Emetic effects of morphine and piritramide

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Background. Successful management of postoperative pain requires that adequate analgesia is achieved without excessive adverse effects. Opioid-induced nausea and vomiting is known to impair patients’ satisfaction, but there are no studies providing sufficient power to test the hypothesis that the incidence of opioid-induced nausea and vomiting differs between μ-opioid receptor agonists. Thus, we tested the hypothesis that the incidence of vomiting and nausea differs between morphine and piritramide.

Methods. In a prospective, randomized, double-blind fashion, we administered either morphine (n=250) or piritramide (n=250) by patient-controlled analgesia (PCA) for postoperative pain relief. We used a bolus dose of 1.5 mg with a lockout time of 10 min. Incidence and intensity (numerical rating scale) of postoperative nausea, vomiting, pain, patient satisfaction (score 0–10), side-effects (score 0–3) and drug consumption were measured.

Results. Mean drug consumption did not differ between the piritramide and morphine groups (30.8 (SD 22.4) mg day⁻¹ vs 28.4 (21.8) mg day⁻¹) during the first postoperative day and there were no significant differences in the overall incidence of nausea (30% vs 27%) and vomiting (19% vs 15%). Intensity of nausea correlated inversely (P=0.01) with morphine consumption but not with piritramide consumption. Pain scores both at rest (2.2 (1.9) vs 2.6 (2)) and during movement (4.4 (2.2) vs 4.9 (2.3)) were slightly but significantly less with morphine.

Conclusions. Opioid-induced emesis was observed in about one-third of the patients using morphine and piritramide for PCA and the incidence of vomiting was one-half of that. Potential differences in the incidence of vomiting during PCA therapy between these μ-opioid receptor agonists can be excluded.

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Successful pain management requires that adequate analgesia is achieved without excessive adverse effects.¹ Opioid agonists evoke emesis and are a risk factor for nausea and vomiting in the late postoperative period² but it is unclear whether side-effects differ between opioid receptor agonists. In fact, the incidence of nausea reported with the opioids morphine and piritramide,³⁴⁵ both of which are commonly used for i.v. patient-controlled analgesia (PCA) in Europe, varies widely. Furthermore, given the wide variation (39–73%) of opioid-induced nausea and vomiting reported across hospitals not explained by the case-mix,³ it is difficult to interpret data reported from different centres.

Differences in opioid receptor effects evoking nausea and vomiting may be explained by the pharmacokinetic or pharmacodynamic characteristics of opioids. In cats, both the incidence of vomiting and development of tolerance differ markedly between different opioids when administered as bolus by the intracerebroventricular (i.c.v.) route.⁷ In addition, tolerance has been suggested to occur only at the central opioid receptor level but not at receptors outside the central nervous system.⁸ Thus, if interaction between opioid agonists and opioid receptors in the central

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Incidence of nausea and vomiting with opioid agonists

chemoreceptive trigger zone (CTZ; area postrema) for a specific opioid is relatively long compared with its peripheral actions, which may be the case with morphine. Tolerance to the emetic actions of opioids could occur earlier or may be more intense. Accordingly, the incidence of opioid-induced nausea and vomiting may well differ between different opioid receptor agonists. Unfortunately, however, there are no studies including a sufficient number of patients to determine accurately whether there is a difference in the incidence of emesis with different opioids.

We therefore tested in a prospective, randomized, double-blind, single-centre study the hypothesis that the incidence of opioid-induced vomiting and nausea differs between morphine and piritramide.

**Methods**

Patients

After obtaining approval of the local ethics committee, 100 patients in a pilot study and 500 patients (ASA I–III) in the main study undergoing abdominal, orthopaedic or gynaecological obstetric surgery were included. After obtaining patient consent, we allocated patients randomly to receive either piritramide or morphine for postoperative i.v. PCA. Patients with a history of drug addiction or psychiatric disease, those receiving monoamine oxidase inhibitors, or those unable to understand the principle of PCA were excluded from the study.

Randomization and blinding

Using a computer-generated random list, anaesthetists allocated 500 patients to receive either morphine or piritramide after surgery. These anaesthetists were not involved in postoperative pain therapy. Subsequently, patients were visited by an assessor twice a day (postoperative pain service) until PCA therapy was terminated.

