analgesic consumption.**

Methods: **Twenty-four patients scheduled to undergo radical prostatectomy were given oral amantadine before and after surgery in a randomized, double-blind, placebo-controlled manner. After surgery, patients received intravenous patient-controlled analgesia with morphine for 48 h. Wound pain intensity, sensitivity to mechanical pressure around the surgical wound, and incidence of bladder spasm pain were assessed. Blood samples were drawn for analysis of amantadine, morphine, and the morphine metabolites. Adverse effects and patient satisfaction were assessed.**

Results: **The cumulative morphine consumption was significantly lower in the amantadine group at all time points (except at 48 h), amounting to a 32% reduction over the 48-h period. Forty-eight hours after surgery, visual analog pain scores to pressure applied near the wound were significantly lower in the amantadine group than in the placebo group. In addition, the number of patients reporting bladder spasm pain was significantly lower in the amantadine group. Plasma concentration of morphine-3-glucuronide was significantly lower at the end of surgery in the amantadine group. Pharmacokinetic analyses showed that the plasma clearance of morphine at 22–24 h after surgery was also significantly lower in the amantadine group.**

Conclusion: **The results suggest that perioperative oral amantadine reduces postoperative opioid consumption by pharmacokinetic mechanisms, although additional pharmacodynamic interactions may also be involved.**

CURRENTLY, a large body of evidence indicates that inadequate treatment of acute pain can have long-lasting effects. Brief noxious stimulation and frank injury may have profound effects on the central nervous system that long outlast the injury.[1] Intraoperative as well as postoperative pain results in a "barrage" of nerve impulses entering the spinal cord and the release, from small-diameter afferent C fibers, of excitatory amino acids and neuropeptides that induce a state of hyperexcitability in spinal dorsal horn neurons, leading to prolonged postoperative pain. This central nervous system plasticity, resembling a sort of "pain memory," is referred to as *central sensitization* and may contribute to persistent pain.

The *N*-methyl-D-aspartate (NMDA) receptor plays an important role in the process of central sensitization.[2,3] Excitatory amino acids, such as glutamate and aspartate, activate the NMDA receptor, leading to an increase in intracellular calcium and activation of second messengers, which stimulate protein kinases and modify neuronal excitability. NMDA receptor activation may also produce longer-lasting changes by stimulating new gene expression.

The role of the NMDA receptor in the development of central sensitization, acute opioid tolerance, and opioid-induced hyperalgesia has led to renewed interest in NMDA receptor antagonists for clinical use in humans.[1,4,5] Ketamine (for review, see Schmid *et al.*[6]) and dextromethorphan[7,8] have been studied almost to the exclusion of other clinically available substances that antagonize the NMDA receptor-ion channel complex.

One of these substances is amantadine (1-aminoadamantane). Amantadine has been in clinical use for more than 20 yr, and although it is used primarily for the treatment of Parkinson disease and as an antiviral drug, evidence shows amantadine to be a noncompetitive NMDA-receptor antagonist.[9,10] Therefore, amantadine may be useful in decreasing pain and analgesic requirements, possibly by preventing postsurgical central sensitization, acute opioid tolerance, and opioid-induced

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hyperalgesia. This randomized, double-blind, placebo-controlled pilot study was designed to evaluate the postoperative analgesic and opioid-sparing effects of amantadine given orally over the perioperative period in patients undergoing radical prostatectomy.

Materials and Methods

Selection and Randomization of Patients

Approval to conduct the study was obtained from the Toronto Hospital Committee for Research on Human Subjects (Toronto, Ontario, Canada). Eligible individuals were men scheduled to undergo radical retropubic prostatectomy. Inclusion criteria were the ability to speak English; age 18–75 yr; American Society of Anesthesiologists physical status class I–III; stable or no significant central nervous system, respiratory, cardiac, hepatic, renal, or endocrine dysfunction and/or any significant sequelae; no history of significant psychopathology; no history of chronic pain or chronic use of opioid and nonopioid analgesics; no previous allergies or adverse reactions to amantadine or opioid analgesics; no ingestion of antitussive medication (dextromethorphan) within 48 h after surgery; no history of alcohol or drug dependency/abuse; and a body weight between 60 and 90 kg with a body mass index of 30 kg/m^2 or less.

