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Oxycodone and ketobemidone for oral premedication

G. Öhqvist [a,*], A. Lindh [a], M. Oja [a], C. Lilja [a], A-S. Andersson [b], L. Westman [a]

[a] *Department of Anaesthesia and Intensive Care, Ersta Hospital, Box 4622, S-11691 Stockholm, Sweden*
[b] *Centre of Gastrointestinal Disease, Research Unit, Ersta hospital, S-11691 Stockholm, Sweden*

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Abstract

In a prospective, randomised and double-blinded study the preoperative sedative effect and the postoperative use of analgesics were compared in 90 patients undergoing inguinal hernia repair under general anaesthesia, premedicated orally with ketobemidone 10 mg, sustained-release oxycodone 10 mg or placebo. All patients had a local infiltration with bupivacaine after wound closure. Oral paracetamol 1 g × 4 and dextropropoyphene 100 mg × 4 were given postoperatively and iv ketobemidone was added if the pain score was >3 on a visual analogue scale from 0 to 10. Oxycodone, ketobemidone and placebo had a similar sedative effect before surgery. The use of ketobemidone after surgery was reduced by 40% in the oxycodone group compared to placebo ($P < 0.05$). No reduction was noted in the ketobemidone group. Conclusion: Sustained-release oxycodone—but not ketobemidone—for oral premedication reduced the postoperative use of opioids after surgery.

Keywords: Oral premedication; Ketobemidone; Oxycodone; Postoperative analgesia; Inguinal hernia repair

1. Introduction

The guidelines for preoperative fasting have changed and oral intake of fluids 2–3 h before induction of anaesthesia is now common practice. Consequently it has become possible and common to avoid injections and instead use oral pre-medication. Various drugs have been recommended. In ambulatory surgery benzodiazepines [1], but also opioids and non steroid anti-inflammatory drugs (NSAID) have been used for premedication [2–4]. Benzodiazepines have good anxiolytic effect but in addition they cause amnesia, which is less favourable in day surgery, and they are without any analgesic effect. An advantage of opioids and NSAIDs is, of course their potential to reduce the opioid consumption during and after surgery [3–5]. The anxiolytic effect of opioids is low in the dose range normally used for premedication. However, when the patient and anaesthesiologist meet before the day of surgery in a relaxed and informative atmosphere, this has in itself a good anxiolytic effect [6].

The aim of the present study was to compare the effect of ketobemidone and sustained-release oxycodone, two opioids with different duration of action, for oral premedication with special reference to the preoperative sedative effect and the possible influence on postoperative need for analgesic drugs.

2. Methods

Ninety adult patients (ASA I-II) scheduled for open, primary inguinal hernia repair were studied with regional ethical committee approval. Informed consent was obtained when the patients and the anaesthesiologist met a few days before surgery. Patients between 20 and 80 years of age without a history of allergic reactions or side effects with paracetamol and opioid-containing oral analgesics were included. Depending on the patients own preference and their age, about 50% of the patients were scheduled by the surgeons for day surgery and the rest were planned to stay over night.

After stratification for age into three groups, 20–39, 40–59 and 60–79 years of age the patients were randomised to receive either ketobemidone, sustained-release oxycodone or placebo as oral premedication. The patients, the staff giving the premedication and those evaluating the patients before and after surgery were blinded.

Approximately 2 h before surgery each patient was administered tablets of paracetamol 1 g and either ketobemidone

* Corresponding author
E-mail address: gun.ohqvist@ersta.se (G. Öhqvist).

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(Ketogan Novum®, Pharmacia) 10 mg or sustained-release oxycodone (OxyContine®, Mundipharma AB) 10 mg or placebo. These doses were chosen following recommendations and routines at other centres.

When the patients arrived in the operating theatre, they were asked if they felt any effect of their premedication and to evaluate it according to a visual analogue scale (VAS) from 0 = no effect at all to 10 = very tired, almost sleeping. The anaesthesia staff also scored the effect of premedication using a similar scale (VAS 0 = no sedation and 10 = sleepy or sleeping). Patients who complained of anxiety or appeared so to the staff received propofol (Propofol® Abbott) 10–30 mg during preparation, before induction of anaesthesia. The respiratory rate at arrival to the operating room (OR) was noted and a rate (breaths/minute) below 10 was classified as respiratory depression. The patients were asked about nausea. Anaesthesia was standardised according to the hospital routine. Propofol (1.5–2 mg/kg) was used for induction and sevoflurane (Sevorane®, Abbot) with addition of fentanyl (Fentanyl®, B. Braun) (0.05–0.1 mg) or alfentanil (Rapifen®, Janssen-Cilag) (0.2–1 mg) for maintenance. A laryngeal mask was used and the patients were on spontaneous ventilation. Standard intraoperative monitoring including ECG, pulse oximetry, capnography and sevoflurane concentration was used. After closure of the surgical wound all patients received a local infiltration with 20 ml of 0.5% bupivacaine (Marcain®, AstraZeneca). Ketobemidone iv, 1–3 mg, was given if the patient was in pain at awakening.

