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Peripheral opioid receptor blockade increases postoperative morphine demands—A randomized, double-blind, placebo-controlled trial

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ABSTRACT

Experimental studies suggest that a large proportion of opioid analgesia can be mediated by peripheral opioid receptors. This trial examined the contribution of such receptors to clinical analgesia induced by intravenous morphine. We hypothesized that the selective blockade of peripheral opioid receptors by methylnaltrexone (MNX) would increase the patients' demand for morphine to achieve satisfactory postoperative pain relief. In a double-blind, placebo-controlled, sequential 2-center trial, 50 patients undergoing knee replacement surgery were randomized (1:1) to receive either subcutaneous MNX (0.9 mg/kg) (hospital I: n = 14; hospital II: n = 11) or saline (hospital I: n = 13; hospital II: n = 12) at the end of surgery. The primary endpoint was the cumulative amount of intravenous morphine administered during the first 8 hours. Secondary endpoints were pain scores at rest and during movement (by numerical rating scale and McGill Questionnaire), vital signs, adverse side effects, and withdrawal symptoms. After MNX, demands for morphine were strongly (by about 40%) increased (hospital I: 35.31 ± 12.99 mg vs 25.51 ± 7.92 mg, $P = 0.03$; hospital II: 35.42 ± 11.73 mg vs 24.80 ± 7.84 mg, $P = 0.02$; pooled data: $P < .001$; means ± SD). Secondary endpoints were similar in all groups ($P > .05$). Thus, a significant proportion of analgesia produced by systemically administered morphine is mediated by peripheral opioid receptors. Drugs that selectively activate such receptors should have the potential to produce powerful clinical pain relief.

1. Introduction

Opioid agonists such as morphine are the gold standard for the treatment of severe pain. Despite widespread use, their clinical effectiveness is hampered by severe adverse effects resulting mainly from activation of μ-opioid receptors in the central nervous system (CNS). Such effects include apnea, euphoria, addiction, and tolerance and have recently led to an epidemic of overdoses, death, and abuse [22,25,30]. Peripherally mediated opioid analgesia is a promising strategy to avoid the deleterious side effects of centrally acting opioids or of nonsteroidal anti-inflammatory drugs (eg, cardiovascular complications, gastrointestinal ulcers, bleeding) [44,45]. In human trials and animal models of inflammatory pain, the selective activation of peripheral opioid receptors has repeatedly been shown to induce powerful analgesia [13,35,39,41,49]. Moreover, animal studies indicate that such receptors can mediate a substantial proportion of analgesia elicited by systemically administered opioids [6,10,11,15,24,31,47]. To assess the fraction of morphine analgesia mediated outside the CNS and the therapeutic potential of novel opioids selectively activating peripheral opioid receptors, this trial examined the contribution of such receptors to analgesia induced by the μ-agonist morphine in surgical patients. To this end, we applied methylnaltrexone (MNX), a μ-antagonist unable to cross the blood-brain barrier because of its quaternary amine structure [4,28]. This compound has been licensed for treatment of opioid-induced bowel dysfunction in palliative care, and retrospective assessments suggested no significant effects on pain in such patients [43]. We hypothesized that the selective blockade of peripheral opioid receptors by MNX will increase the patients' demand for intravenous (i.v.) morphine to achieve satisfactory postoperative pain relief.

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2. Methods

2.1. Patients

Eligible patients were adults (18 to 83 years) scheduled to undergo knee joint replacement surgery under general anesthesia. Exclusion criteria were chronic treatment with opioids or steroids, gastrointestinal dysfunction, alcohol or drug abuse, pregnancy, and major comorbidities (Table 1). Participants received extensive verbal and written explanations and gave written informed consent before inclusion in the study.

2.2. Study design

This was an investigator-initiated randomized, double-blind, placebo-controlled, sequential trial at 2 hospitals in Germany. On the day before surgery, patients were familiarized with the patient-controlled i.v. analgesia (PCA) pump (Master PCA, Fresenius Kabi GmbH, Bad Homburg, Germany), the numerical rating scale (NRS) ranging from no pain (0) to unbearable pain (10), and the McGill pain questionnaire [3,17,38]. Baseline data were collected, and nonsteroidal analgesic medication was discontinued. On the morning of surgery, patients received oral midazolam (7.5 mg, or 3.75 mg if body weight was below 50 kg or age was above 70 years). General anesthesia was conducted with continuous infusions of propofol (4.0 to 12.0 mg/kg/h), sufentanil (total dose 20 to 50 μg), muscle relaxants, and supplementary inhalational anesthetics as needed (hospital I: n = 5; hospital II: n = 18). Neither regional anesthetic procedures nor other perioperative analgesic drugs were allowed. For prophylaxis of postoperative nausea and vomiting, 1.25 mg dehydrobenzperidol and 8.0 mg dexamethasone were administered i.v. Ondansetron (up to 8.0 mg i.v.) was allowed for emesis if needed.