A member of the Acute Pain Research Unit saw all eligible patients in the preadmission clinic, where they were screened for suitability and interest. Patients were informed of the nature of the study and introduced to the visual analog scale (VAS), the patient-controlled analgesia (PCA) pump, and pressure algometry.

For the purpose of this preliminary study, it was decided to recruit 20 patients. Based on an anticipated attrition rate of 15–20% due to complications, adverse effects, protocol violations, and patient withdrawal, a total of 24 patients were recruited.

Patients were randomly assigned to one of two groups based on a predetermined randomization schedule.[11] Patients in the amantadine group received amantadine in a dose of 200 mg on the evening before surgery; 200 mg at 1 h before surgery; and 100 mg at 8, 20, and 32 h after surgery. Patients in the placebo group received placebo capsules at the same time as the patients in the amantadine group. Amantadine and placebo capsules were prepared by the Toronto General Hospital Pharmacy. One whole 100-mg amantadine capsule (Lot: 9AD0721; exp.: November 2001; Endo Pharmaceuticals, Chadds Ford, PA) was inserted into a No. 2 empty red gelatin capsule. For placebo capsules, No. 2 empty red gelatin capsules were filled with Lactose powder (Lot: 127665/12243; Bio-Health, Dawson Traders Limited, Toronto, Ontario, Canada). The amantadine and placebo capsules were coded and dispensed on a patient-by-patient basis by the pharmacy along with a sealed, opaque envelope containing the patient's number and group allocation. If the attending anesthetist/Acute Pain Service physician determined it to be necessary for optimal patient management, the envelope was to be opened and the code was to be broken.

The study was double blind in that all patients and personnel involved in patient care, data collection, scoring, and entry were unaware of the group to which the patient had been assigned.

General Anesthesia

Midazolam, 1–2 mg, was administered intravenously to all patients 10 min before the anticipated time of induction of general anesthesia. A dosage of 2.5 μg/kg fentanyl was administered 60 s before induction with thiopentone (3–5 mg/kg). Muscle relaxation and tracheal intubation were facilitated with rocuronium bromide (0.6–0.9 mg/kg). Anesthesia was maintained with 60%/40% N_2O–O_2 and isoflurane aimed at an end-tidal concentration of 0.6%. Muscle relaxant was given as necessary. Morphine (75 μg/kg) was given intravenously to maintain blood pressure and heart rate within 10% of baseline values. At the conclusion of surgery, neuromuscular blockade was reversed (when necessary) with neostigmine (0.05 mg/kg) and glycopyrrolate (0.01 mg/kg). During the surgical procedure, patients were continuously monitored with an electrocardiogram, a pulse oximeter, a temperature probe, and an end-tidal carbon dioxide and end-tidal gas analyzer.

Postoperative Pain Management

Immediately on arrival in the PACU, the PCA pump (Abbott Life Care Infuser; Abbott Laboratories, Chicago, IL), loaded with morphine, was attached to the patient's intravenous access. When the patient reported pain, a loading dose of 50 μg/kg morphine was given through the PCA pump by the attending nurse. If the patient continued to experience pain, further increments of 50 μg/kg were given through the PCA pump until the patient was comfortable. Every 10 min during the patient's stay in the PACU, the patient was asked whether he needed pain relief. An affirmative response was followed by administration of another 50 μg/kg bolus of morphine. This procedure was continued until the patient no longer requested pain relief and/or was alert enough to use the PCA pump himself.

The PCA pump was programmed to administer a bolus of 1 mg morphine with a lockout time of 5 min and a 4-hourly maximum dose of 40 mg. No background infusion was delivered. PCA was continued until the end of the study, 48 h after surgery. After the patient was transferred from the PACU to the ward, the PCA pump was the sole method of providing pain relief and was overseen by the research team and the Acute Pain Service of the Department of Anesthesia. No other analgesics were administered during the study period. If the patient rated his pain as 6 or higher on a VAS for a period

of 1 h, the PCA bolus dose was increased to 1.5 mg morphine. When required, bladder spasm pain was treated with 5 mg oxybutynin three times a day.