At the postoperative ward, according to our routine, the patients received paracetamol (Alvedon®, AstraZeneca) 1 g and dextropropoxyphene (Dexofen®, AstraZeneca) 100 mg every 6 h starting 4–6 h after surgery. The patients were informed to report pain using a visual analogue scale from 0 = no pain to 10 = most severe pain. Pain score was evaluated every second hour and when the patients reported pain Ketobemidone 1–2 mg was given iv if VAS was more than 3 and repeated until the score was 3 or below. Pain at rest, sedation and nausea were noted in the protocol at 2 and 4 h and for patients staying over night also at 8 h after surgery. The consumption of analgesics was recorded.

After discharge from hospital paracetamol was continued 1 g × 4 and combined with dextropropoxyphene 100 mg × 4 or tramadol (Tradolan®, Nordic Drugs) 50 mg × 4 or codeine (Citodon®, AstraZeneca) 60 mg × 4. The first and second day after surgery the patients were contacted by phone and VAS score for pain at rest and mobilisation was recorded and they were also inquired about nausea.

3. Statistics

The primary variable was total opioid consumption (ketobemidone) after surgery. We considered a difference of 5 mg ketobemidone (mean value) between the groups was clinically interesting. To detect such a difference with 80% power 16 patients in each group was considered to be sufficient.

Analysis of variance was used for parametric variables and x^2 test for non parametric variables, with P values < 0.05 considered statistically significant.

4. Results

Out of 90 patients enrolled in the study four were women. Stratfication for age resulted in 18 patients in the youngest group (20–39 years of age) and 36 patients in each of the other groups (40–59 and 60–79 years respectively). One patient was excluded due to a change in surgical technique to a laparoscopic operation. Twenty nine patients received ketobemidone, 30 sustained-release oxycodone and 30 placebo. The proportions of patients undergoing day surgery and staying over night were similar in the three groups (Table 1). The groups were comparable with respect to age, weight, duration of surgery and distribution of gender and there was no difference in the time interval between premedication and the evaluation at the arrival in the OR (Table 1).

The VAS scores for sedation at the arrival in the OR are given in Fig. 1. There was no difference between the groups. The subjective evaluation by the patient and the evaluation by the anaesthesia staff were almost identical. There was no difference in the number of patients given propofol for sedation (Table 1). No patient had respiratory depression. Three patients reported nausea, two after ketobemidone and one after placebo. Anaesthetic management, including the number of patients without opioids during anaesthesia and the proportion of patients having fenanyl and alfentanil respectively, was similar in the groups (Table 1).

The VAS score for pain (mean ± S.D.) at 2, 4 and 8 h is shown in Fig. 2 and did not differ between the groups. Mean pain score was < 4 in all groups at 2, 4 and 8 h after surgery. The VAS score for tiredness (mean ± S.D.) and the number of patients with nausea are given in Table 2. There was no difference between the groups.

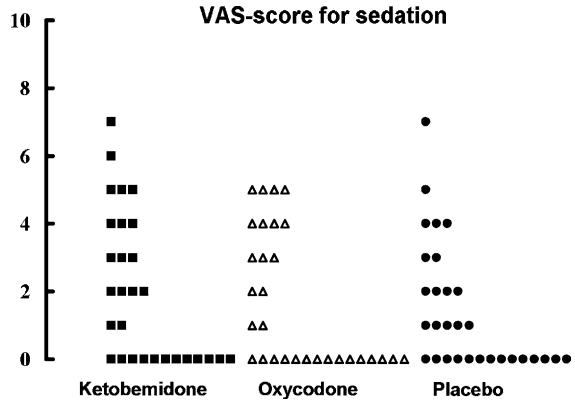

Fig. 1. Distribution within the groups of VAS-scores for sedation given by the patients at the arrival in the operating theatre.

