ACUTE PAIN SECTION

Original Research Article

Beneficial Effect of Amantadine on Postoperative Pain Reduction and Consumption of Morphine in Patients Subjected to Elective Spine Surgery

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Abstract

Objective. To analyze the effect of coadministration of morphine and amantadine on postoperative pain reduction and morphine consumption in patients after elective spine surgery.

Methods. In double-blinded study, 60 patients (ASA physical status I-II) were randomized into two groups. Group A was given oral amantadine 50 or 100 mg 1 hour before surgery and 8, 20, 32 hours after operation. Group P received placebo at identical times. Pain was assessed using numerical rating scale before first administration of morphine and in 2, 3, 4, 6, 24, and 48 hours after operation. The amounts of morphine consumed were recorded up to 48 hours after surgery. Blood samples were taken twice in 2 hours after surgery and plasma levels of morphine and its main metabolites were measured.

Results. As compared with placebo, amantadine significantly reduced intra-operative Fentanyl use and sensation of postoperative pain. Up to 48 hours after operation, the cumulative consumption of morphine was 25% lower in the amantadine group. Moreover, intensity of nausea and vomiting tended to be lower in A group. Starting from 12th hour after surgery, the level of postoperative sedation was lower in patients who received amantadine, as compared with placebo group. No significant differences in plasma levels of morphine and its metabolites were observed between A and P groups.

Conclusions. Pre- and postoperative administration of amantadine significantly reduced fentanyl use during operation, as well as reduced the postoperative pain and decreased morphine consumption in young patients undergoing orthopedic surgery.

Key Words. Postoperative Pain; Amantadine; Analgesia; Morphine; NMDA Receptor Antagonist

Introduction

During the surgical procedure of scoliosis correction, large surgery extent and long-lasting strong nociceptive stimulation lead to postoperative pain formation of greater intensity compared with other orthopedic interventions. In these patients, duration of postoperative symptoms is longer, and may lead to persistent pain formation due to developing neuroplastic changes in the central nervous system [1,2]. The most common drugs in the treatment of acute postoperative pain are still opioids, but their use is limited by adverse effects and the development of tolerance, especially when these drugs are administrated in high doses or for a long period of time. It has been shown that the coadministration of drugs, such as nonsteroidal anti-inflammatory drug, Paracetamol, or N-methyl-D-aspartate (NMDA) receptor antagonists, can minimize side effects and enhance analgesic action of morphine [3–7]. It has been also reported that NMDA antagonists (such as
memantine, dextromethorphan, amantadine) may affect postoperative consumption and prevent tolerance to morphine; however, the mechanism of this interaction is still not clear [6,8–12]. Amantadine has been used for over 20 years in the treatment of Parkinson’s disease and as an antiviral drug. It has been reported to possess ability to block NMDA receptors [13,14]. However, the mechanism of amantadine and morphine interaction is not entirely clear; some reports suggested that amantadine might favorably change morphine pharmacokinetics [15]. There are only few clinical trials with use of amantadine as coanalgesic in postoperative pain treatment in cancer patients (mastectomy, prostatectomy) [15–18]. There is lack of similar studies in orthopedic patients.

Therefore, the main aim of our study was to evaluate the influence of amantadine, administrated in pre- and postoperative period, on pain and morphine consumption in young patients after elective spine surgery. With a view to find possible pharmacokinetic mechanism of such interaction, we assessed the influence of conoadministration of amantadine on plasma concentrations of morphine and its main metabolites: morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G).

Methods

Patient Selection

Sixty ASA physical status I-II patients undergoing spine surgery because of idiopathic scoliosis were enrolled to this double-blinded, placebo-controlled, randomized study, approved by an Ethical Committee of the Jagiellonian University School of Medicine. All participants (and parents) signed informed consent and were given full explanation of postoperative analgesia, actions of amantadine, as well as numerical rating scale (NRS) 24 hours before surgery (demographic data are shown at Table 1). Patients with ASA score III (with chronic kidney, lungs, gastrointestinal tract, liver, or cardiovascular diseases), pregnant or breastfeeding women, patients with body mass index < 18 kg/m², and with allergy to any of the study medications and taking medications that could significantly interact with amantadine (tramadol, paracetamol, dextromethorphan, pseudoephedrine, atropine, antipsychotic medications) were excluded.