If a patient required intravenous analgesia beyond the 48-h study period, PCA morphine was continued as per the Acute Pain Service protocol.

Pain Assessment Instruments

Visual Analog Scale. The VAS provides a simple, efficient, and minimally intrusive measure of pain intensity that has been used widely in research settings in which a quick index of pain is required and to which a numerical value can be assigned.[12] The VAS consists of a 10-cm horizontal line, with the two endpoints labeled "no pain" and "worst possible pain," respectively. The patient marked the 10-cm line at the point that corresponded to the level of pain intensity experienced at that time. The distance (in centimeters) from the low end of the VAS and the patient's mark was used as a numerical index of pain intensity. Pain was assessed with patients at rest (VAS-R) at 1, 2, 3, 6, 12, 24, 36, and 48 h after surgery. Pain was also assessed after standardized mobilization (VAS-M) at 24 and 48 h by asking patients to roll from a supine to a side-lying position and perform two maximal inspirations before rating their pain.

McGill Pain Questionnaire. The McGill Pain Questionnaire (MPQ) was developed by Melzack[13] to obtain quantitative and qualitative measures of the experience of pain. The MPQ yields two global scores, the pain rating index and the present pain intensity, which have been found to provide valid and reliable measures of pain.[12,13] The pain rating index is the sum of the rank values of the words chosen from 20 sets of qualitative words, with each set containing two to six adjectives that describe the sensory, affective, and evaluative properties of pain. The lists of pain descriptors are read to the patients, who are asked to choose the word in each category that best describes their pain at the moment. The present pain intensity is rated on a scale of 0–5 as follows: 0 = none, 1 = mild, 2 = discomforting, 3 = distressing, 4 = horrible, and 5 = excruciating. The MPQ was administered at 24 and 48 h after surgery.

Pressure Threshold Meter. Sensitivity to mechanical pressure around the surgical wound was assessed using a Pressure Threshold Meter (Pain Diagnostics and Thermography Inc., Great Neck, NY). The Pressure Threshold Meter is a force gauge with a rubber tip (1 cm^2 in diameter) and a 10-kg range in 0.1-kg divisions. The Pressure Threshold Meter is used to obtain quantitative assessments of muscle/deep tissue tenderness in response to applied pressure.[14] The pain perception threshold was determined by applying pressure and recording (in kg/cm^2) the level at which the patient first reported pain. The patient then rated, on a 10-cm VAS, the intensity of the pain induced by the Pressure Threshold Meter. Baseline pain perception thresholds were obtained from the left and right of midline on the abdomen at the level of T9 on the morning of surgery before the operation. Postoperatively, pain perception thresholds were obtained 5 cm from the left and right edges of the wound dressing at 24 and 48 h after surgery.

Assessment of Adverse Effects

Sedation. Postoperative sedation was assessed at 1, 2, 3, 6, 12, 24, 36, and 48 h after surgery using a five-point modified sedation scale (0 = alert and orientated, 1 = awake but drowsy, 2 = sleeping but arousable by verbal commands, 3 = sleeping but arousable by tactile stimuli, and 4 = comatose).[15]

Nausea and Vomiting. Postoperative nausea and vomiting were assessed at 1, 2, 3, 6, 12, 24, 36, and 48 h after surgery. Nausea was measured using a 10-cm horizontal VAS with endpoints labeled "no nausea" and "extreme nausea." At the end of the study, a retrospective overall nausea score was obtained using the same scale. Vomiting was assessed as present or absent.

Pruritus. Postoperative pruritus was assessed at 1, 2, 3, 6, 12, 24, 36, and 48 h after surgery using a 10-cm horizontal VAS with endpoints labeled "no itching" and "extreme itching."

Other Adverse Effects. The presence of insomnia, dizziness, nervousness, and dry mouth was assessed at 24 and 48 h after surgery using a four-point scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe).