Table 1
Demografic data, time from premedication to evaluation, duration of surgery and opioids used during anaesthesia (mean values ± S.D.) and the number of patients having propofol at the arrival in OR in the three groups

	Ketobemidone	Oxycodone	Placebo
Number of patients, M/F	28/1	29/1	28/2
Day surgery/Patients staying over night	16/13	16/14	14/16
Age years	58.4 ± 16.1	57.3 ± 14.2	53.5 ± 15.2
Weight kg	79.1 ± 10.1	78.3 ± 9.1	77.1 ± 11.9
Time from premed. to evaluation, min	106.4 ± 50.6	102.3 ± 4.6	113.2 ± 56.2
Duration of surgery min	40.3 ± 15.4	42.1 ± 12.5	40.8 ± 14.0
Anaesthesia			
Number of patients having:			
Fentanyl 0.05–01 mg	6	6	8
Alfentanil 0.5–1 mg	20	20	19
No opioid	3	4	2
Number of patients given 10–30 mg of propofol for sedation	4	4	2

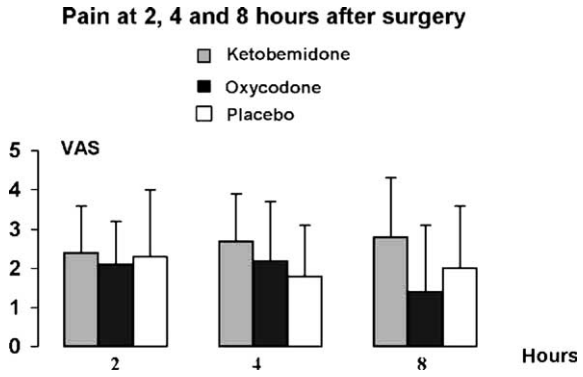

Fig. 2. Pain scores (mean ± S.D.) in the groups 2, 4, and 8 h after surgery.

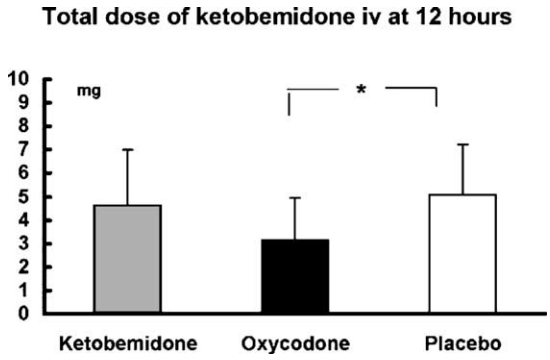

Fig. 3. The dose of iv ketobemidone (mean ± S.D.) used in the three groups during the first 12 h in order to keep pain score below 4. (* $P < 0.05$).

The total dose of iv ketobemidone including the dose given after awakening in the OR and during the first 12 h postoperatively is shown in Fig. 3. Only the dose given in the oxycodone group, 3 mg, differed from placebo, 5 mg ($P = 0.049$).

Eighty-one patients were interviewed during the first and second postoperative day. All had paracetamol plus dextropropoxyphene (68 patients) or tramadol (8 patients) or paracetamol combined with codein (5 patients). Most of the patients reported no or little pain and the mean scores both at rest and mobilization were low in all groups (Table 3). However, 13% of the patients had moderate or severe pain (pain score more than 3) at rest and 34% at mobilization 24 h after surgery and the corresponding numbers were 9 and 30% respectively on the second post-operative day. No differences

Table 2
VAS score (mean ± S.D.) for tiredness and the number of patients with nausea at 2, 4, and 8 h after surgery

	Ketobemidone	Oxycodone	Placebo
Number of pat evaluated at 2 h	27	28	30
Tiredness, VAS	2.6 ± 1.9	1.6 ± 1.9	2.5 ± 2.8
Patients with nausea	2	3	3
Number of pat evaluated at 4 h	27	26	29
Tiredness, VAS	2.9 ± 2.3	1.5 ± 2.6	1.8 ± 1.9
Patients with nausea	1	1	1
Number of pat evaluated at 8 h	11	14	14
Tiredness, VAS	3.2 ± 2.2	1.0 ± 3.4	2.1 ± 2.3
Patients with nausea	2	0	1

Table 3
VAS score (mean ± S.D.) for pain at rest and mobilization and the number of patients with nausea on the first and second day after surgery

	Ketobemidone	OxyContin	Placebo
First day after surgery			
Number of patients interviewed	27	29	29
Pain at rest VAS	2.7 ± 2.3	1.7 ± 1.6	2.0 ± 2.1
Pain at mobilisation VAS	3.7 ± 2.4	2.7 ± 1.5	2.0 ± 2.3
Nausea number of patients	0	0	2
Second day after surgery			
Number of patients interviewed	24	29	28
Pain at rest VAS	1.7 ± 1.0	1.5 ± 1.3	1.5 ± 1.5
Pain at mobilisation VAS	3.1 ± 1.5	2.6 ± 1.7	2.2 ± 2.1
Nausea number of patients	0	1	0

were noted regarding pain at rest, pain at mobilization, tiredness and nausea between the three groups (Table 3).