In a pilot study, 24 patients were randomized to 4 groups (n = 6 each) receiving subcutaneous (s.c.) 0.15 (n = 4), 0.3 (n = 4), 0.6 (n = 4), or 0.9 (n = 4) mg MNX/kg or 0.9% saline (n = 2 per group) at the end of surgery in a double-blind manner. Postoperative morphine consumption and pain scores were assessed for 72 hours. The data indicated 0.9 mg MNX/kg as an appropriate dose. The protocol was adapted accordingly, resubmitted, and approved by the ethics committees.

In the main study, a computerized random numbers generator and numbered sealed envelopes were used to allocate patients, in a 1:1 ratio, to receive either s.c. MNX (0.9 mg/kg) or 0.9% saline (0.045 mL/kg) immediately before termination of general anesthesia by the anesthesiologist who was not involved in postoperative data collection or further treatment. For each patient randomized, the next available number was used. All personnel involved in postoperative assessments and all patients were blinded to the treatment group.

Upon arrival in the postoperative care unit, i.v. morphine (3.0 mg/10 min) was titrated according to standardized operating procedures until sufficient pain relief was achieved (NRS at rest $\leqslant$4). Thereafter, patients used the PCA pumps containing morphine (MSI, Mundipharma, Limburg, Germany) (1.2 mg/mL) for 24 hours. The bolus volume was 1.0 mL, and lockout time was 10 minutes without background infusion. Upon the patient's request, supplemental i.v. morphine was allowed as rescue medication. Patients stayed in the postoperative care unit until the next day.

The study protocol complied with the Declaration of Helsinki and was approved by the state ethics committees of Berlin (LAGeSo, 08/0549–ZS EK 12) and Brandenburg (Landesärztekammer, AS 67/2012), and by the Federal Institute for Drugs and Medical Devices (BfArM, Bonn, Germany; No. 4034952). The trial is registered at Eudra-CT-2008-003256-29.

Qualified independent personnel monitored the trial, performed on- and off-site audits, and assured scientific integrity. Data were entered into duplicate databases that were compared for identity to generate the final database, which was subjected to an external spot-check audit. All monitoring and auditing reports are available online and attest proper study performance and data management. All authors had full access to the data, and vouch for the integrity and completeness of the data and analyses and for the fidelity to the protocol (available online).

2.3. Assessments

Based on MNX pharmacokinetics [9,48], the primary endpoint was defined as the cumulative postoperative morphine consumption in milligrams over the first 8 postoperative hours. Morphine delivery was documented hourly over 24 hours. Secondary outcomes included pain at rest and during movement (lifting the operated leg for 10 cm), evaluated hourly for 12 hours and once again after 24 hours by NRS. If asleep, patients were awakened for the assessment. Inability to lift the leg due to pain was defined as an NRS score of 10. Before and 24 hours after surgery, pain at rest and during movement was additionally assessed by the McGill Pain Questionnaire.

Blood pressure, electrocardiography, heart rate, respiratory rate, oxygen saturation (by pulse oximetry), sedation (by observer's assessment of alertness/sedation scale [5]), opioid withdrawal symptoms (eg, sweating, lacrimation, restlessness), and other side effects (eg, nausea, vomiting, dry mouth, itching, dizziness, skin reactions) were recorded hourly for 12 hours. Bowel movement, flatus, and abdominal pain were assessed on the day of surgery and on the next day. All adverse effects were rated either as mild (transitory, not incapacitating), moderate (annoying, limiting normal activity), or serious (incapacitating, complicating, life threatening).

2.4. Statistics

Power calculations for the main study were based on the primary endpoint, on previous trials [16,42], and on our pilot dose-finding study. Assuming a standard deviation (SD) of 5.4 mg with a difference of 6.3 mg between the MNX and the saline group, 32 patients (16:16) would be needed. Using a sequential design [19] and estimating a 20% dropout rate, a final number of 50 patients (25:25) were determined. The protocol prespecified an

Table 1
Inclusion and exclusion criteria.

Inclusion criteria
Elective knee joint replacement under general anesthesia
Capable of giving written informed consent
Male or female
18 to 83 years old
Exclusion criteria
Chronic opioid treatment (>3 weeks with >10 mg morphine equivalents/d)
Chronic pain with psychiatric/psychosomatic component
Abuse of drugs or alcohol, psychiatric/mental disease
Rheumatoid arthritis with chronic steroid or opioid medication
Chronic pulmonary disease with systemic steroid medication; pulmonary hypertension
Severe heart failure (New York Heart Association class $\geqslant$III); peripheral vascular disease
Diabetes mellitus with peripheral polyneuropathy (sensory deficit), ulcers/necrosis/infections
Paralysis, neurological deficits
Gastrointestinal dysfunction/inflammation, ileus
Acute infections, cancer, HIV, hepatitis
Pregnancy; emergency surgery
Intolerance reactions to methylnaltrexone
Participation in other trials
Surgery longer than 3 hours