Patient Satisfaction

A four-item satisfaction questionnaire was administered at the end of the study to all patients (1 = very dissatisfied, 2 = somewhat dissatisfied, 3 = somewhat satisfied, and 4 = very satisfied). Patients rated their satisfaction with the care they received from their physician, nurses, and other staff and their pain control and overall hospital experience.

Analysis of Plasma Amantadine, Morphine, and Morphine Metabolites

For analysis of amantadine and morphine plasma concentrations, a venous blood sample was taken 1 h before induction of anesthesia (before the second dose of amantadine was administered), immediately after skin closure, and at 24 and 48 h after surgery. Blood samples were collected in 10-ml heparinized tubes and centrifuged immediately, and the plasma was removed and kept at −20°C until analysis. We used the method reported by Bras *et al.*[16] for the analysis of amantadine. For quantification, plasma samples were extracted with toluene, converted to acetylamantadine, and then analyzed by gas chromatography using a nitrogen-specific detector.

For analysis of morphine, morphine-3-glucoronide (M3G), and morphine-6-glucoronide (M6G), plasma samples were extracted using a solid-phase extraction method described by Gerostamoulos and Drummer,[17]

with hydromorphone as the internal standard. After the extraction and reconstitution, samples were quantified by high-performance liquid chromatography with both electrochemical and fluorescent detection according to Meng *et al.*[18]

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS for Windows, release 9.0; SPSS, Chicago, IL) and Primer of Biostatistics (version 4.0; McGraw-Hill, New York, NY).[19] Background demographic data and clinical variables were compared using two-tailed *t* tests (for continuous data) and Pearson chi-square tests (for frequency data). No intent-to-treat analysis was performed.

Primary Outcome Measure. Cumulative morphine consumption was analyzed by one-tailed *t* test.

Secondary Outcome Measure. Morphine consumption between intervals bounded by VAS pain scores at rest (VAS-R) was analyzed by *t* tests using the Bonferroni type I error rate correction for multiple comparisons (α/n). VAS-R, VAS pain scores on movement (VAS-M), and pain perception threshold were analyzed by analysis of variance or analysis of covariance (using the baseline value as covariate). MPQ total pain rating index and MPQ present pain intensity were analyzed by Mann–Whitney U test. Adverse effects and patient satisfaction scores were analyzed by Pearson chi-square test for two-way tables.

Pharmacokinetic Analysis. The clearance rate of morphine was calculated in those patients who did not use PCA morphine from 22 to 24 h after surgery (three patients per group), assuming a steady state, and also for the group as a whole. This clearance rate was calculated by the ratio of the total PCA morphine used between 22 and 24 h and the resultant serum concentration of morphine measured at 24 h after surgery. Clearance rate was normalized for body weight and compared between the amantadine and placebo groups by two-tailed *t* test. Serum concentrations of morphine and its metabolites M3G and M6G were also compared between the groups by two-tailed *t* test.

All data are presented as mean ± SD unless otherwise specified. $P < 0.05$ was considered statistically significant.

Results

Three patients withdrew from the study. One patient in the placebo group decided against participating in the study on the morning of surgery before the procedure. Another patient in the placebo group was given additional analgesics (nonsteroidal antiinflammatory drugs) after surgery. One patient in the amantadine group withdrew on the morning of the scheduled procedure because his surgery had been cancelled. These three patients were not followed up after withdrawal, and their postoperative pain was treated as per the Acute Pain Service protocol. Therefore, data are available from 10 patients in the placebo group and 11 patients in the amantadine group. There were no significant differences between the groups in demographic and clinical variables (tables 1 and 2).