Study Design

Two sets of the tablets (containing amantadine and placebo, blinded) were prepared by Pharmacy Unit, Krakow University Hospital. Patients were enrolled by staff of Division of Anesthesiology and Intensive Care, Department of Orthopedics and Rehabilitation. The allocation sequence was generated using online random number calculator (http://www.graphpad.com/quickcalcs/randomize2.cfm) and was kept in Chair of Pharmacology. In every case, the assignment was done according to the sequence via phone by independent person from Chair of Pharmacology. The study was blinded for patients, persons performing premedication, anesthesia, and surgery, as well as for nursing personnel.

Patients were allocated to amantadine group (A) (N = 30) or placebo group (P) (N = 30). Group A was given amantadine (Amantix® 100 mg tablets) in doses depending on the body mass of patients, according to following regimen:

- For patients with body weight 30–59 kg, the single doses of 1/2 tablet (50 mg) were given in the evening before operation, then 1 hour before surgery and 8, 20, 32 hours after operation.
- For patients with body weight 60–80 kg, the single doses of 1 tablet (100 mg) were given in the evening before operation, then 1 hour before surgery and 8, 20, 32 hours after operation.

Group P was given placebo (lactose) following the same schedule.

General Anesthesia

All patients were premedicated with 15 mg of oral midazolam 1 hour before surgery followed by i.v. administration of 1–2 mg of midazolam immediately prior to induction of anesthesia. General anesthesia was induced with thiopental (3–5 mg/kg) and fentanyl (2.5 µg/kg). Anesthesia was maintained with 60% nitrous oxide in oxygen and isoflurane (up to 0.6%). During surgery, the patients were given fentanyl in initial dose of 20 µg/kg, then depending on the presence of clinical correlates of pain (tachycardia, rise in blood pressure) in consecutive doses of 0.7–2 µg/kg. The last dose of fentanyl was administered 30 minutes before end of surgery.

Following tracheal extubation after the surgery, patients were transferred to the postanesthetic care where

Table 1  Demographic and surgery data of patients enrolled in the study (mean ± SD)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (N = 30)</th>
<th>Amantadine (N = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (F/M)</td>
<td>25/5</td>
<td>27/3</td>
</tr>
<tr>
<td>Age (years)</td>
<td>16.5 ± 2.7</td>
<td>16.1 ± 2.5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>52.4 ± 2.7</td>
<td>52.1 ± 6.8</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>20.08 ± 2.7</td>
<td>20.04 ± 2.42</td>
</tr>
<tr>
<td>Surgery time (minute)</td>
<td>183 ± 28.2</td>
<td>203 ± 51.0</td>
</tr>
<tr>
<td>Total fentanyl use during surgery (mg/kg)</td>
<td>0.13 ± 0.03</td>
<td>0.09 ± 0.03*</td>
</tr>
<tr>
<td>Total fluid intake (mL)</td>
<td>2,963 ± 529</td>
<td>3,125 ± 767</td>
</tr>
<tr>
<td>Crystalloid intake (mL)</td>
<td>2,710 ± 528</td>
<td>2,823 ± 766</td>
</tr>
<tr>
<td>Colloid intake (mL)</td>
<td>300 ± 251</td>
<td>303 ± 248</td>
</tr>
<tr>
<td>Blood loss (mL)</td>
<td>368 ± 165</td>
<td>447 ± 305</td>
</tr>
<tr>
<td>Diuresis (mL)</td>
<td>802 ± 261</td>
<td>915 ± 570</td>
</tr>
</tbody>
</table>

* P < 0.05 vs placebo group.
SD = standard deviation.
midazolam (0.1 mg/kg/h for 1 hour after operation) and morphine were given.