5. Discussion

Optimal treatment of perioperative pain is important for many reasons. It is of value in itself for humanitarian reasons. Inadequate treatment of acute pain may also develop into a situation of long lasting pain. In the current study a postoperative regimen with infiltration of local anaesthetics—effective mainly during the first hours after surgery—combined with scheduled paracetamol and dextropropoxyphene provided satisfactory pain control in most patients. In some patients in our study, however, this regimen was not sufficient and an opioid was added. In day surgery patients are often discharged only a few of hours after surgery and if prolonged pain is anticipated an analgesic regimen with a prolonged effect is favourable.

Premedication with analgesics has been recommended in order to facilitate pain control in the postoperative period [3–5]. In the current study we compared ketobemidone (duration 4–6 h) and sustained-release oxycodone (10–12 h effect) as premedication. The main result was an ability of sustained-release oxycodone to reduce the need for additional opioid in the early postoperative period, which supports the recommendation. A reduction of the amount of ketobemidone used in the oxycodone group by about 40% compared to placebo was found. A similar effect was, however, not observed in the ketobemidone group. Most probably the explanation for this difference was that the effect of ketobemidone had worn off during the period when local anaesthesia was effective. However, oxycodone with a slow release during 10–12 h had a lasting effect [7]. Oral morphine for premedication, which has a similar duration as ketobemidone, was studied by Beer et al. in patients undergoing face surgery under local anaesthesia [5]. They reported an improved pain management after surgery with morphine compared to placebo. The discrepancy may be explained by the different local anaesthetics used and different timing. Beer used lidocaine and it was applied before surgery, while we used bupivacaine with a reported duration of 5–6 h [8] and applied it at the end of surgery.

The lack of sedative effect after sustained-release oxycodone as well as ketobemidone compared to placebo at the arrival in OR was somewhat unexpected but in accordance with Beers findings after oral morphine for premedication. In our study 41 patients scored 0 (VAS) for sedation and the mean score was very low in all groups. Most patients, however, were satisfied. In well-informed patients subjected especially to minor surgery there is seldom a need for sedative premedication [5]. In the study of Beer a majority (61%) of patients interviewed regarding their preference with regard to sedative or analgesic properties of the premedication, preferred pain reduction to sedation. In the present study, those ten patients who complained of or showed signs of anxiety at arrival in OR 10–30 mg of iv propofol had a very good effect. A high patient satisfaction has been reported with iv propofol for anxiolysis [9].

A possible effect of premedication on the time for discharge from hospital in day surgery was discussed by Barnung [10]. Postoperative tiredness and nausea are symptoms that—in addition to pain—may delay discharge in day surgery. Thus it was interesting to notice that—despite a long lasting analgesic effect—these symptoms were not more frequent in the oxycodone group compared to placebo. We did not, however, address the specific question of readiness for discharge in our study.

In a descriptive study of postoperative pain the first week after open inguinal hernia repair performed under local anaesthesia, 25% of the patients reported moderate–severe pain at rest and 66% had pain at coughing and mobilization on the first postoperative day [11]. The numbers were still high, 20 and 45% respectively, on the second postoperative day. The percentages of patients reporting moderate–severe pain when interviewed the first and second day after surgery in the current study were lower. There are probably several factors involved, which may explain the differences. All patients in the study by Callesen were operated under local anaesthesia and were discharged within a few hours after surgery while in our study surgery was performed under general anaesthesia and the patient stayed in hospital for 4–6 h or over night (50%) with a strict regimen for pain control during hospital stay. Different medication after discharge, tenoxicam+paracetamol in the study by Callesen and dextropropoxyphene+paracetamol in our study, might also have contributed to differences in pain scores the first 2 days after surgery. Furthermore, somewhat different scales for scoring the severity of pain were used in the two studies and make a direct comparison difficult.

6. Conclusion

Sustained-release Oxycodone and Ketobemidone has been compared for oral premedication. Their sedative effect before surgery did not differ from a placebo group. Oxycodone—but not ketobemidone—reduced the need for opioids in the early postoperative period. This lasting analgesic effect is an advantage especially in ambulatory surgery when the patients are discharged early.

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