Table 1. Demographic and Clinical Information Obtained at the Preadmission Visit

Variable	Placebo	Amantadine
Age, yr	61 ± 7.2	59 ± 4.9
Height, cm	179 ± 6.1	178 ± 6.8
Weight, kg	83 ± 9.5	89 ± 16.8
Body mass index, kg/m^2	26 ± 2.9	28 ± 4.3
Frequency of ASA status (I:II:III)	6:4:0	2:8:1
Preoperative pain, %	30	36
No. of previous surgical procedures	2.1 ± 1.5	1.7 ± 1.1
Days between preadmission and surgery	11 ± 7.3	10 ± 3.8
Baseline PPT, kg/cm^2	8.3 ± 2.7	8.3 ± 1.9

Data are mean ± SD unless otherwise stated.

ASA = American Society of Anesthesiologists; PPT = pain perception threshold.

Morphine Consumption and Pain Scores

Cumulative morphine consumption was significantly lower in the amantadine group compared with the placebo group at all time points, except at 48 h after surgery ($P = 0.0515$; fig. 1). The mean difference of 24 mg represents a 32% reduction in morphine consumption over the 48 h period (amantadine: 51.4 ± 24.0 mg; placebo: 75.3 ± 38.9 mg). Morphine consumption between intervals bounded by VAS-R pain assessments was significantly lower in the amantadine group compared with the placebo in the first hour after surgery ($P = 0.004$) but not afterward, although the latter group consistently required more morphine across the entire study period (fig. 2). VAS-R pain scores did not differ significantly between the groups over time, consistent with

Table 2. Intraoperative Data for the Two Groups

Variable	Placebo	Amantadine
Time between preoperative capsule and incision, min	101 ± 39.5	98 ± 37.7
Surgery duration, min	188 ± 73.8	169 ± 36.2
Time between closure and arrival in PACU, min	17.4 ± 6.4	22.9 ± 9.4
Total morphine during surgery, mg	12.5 ± 6.4	12.8 ± 4.6
Total fentanyl during surgery, μg	211 ± 28.7	224 ± 37.7
Fluid intake, ml	4,550 ± 1,531	4,564 ± 871
Crystalloid intake, ml	3,450 ± 1,136	3,527 ± 535
Colloid intake, ml	950 ± 284	955 ± 350
Blood loss, ml	1,170 ± 596	980 ± 334
Urine output, ml	389 ± 343	334 ± 363

Data are mean ± SD.

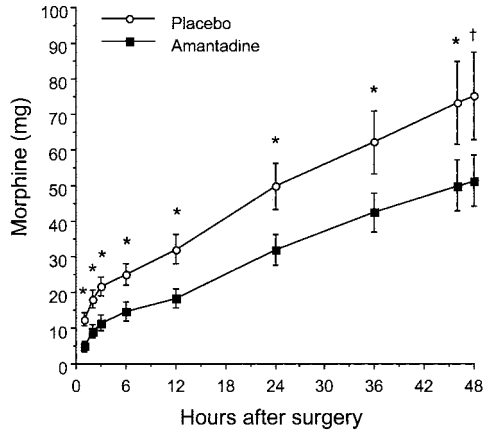

Fig. 1. Cumulative patient-controlled analgesia morphine consumption. Statistically significant differences were noted at all time points except at 48 h after surgery (* $P < 0.05$, † $P = 0.0515$, one-tailed *t* test).

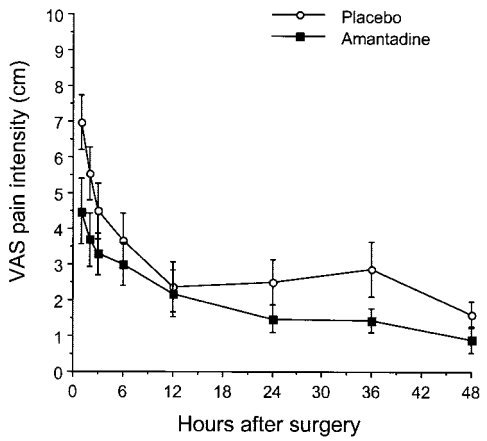

Fig. 3. Pain intensity at rest as measured with visual analog scale (VAS) scores. No statistically significant differences were noted.

the appropriate use of the PCA pump (fig. 3). The number of patients reporting bladder spasm pain was significantly lower in the amantadine group at 48 h ($P = 0.02$), and the pain was less intense (table 3). In addition, at 48 h after surgery, sensitivity around the surgical wound as measured with pressure algometry was significantly lower in the amantadine group compared with the placebo group ($P = 0.04$; table 3). Significant differences between the groups were not found in the MPQ scores at any time point (data not shown).