While 458 of 500 randomized patients used the PCA on the first postoperative day, 311, 165 and 91 patients used PCA on the second, third and fourth postoperative days, respectively.

This study was double blind since patients, surgeons, assessors and the nurses caring for the patients after surgery did not know which opioid was given to an individual patient. Information on the opioid applied was noted in the anaesthesia record, available only in emergency situations.

Establishment of PCA regimen and bolus dose (pilot study)

To assess effects for power analysis and to assure feasibility of the main study, we investigated PCA with morphine (n=50) and piritramide (n=50) in a pilot study. We used a bolus dose of 1.5 mg with a lockout time of 10 min. Pain intensity (0–10 numeric rating scale (NRS)), number of bolus injections administered and overall opioid consumption were recorded daily after surgery.

**Stability of piritramide (pilot study)**

Piritramide (Dipidolor®, Janssen-Cilag GmbH) was diluted with normal saline to achieve a concentration of 1 mg ml⁻¹ and its concentration under two different storage conditions (2–8°C and room temperature) was assessed over a 40-day period. In this pilot study, piritramide solutions were stored in 100-ml PVC containers (Multifuse, B. Braun, Melsungen, Germany), which were also used later for PCA during the main study.

After ensuring linearity of analysis of piritramide concentration in a dilution series, the concentrations of the solutions stored in the containers were measured by UV spectrophotometry (Kontron, mod. Uvikon 810, detection wavelength 258 nm). Interday precision was 1.1%.

We also tested the solutions for piritramide degradation products by high-performance liquid chromatography (HPLC system Merck-Hitachi; L-6200 pump, L-4000 UV detector, D-2500 Chromato integrator) when stored at room temperature. We injected samples into a LiChrosorb column (RP 18, Merck). The mobile phase consisted of ammonium acetate 10%, methanol and acetonitrile in the ratio 31:45:24 and was stabilized at pH 7.2 using acetic acid. The flow rate was 1.4 ml min⁻¹ and the injection volume was 50 µl.

Main study

Five hundred patients received either morphine (n=250) or piritramide (n=250) by PCA in a randomized (computer-generated random lists), double-blind, prospective fashion. Choice of the anaesthetic technique was left to the anaesthetist responsible, who was not taking part in this study. Anaesthetic technique, dose of opioids given during surgery and duration of surgery and anaesthesia were recorded.

For the PCA, an infusion pump (Braun Multifuse, Melsungen, Germany) was filled with opioid 100 mg in normal saline 100 ml stored in a refrigerator at 2–8°C and connected to the patients peripheral or central venous catheter. Since pain scores and opioid consumption had not been different between the piritramide and morphine groups in the pilot study, we used the same opioid concentrations, bolus dose (1.5 mg), and lockout time (10 min) during the main study.

PCA was initiated in the recovery room or intensive care unit after extubation. PCA was initiated following an initial loading dose of the appropriate opioid to achieve a pain NRS of 3 or less. The decision about duration of PCA was left to the patient and the anaesthetist responsible (postoperative pain service).
Measurements

To ensure group comparability, we assessed the following criteria considered critical to the risk of postoperative nausea and vomiting:9 gender, smoking and history of postoperative nausea and vomiting and/or motion sickness. The incidence and intensity of side-effects were recorded daily. Questions from a standardized questionnaire were read to the patient in a standardized manner without the assessor giving any other comments, and the patient was asked for a subjective rating of the intensity of nausea, vomiting, sedation, and pruritus on an NRS (0=no, 1=mild, 2=moderate, 3=strong).

Patients were asked daily to rate pain intensity at rest and during movement on an 11-point NRS (0=no pain; 10=worst pain imaginable). An 11-point NRS was also used at the end of therapy to assess patients’ satisfaction with postoperative pain management (0=very satisfied; 10=very dissatisfied).

Data sampled by the PCA pump’s microprocessor (beginning and end of PCA treatment, opioid consumption, alarms) were transferred to a personal computer at the end of pain treatment using its IR interface.

Statistics

Determination of the sample size was based on the incidence of vomiting as a primary endpoint. Power was defined as 0.80, and the two-sided level of significance was defined as 0.05. Referring to the results of the pilot study, the following proportions had been expected and were considered clinically significant: P1(morphine)=0.15; P2(piritramide)=0.25. The sample size calculated to find a significant difference between the incidence of vomiting with morphine and piritramide was 250 subjects per group.