Postoperative Morphine Administration

Morphine (Morphini Sulphas, 10 mg amp.; Polfa Warsaw S.A., Warsaw, Poland) was given i.v., titrated to patient comfort, in doses of 50 μg/kg every 5 minutes as required (nurse-controlled analgesia). The first dose (50 μg/kg) was given when the patient reported pain for the first time. If patient did not achieve relief, two consecutive doses (50 μg/kg each) of morphine were given at 5-minute intervals. Then, this collective dose (considered as effective therapeutic dose) was administered on patient’s request by nursing staff when patient reported pain of 4 or higher intensity (according to NRS). The obligatory, refractive time between consecutive doses of morphine was 15 minutes. During postoperative period, patients were not treated with any other analgesic drug.

Samples of blood were taken twice: after first use of morphine, at the time of peak formation of morphine metabolites (20 minutes after the administration of last incremental dose of morphine), and just prior to the next dose of morphine given on patient’s first demand (nadir of clinical action of morphine). The consumption of morphine was charted for all patients up to 48 hours after surgery.

Pain Measurement

Subjective pain intensity scores were graded on self-rating NRS from 0 (“no pain”) to 10 (“unendurable pain”) before first administration of morphine and in 2, 3, 4, 6, 24, and 48 hours after operation.

Postoperative Assessment

Postoperative nausea/vomiting and pruritus intensity were measured using self-rating NRS from 0 (“no effect”) to 10 (“extreme effect”) in 2, 3, 4, 6, 12, 24, and 48 hours after surgery.

Postoperative sedation was assessed by nursing personnel using a simple 5-point sedation scale (0 = “awake, active”; 1 = “awake, calm”; 2 = “sleeping but responsive to verbal commands”; 3 = “sleeping but responsive to tactile stimuli”; 4 = “sleeping, nonreactive”) at first, second, third, and fourth hours after surgery; then single measurements were done between fifth and sixth hours, 7th–12th hours, and 12th–24th hours after operation; the last measurement was done 48 hours after operation.

Measurement of Amantadine, Morphine, and Metabolite Concentration in Patients’ Plasma Samples by Liquid Chromatography-Mass Spectrometry (LC-MS) Method

The plasma concentrations of amantadine, morphine, M3G, and M6G were measured at two time points—20 minutes after the last increment of the first postoperative use of morphine (I) and just prior to the next dose of morphine given on patients’ request (II). The choice of the time points was based on results of our preliminary study on morphine pharmacokinetic after IV administration. The maximum peak concentrations ($C_{\text{max}}$) both for the M3G and M6G were observed at 20 minutes after i.v. morphine administration (data not shown). Thus, plasma concentrations of main morphine metabolites were sampled at the time of reaching of $C_{\text{max}}$ and again, at the moment, when patient felt pain strong enough to request the second dose of morphine. Plasma was obtained by centrifugation for 4 minutes in 2,600 g. Extraction of examined drugs from plasma was performed according to our earlier investigations [19]. Liquid-liquid extraction with ethyl acetate was performed to extract morphine and amantadine, with two internal standards: codeine and memantine. Solid phase extraction was used to extract morphine glucuronides. Plasma concentrations of morphine, glucuronides, and amantadine were measured using an LC-MS method, using a Thermo Finnigan LCQ (San Jose, CA, USA) mass spectrometer, coupled with TSP HPLC system (Finnigan). Chromatographic separation of morphine and amantadine was achieved on RP Purospher C18-e column (Merck, Darmstadt, Germany)—2 mm i.d. ¥ 125 mm, 5 um, while morphine glucuronides were separated on RP Superspher 100 C18e column (Merck)—2 mm i.d. ¥ 125 mm, 4 um, according to earlier protocol [19]. Morphine and amantadine mass detection was done in selected ion monitoring (SIM) scan type mode with atmospheric pressure chemical ionization (APCI) ion source, and for morphine glucuronides in selected reaction monitoring (SRM) scan mode, with electrospray ionization (ESI) source. Obtained data were analyzed with Xcalibur software (Thermo Finnigan). Concentrations of all analyzed substances were calculated using calculated regression curves constructed by fitting linear regression model to the concentration vs peak-area ratio. Calculated validation parameters for all established analytical methods were highly satisfactory (correlation factors $R$ were in range 0.9982–0.9995, levels of detection 0.28–3.36 ng/mL, levels of quantitation 0.94–11.21 ng/mL).