Adverse Effects and Satisfaction Scores

The incidence of adverse drug effects did not differ significantly between the groups (data not shown). At the end of the study, all patients reported being "somewhat" or "very" satisfied with the quality of care they received across the five satisfaction indicators. The only indicator that showed a significant difference between the groups was satisfaction with pain control. All patients in the amantadine group reported being "very satisfied" with the quality of their pain control, compared with only 70% of the patients in the placebo group ($P = 0.05$).

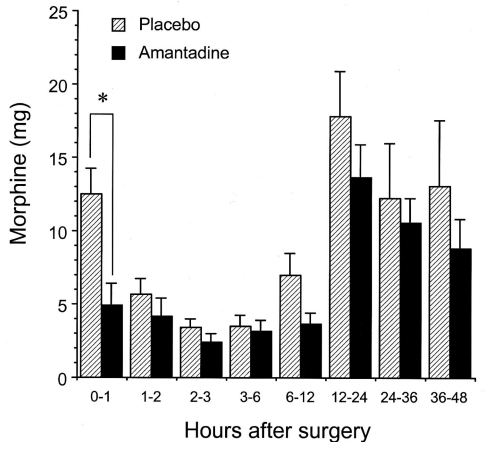

Fig. 2. Patient-controlled analgesia morphine consumption between intervals bounded by visual analog pain assessments in rest. A statistically significant difference was found at 1 h after surgery (* $P = 0.004$, *t* test with Bonferroni type I error rate correction for multiple comparisons).

Pharmacokinetic Analysis

Serum concentrations of morphine at the end of surgery tended to be higher in the amantadine group than in the placebo group (34.9 ± 8.3 *vs.* 22.5 ± 2.3 ng/ml, respectively), but this difference did not reach statistical significance. At 24 and 48 h after surgery, serum concentrations of morphine were similar between the groups, despite the amantadine group having received significantly less morphine. The plasma clearance of morphine at 22–24 h after surgery was significantly

Table 3. VAS-M, Incidence and Intensity of Bladder Spasm Pain, PPT Obtained 5 cm Lateral to the Wound Dressing, and VAS Pain Intensity in Response to Pressure

Assessment Time/Pain Measure	Placebo	Amantadine
24 h		
VAS-M pain, cm	4.8 ± 2.5	4.1 ± 2.8
Bladder spasm pain		
No. of patients	3	0
VAS pain, cm	0.6 ± 0.3	0
PPT, kg/cm^2	3.9 ± 3.4	4.3 ± 2.5
VAS pain at PPT, cm	4.3 ± 2.6	4.1 ± 2.5
48 h		
VAS-M pain, cm	3.3 ± 1.9	3.0 ± 1.9
Bladder spasm pain		
No. of patients	4*	1
VAS pain, cm	2.7 ± 3.8	0.1
PPT, kg/cm^2	3.4 ± 2.6	3.5 ± 2.4
VAS pain at PPT, cm	4.3 ± 1.8†	2.4 ± 1.2

Data are mean ± SD unless otherwise stated.

* $P = 0.02$, placebo *vs.* amantadine by Fisher exact test. † $P = 0.04$, placebo *vs.* amantadine by analysis of variance.

PPT = pressure pain threshold; VAS = visual analog scale; VAS-M = visual analog scale pain on movement.

lower in the amantadine group (0.68 ± 0.47 $l \cdot h^{-1} \cdot kg^{-1}$) than in the placebo group (1.17 ± 0.55 $l \cdot h^{-1} \cdot kg^{-1}$) ($P < 0.05$). This was true for the sample as a whole and for the three patients per group who did not use PCA morphine from 22 to 24 h after surgery. The clearance values for the placebo group were identical to reference values in adults.[20] The plasma concentrations of M3G at the end of surgery were significantly lower in the amantadine group (74.1 ± 15.1 ng/ml) as compared to the placebo group (122.9 ± 17.4 ng/ml) ($P = 0.048$). There were no significant differences between the groups in concentrations of M6G.