We tested the hypothesis that the incidence of vomiting or nausea differs between morphine and piritramide using the χ²-test. Data are presented as the absolute and relative number of patients in contingency tables. Secondary endpoints such as scores for analgesia, vomiting and nausea were evaluated in a descriptive/exploratory analysis (mean, SD, median, ranges) and exploratory P values were calculated by the Mann–Whitney U-test and by non-parametric correlation (Pearson rank correlation) as appropriate. Statistical measures and exploratory P values were used to check the comparability of data documented at baseline. An α error less than or equal to 5% was chosen to reject the hypothesis. The software SPSS (V 10.0, SPSS Inc.) was used for statistical analysis.

Results

Sex, age, weight, height and type of anaesthesia and surgery (Table 1) did not differ significantly between groups. While duration of PCA therapy was similar between the groups (3.30 vs 3.27 days), surgery was slightly shorter in the piritramide group (140 (SD 77) min vs 156 (91) min, P=0.03).

On postoperative day 1 there were no significant differences in the overall incidence of vomiting (15% vs 19%) or nausea (27% vs 30%) between the morphine and piritramide groups (Fig. 1). The intensity of nausea correlated inversely (r=–0.18, P<0.01) with morphine but not with piritramide consumption on postoperative day 1.

There was no significant difference in opioid usage in total or on postoperative day 1 between the piritramide and morphine groups (postoperative day 1: 30.8 (22.4) mg; range 0–130 mg vs 28.4 (21.8) mg; 1.5–121.5 mg). In patients who

<table>
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<th>Table 1</th>
<th>Patient characteristics. Differences between the groups were not significant, with the exception of duration of surgery (P=0.03)</th>
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<tr>
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<tr>
<td>Age (yr)</td>
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Fig 1 Incidence of side-effects of all patients using patient-controlled anaesthesia (n=458) on postoperative day 1 (exact numbers are given above the bars). There was no difference in the incidence of side-effects with morphine compared with piritramide.
used PCA during the whole four-day observation period (n=91), a significant decrease (P<0.001) in opioid consumption occurred over time and was paralleled by a significant decrease in sedation score (1.3 (1) on day 1 vs 0.8 (0.84) on day 4; P<0.001). Incidence and intensity of other side-effects did not change between the postoperative days 1 and 4. There were no differences in pruritus and sedation scores between the two groups (Fig. 1).

Pain scores at rest (2.2 (1.9) vs 2.6 (2)) and during movement (4.5 (2.2) vs 4.9 (2.3)) were significantly lower with morphine PCA (Fig. 2) while patients’ satisfaction was excellent (1.1 (1.2) in both groups).

When storing piritramide solution in the refrigerator (i.e. at 2–8°C), a significant but minor (<5%) increase in piritramide concentration occurred over a 40-day observation period. When stored at room temperature, the increase was greater (Fig. 3) but was also less than 5% during a 4-day period, as performed for PCA therapy in our study. No degradation products were found.

Discussion

Our main finding is that the incidence of vomiting and emesis during postoperative PCA does not differ with the opioid agonists morphine and piritramide.

We compared emesis and vomiting with morphine and piritramide at doses considered to be equipotent on a mass basis from the results of a pilot study. Incidence of vomiting rather than nausea was the main endpoint, since the former is easier to quantify and, we speculated, may have a greater influence on patient satisfaction. Furthermore, vomiting during opioid-evoked sedation may expose the patient to an increased risk of pulmonary aspiration.10 11

Postoperative nausea and vomiting are strongly influenced by many variables, including gender, smoking, and history of postoperative nausea and vomiting and/or motion sickness.9 To minimize a bias on the incidence of opioid-induced nausea and vomiting, we ensured group comparability in terms of these variables. Duration of anaesthesia and use of inhalational anaesthetics may also influence the incidence and intensity of postoperative nausea and vomiting.12–15 Although in our study duration of surgery was slightly shorter in the morphine group, there was no difference in the anaesthetic techniques used or the opioid dose injected during surgery. It is therefore unlikely that slightly shorter surgery may have biased our results, as the effects of anaesthesia are only observed in the immediate postoperative period.2

We did not analyse side-effects on the day of surgery as volatile anaesthetics are the main cause of nausea and vomiting in the early postoperative hours and it is therefore difficult to show the impact of other interventions known to influence nausea and vomiting.2 As the incidence of nausea and vomiting in the post-anaesthesia care unit is only half of that observed in the further postoperative follow-up period,16 we considered that differences in the incidence
of vomiting between the piritramide and morphine PCA regimens would be most easily detected on postoperative day 1.