Statistics

Significance of differences between groups was established by one-way analysis of variance followed by post hoc Sheffe’s test. Data were presented as mean ± standard deviation. A value of $P < 0.05$ was considered to be significant. NRS pain scores underwent Mann–Whitney analysis with Bonferroni correction for multiple comparisons. All statistical analyses were performed with STATISTICA v. 5.0 (StatSoft, Krakow, Poland); the power of tests was calculated using Power Analysis (a part of STATISTICA v. 5.0).

Results

All enrolled patients have completed the study. No adverse effects specifically attributable to amantadine were observed (nausea, nervousness, blurred vision, agitation, unusual anxiety, or irritability). Demographic data...
did not differ among groups (Table 1). Surgery data did not differ statistically among the groups except the total use of fentanyl during surgery, which was significantly lower in group A (Table 1).

The dose of morphine providing relief immediately after surgery differed significantly between groups (7.72 ± 1.78 vs 9.47 ± 3.53 mg, \( P = 0.03 \)). Also, total consumptions of morphine in the first 6, 24 hours and during the second day after surgery were significantly lower in group A (Figure 1). Time to the first dose of morphine after surgery on the patient’s request was significantly longer in group A compared with group P (59.53 ± 43.46 minutes vs 30.00 ± 18.35 minutes, \( P = 0.0064 \)).

Importantly, pain intensity score (NRS) was significantly lower in A group of patients compared with their placebo counterparts up to sixth hour after surgery (Figure 2). Starting from sixth hour after operation, as well as in the first and second days after operation, the pain scoring in A group was still lower than P group; however, the difference did not reach statistical significance (Figure 2).

Morphine, M3G, and M6G concentrations did not show any significant differences between placebo and A group (Table 2). Analysis of M3G/M, M6G/M, and M6G/M3G ratios showed that amantadine did not influence morphine glucuronidation, either in term rate of morphine metabolism or promotion of any of glucuronide formation (Table 2).

Analysis of main adverse effects of morphine did not show any differences in intensity of pruritus between patients administrated with amantadine and patients with placebo.

**Figure 1** Cumulative morphine consumption (mg) in indicated time periods after operation in patients treated with amantadine or placebo. *\( P < 0.05 \) vs placebo group.

**Figure 2** Mean pain intensity measured with numerical rating scale (NRS) in patients treated with amantadine or placebo. *\( P < 0.006 \) vs placebo group (Bonferroni correction).
for the whole observation period. Intensity of nausea/vomiting was generally lower in A group, but only at fourth hour after surgery this difference reached statistically significance. Differences in the intensity of postoperative sedation were not observed during the first 12 hours after surgery. Starting from 12th hour after surgery, sedation scores in the A group were statistically lower than in the placebo group (Table 3).

### Discussion

Opioids are widely used in the treatment of postoperative pain; however, their use is associated with numerous side effects such as nausea, vomiting, itching, excessive sedation, or respiratory depression. It has been shown that NMDA receptor antagonists may potentiate analgesic action of opioids and attenuate development of tolerance [3,5,20]. This is why coadministration of opioids and NMDA receptor antagonists in pre- and postoperative periods may improve analgesia and decrease occurrence of adverse effects of opioids. There were several attempts to use various NMDA receptor antagonists as coanalgesics postoperatively (for review, see: [9,20]). Both positive and negative results were reported. The most commonly used ketamine and dextromethorphan produced a significantly analgesic benefit in 58% and 67% of studies [9]. In present study, we used amantadine—NMDA receptor antagonist—as a coanalgesic drug in young patients undergoing extensive orthopedic surgery. Amantadine is a well-known drug, commonly used in the treatment of Parkinson’s disease; it shows also antiviral activity, which is exploited in the treatment of influenza type A. According to literature, amantadine in lower concentrations acts predominantly as an NMDA receptor antagonist, while in higher concentrations it can interact with other types of receptors, as well as may influence the release of dopamine from presynaptic bulb [13–15,21]. In our study, plasma levels of amantadine were relatively low, within range of action on NMDA receptors.