Discussion

The main finding of this preliminary study is a reduction of cumulative morphine consumption in the amantadine group of 32% compared with the placebo group (fig. 1). Although a statistically significant difference could not be demonstrated at 48 h after surgery ($P = 0.515$), all other time-points (up to 47 h) showed P values less than 0.05. Morphine consumption between intervals bounded by VAS-R pain assessments was significantly lower only in the first hour after surgery, although the patients in the placebo group consistently required more morphine at each interval across the entire study period (fig. 2). Furthermore, despite the fact that the total dose of morphine given during surgery was virtually identical between the groups, the amantadine group showed a significantly lower M3G concentration and a tendency for a higher morphine concentration at the end of surgery than did the placebo group.

Taken together, these findings can be explained by a pharmacokinetic interaction between amantadine and morphine resulting in inhibition of the 3-glucuronidation of morphine. Because more than 50% of morphine is metabolized to M3G (and only approximately 10% to M6G),[21] less 3-glucuronidation of morphine would result in higher morphine concentrations and lower M3G concentrations. This would increase the systemic exposure to a given dose of morphine, resulting in a greater analgesic effect and lower morphine requirements in the amantadine group.

To further explore a possible pharmacokinetic interaction between amantadine and morphine, morphine plasma clearance was calculated at 22–24 h after surgery. A significantly lower morphine plasma clearance rate was found in the amantadine group, which, in conjunction with the above findings, implies that the 3-glucoronidation of morphine is inhibited by amantadine. A potential site of interaction between these two drugs is the renal tubular cell, because both morphine and amantadine share the organic cation transport system.[22–24] Studies have shown that tubular secretion of morphine is fourfold to fivefold higher than its glomerular filtration, which means that competitive inhibition of its tubular secretion may be important.[24] To the best of our knowledge, the unexpected finding of pharmacokinetic interactions between these drugs has not been sought or described before. It emphasizes the critical value of considering pharmacokinetic mechanisms when performing studies of drug interactions.

At 48 h after surgery, sensitivity around the surgical wound as measured with pressure algometry was significantly lower in the amantadine group compared with the placebo group. By applying pressure algometry 5 cm from the wound, we hoped to mainly assess secondary hyperalgesia, although we recognize that this blunt stimulus could stretch the wound so that the measure may be confounded with primary hyperalgesia. Recently, it has been shown that opioids activate not only antinociceptive systems but also pronociceptive systems, causing acute opioid tolerance and opioid induced hyperalgesia. These phenomena seem to stem from a common NMDA receptor–dependent mechanism.[4,5] It can be hypothesized that the lower morphine consumption in the amantadine group, produced by the pharmacokinetic interaction between amantadine and morphine, led to the development of reduced mechanical sensitivity around the surgical wound on the second postoperative day. However, we cannot exclude the possibility that the NMDA receptor antagonist properties of amantadine may have contributed to a reduction in the development of acute opioid tolerance and/or opioid-induced hyperalgesia, resulting in lower morphine consumption and reduced mechanical sensitivity around the surgical wound. Furthermore, there is evidence from animal studies that NMDA receptor antagonists inhibit spinal neuronal and reflex response to urinary bladder distension, suggesting an action of NMDA receptor antagonists on pain originating from the bladder.[25,26] This might explain the finding of the lower incidence of bladder spasm in the amantadine group.