We were interested in the stability of piritramide during storage and application, which has to be ensured when making statements about drug dosage and effects. While stability of morphine has been shown previously,17 no data were available for piritramide. Thus, in our pilot study piritramide was stored in the same containers that would be used during the study. During storage in the refrigerator and for 4 days at room temperature, we observed a minor increase in piritramide concentration with time of storage. This is likely to be the result of evaporation of water across the PVC reservoir since a gradual increase in drug concentration, indicating loss of water through the PVC container, has been described previously with morphine.18 However, during a 4-day period (i.e. the maximum time interval used in our study), the increase in piritramide concentration was less than 5% and no degradation products were observed. Thus, adequate stability of piritramide in the storage conditions used in our study was ensured.

Several studies report data on the incidence of nausea and vomiting during postoperative pain therapy. However, with some studies,12–16 whilst presumably administering equipotent dosages of different opioids during surgery, comparable analgesia at the time of emesis or nausea has not been assured. In contrast, by using PCA techniques, we assured patient-determined pain scores at the time of assessment of effects.

Furthermore, many studies have addressed analgesia after a single opioid dose in outpatients,13–15 a setting hardly relevant for prolonged intrahospital postoperative pain therapy.

A few studies have reported comparative data on the incidence of emesis and vomiting with morphine or piritramide treatment.3–5 One study of 240 patients reported a lower incidence of nausea and vomiting with piritramide (2.5–15% for different doses) compared with 32% after morphine treatment.4 However, results may have been biased as a higher number of women, known to have a higher incidence of postoperative nausea and vomiting,11 was included in the morphine group. In contrast, no difference in the incidence of nausea and vomiting was reported when piritramide and morphine were given by PCA.5 However, since only 92 patients were included, the latter study7 lacked statistical power.

In general, insufficient sample size flaws the impact of most of the studies addressing side-effects of postoperative opioid therapy.12–15 In contrast, we included 500 patients after performing a sample size estimation from a pilot study (n=100). To our knowledge, there are no other studies on postoperative pain therapy that provide sufficient power to exclude a difference in the incidence of opioid-induced vomiting.

While our data show that the incidence of vomiting during PCA is similar with the opioid agonists piritramide and morphine, we found an inverse dose–emesis ratio with morphine, but not with piritramide. We cannot comment as to whether this is a significant finding or a random observation as we did not primarily intend to test the dose–response ratio. However, differences in the dose–emesis ratio may be the result of differences in the onset and/or degree of tolerance of the emetic receptors with morphine and piritramide.

In fact, opioid-evoked emesis mediated via the brainstem CTZ decreases with repetitive i.c.v. opioid administration, and development of acute tolerance to emetic opioid effects differs between different opioids.7 In particular, morphine, when injected i.c.v. a second time 1 h after a first injection, does not evoke vomiting, whereas it elicited vomiting on the first injection in 75% of cats. This may be a reflection of the pharmacokinetic and pharmacodynamic behaviour of morphine, suggesting that its agonist effects at the CTZ last much longer than its elimination half-life in plasma.19 20 In contrast, there is no evidence for differences between brain and plasma clearance of piritramide.21 Thus, duration of interaction between morphine and opioid receptors in the CTZ may last longer compared with piritramide, and tolerance to its emetic actions may occur earlier or be more intense.

In accordance with the results of others,22 opioid was associated with a high incidence of sedation. Given the very high degree of patient satisfaction, however, sedation does not seem to bother patients.

Surprisingly, in our study, analgesia was perceived to be significantly better in the morphine group. Although the mean difference of 0.4 on the NRS (17% change compared with piritramide) may be considered small,23 observed differences in pain scores between the two opioid-receptor agonists despite using PCA suggests that mitigation of pain is not the only endpoint to which patients titrate. This suggestion is supported by the observation that both craving for opioid intake and patients’ preferences vary between opioids, even when the optical isomers of the same opioid are given.24 Thus, consumption during PCA of specific opioids may not depend solely on analgesic potency and requirements for analgesia but also on euphoric effects or other side-effects.

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