The main finding of this study is that the low doses of amantadine, devoid of any important adverse effects, resulted in reduction of pain in the patients treated with morphine in postoperative period. Our observation is in agreement with previous studies. Pud et al. found that in the cancer patients amantadine reduced neuropathic pain by 40% [16]. Snijdelaar et al. observed that perioperative use of amantadine caused a 32% reduction of morphine consumption and significantly lower pain scores in patients who underwent prostatectomy [15]; moreover,

### Table 2

<table>
<thead>
<tr>
<th>Group</th>
<th>Time Period of Observation (Hours after Surgery)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 hour</td>
</tr>
<tr>
<td>Amantadine</td>
<td>1.97 ± 0.71</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.9 ± 0.55</td>
</tr>
<tr>
<td>*</td>
<td>0.73</td>
</tr>
</tbody>
</table>

* = P < 0.05 vs placebo group.

SD = standard deviation.
the coanalgesic action of amantadine was very durable (up to 48 hours after surgery) [15]. In our study, there was significant reduction of pain intensity in patients treated with amantadine for the first 6 hours after surgery; however, this action was gradually decreasing from 68% at first hour to 36% at sixth hour and became negligible at 12th hour after surgery. Three main differences between current study and that of Snijdelaar et al. may explain the different outcome, namely the dosage of amantadine (smaller doses in current study), age of patients (much younger patients in current study), and different kind of surgery. Clearly, further studies are required to evaluate which factors are critically involved in determination of timescale of coanalgesic action of amantadine.

Importantly, in current study preoperative amantadine administration resulted in the twofold prolongation of the time to request of the first dose of morphine after surgery; premedication with amantadine also significantly reduced the average consumption of fentanyl during surgery. Altogether, our findings are of potential clinical importance and support the notion that amantadine could be useful as an efficient coanalgesic drug in surgery patients.

Interestingly, amantadine administrated in the perioperative period decreased postoperative morphine consumption. Although the most plausible explanation of this phenomenon is the pharmacodynamic enhancement of analgesic action of morphine by amantadine via NMDA receptor blockade [22], study of Snijdelaar et al. suggested pharmacokinetic basis for interaction—interference of amantadine with morphine degradation [15]. Overall, our results do not support the pharmacokinetic concept of coanalgesic interaction between amantadine and morphine. Morphine is metabolized mainly to pharmacologically inactive M3G. In contrast with M3G, M6G, formed in smaller amounts, is even stronger analgesic than morphine. In our study, the levels of morphine and its two metabolites—M3G and M6G—did not differ between patients treated with amantadine and placebo. However, this is somehow surprising regarding lower dosage of morphine in patients treated with amantadine. Yet, our study was aimed mainly to estimate the influence of amantadine administration on postoperative pain sensation and should be considered preliminary as far as pharmacokinetics of morphine is involved. A more formal pharmacokinetic study, with use of various doses of amantadine, under strict steady state conditions is required to clarify our results.

Our study has also other limitations. It has been shown that both the gender of patients and the age of patients may influence amantadine efficacy in postoperative setting [21,23]. Although a posteriori power analysis of NRS comparisons revealed the power of 85.6% (at 1% alpha error level), taking into account the high variability of NRS, this study could not be powered enough to ultimately determine amantadine efficacy and should be considered as preliminary. All questions warrant further investigation in larger studies.

**Conclusions**

Perioperative administration of amantadine as coanalgesic agent caused the reduction of postoperative pain and lowered morphine consumption in young patients after elective spine surgery. In these patients, administration of amantadine before operation reduced the average consumption of fentanyl during surgery and prolonged time to the first request of morphine after operation. Action of amantadine was not associated with significant changes in plasma levels of main morphine metabolites, suggesting that its beneficial effect on postoperative pain is not of pharmacokinetic origin.

**Acknowledgment**

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**References**


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