In the current study, mean amantadine plasma concentrations ranged from 275 to 803 ng/ml (table 4). At these concentrations, amantadine mainly interacts with the NMDA receptor, and higher concentrations are necessary for interactions with other receptors and/or neurotransmitter systems.[9]

Little has been published describing the use of amantadine for its analgesic properties, and with one exception,[27] these publications relate to treatment of chronic neuropathic pain and not acute postoperative pain.[28,29] In contrast to the results of the current study, Gottschalk *et al.*[27] did not find a postoperative opioid-sparing effect when a single dose of 200 mg amantadine or saline was given intravenously 30 min before induction of general anesthesia in women undergoing abdominal hysterectomy. However, in that study, patients in the amantadine group were younger than patients in the control group, raising the possibility that the opioid-sparing effects of

Table 4. Plasma Concentrations (ng/ml) of Amantadine, Morphine, M3G, and M6G

Substance/Group	Time			
	2 h before Surgery	At Skin Closure	24 h after Surgery	48 h after Surgery
Amantadine				
Placebo	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Amantadine	275.9 ± 70.2	803.4 ± 184.6	563.5 ± 153.8	366.5 ± 146.2
Morphine				
Placebo	0.0 ± 0.0	22.5 ± 7.3	19.4 ± 7.9	18.2 ± 8.8
Amantadine	0.0 ± 0.0	34.9 ± 26.5	22.0 ± 14.3	19.0 ± 9.8
M3G				
Placebo	0.0 ± 0.0	123.0 ± 52.5*	111.4 ± 105.8	91.3 ± 103.6
Amantadine	0.0 ± 0.0	74.1 ± 47.8	46.0 ± 26.0	38.0 ± 18.2
M6G				
Placebo	0.0 ± 0.0	36.2 ± 12.3	22.7 ± 14.2	24.8 ± 20.0
Amantadine	0.0 ± 0.0	37.4 ± 23.7	22.3 ± 7.7	20.9 ± 6.9

Data are mean ± SD.

* $P = 0.048$ placebo *vs.* amantadine by two-tailed *t* test.

M3G = morphine-3-glucuronide; M6G = morphine-6-glucuronide.

amantadine may have been offset by the increased opioid requirements typically seen in younger *versus* older patients,[30] thereby leading to the absence of a difference in outcome between the two groups. In addition, patients in the amantadine group had significantly more intense preoperative pain on the day of surgery than did patients in the control group. The difference in preoperative pain intensity may have masked the effect of amantadine. Alternatively, the efficacy of amantadine may been reduced in much the same way that presurgical pain has been found to be less responsive to preoperative treatment with analgesics, perhaps because central sensitization had already been established before surgery.[31]

Apart from the influence of these confounding factors, there are two major differences between the current study and that of Gottschalk *et al.*[27] that may explain the different outcomes; namely, the dosing schedule of amantadine (multiple dose *vs.* single dose) and the sex of the patients. A higher dose of amantadine and its continuation after surgery might have yielded the same effects as in the current study. Further research is required to evaluate whether the opioid-sparing effects we observed are sex related.

The current study has several limitations. First, this pilot study enrolled a relatively small number of patients. This might explain why, despite the 32% reduction in 48 h morphine consumption in the amantadine group, no differences in morphine-related side effects were found. Based on the data from this preliminary study, we calculated the sample size required for an adequately powered, larger-scale clinical trial comparing amantadine and placebo (SPSS Sample Power, release 1.0). Using a type I error rate of 5% (two tailed), increasing the sample size to 32 patients per group would yield a power of 80% to detect a mean difference of 24 mg morphine (using a pooled SD of 33.4 mg) at 48 h after surgery. A second limitation is that patients in this study were only observed for up to 48 h after surgery. The study cannot address the question of whether perioperative amantadine influences pain and analgesic consumption in the longer term. The results of this pilot study should be confirmed in a larger trial using a more extensive method of assessing hyperalgesia (*e.g.*, quantitative sensory testing) and a longer follow-up. Also, a formal pharmacokinetic study under strict steady state conditions should be performed to definitely confirm our results.

In conclusion, perioperative oral amantadine, but not placebo, was associated with lower postoperative morphine requirements, less intense mechanical sensitivity around the surgical wound, and a reduced incidence of bladder spasm pain in patients after radical prostatectomy. The unexpected finding of a pharmacokinetic interaction between amantadine and morphine explains the finding of lower postoperative morphine requirements, although additional pharmacodynamic effects involving the NMDA receptor may also be involved.

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