Epidural oxycodone or morphine following gynaecological surgery†

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Background. The analgesic action of oxycodone is of rapid onset, in contrast to morphine, and is mediated by kappa-opioid receptors of the spinal cord. We compared analgesia and side-effects of epidural oxycodone with those of morphine after gynaecological surgery.

Methods. We studied prospectively in 75 women in a double-blind, randomized manner: epidural morphine 6 mg day\(^{-1}\) (n=25), epidural oxycodone 6 mg day\(^{-1}\) (n=25) and epidural oxycodone 12 mg day\(^{-1}\) (n=25). All patients underwent gynaecological surgery under general (isoflurane and nitrous oxide) and epidural anaesthesia. Visual analogue scale (VAS) pain scores at rest and on coughing, verbal descriptive scale (VDS) satisfaction scores, sedation scores, pruritus scores and nausea/vomiting scores were recorded for 3 days after surgery.

Results. VAS pain scores at rest in patients who received oxycodone 6 mg day\(^{-1}\) were higher than in patients who received morphine 6 mg day\(^{-1}\) at 6 h and on the first postoperative day and were significantly higher than in patients who received oxycodone 12 mg day\(^{-1}\) on the first postoperative day. Scores for nausea, vomiting and pruritus in patients who received oxycodone 6 mg day\(^{-1}\) and 12 mg day\(^{-1}\) were lower than those in patients who received morphine. No significant differences were seen in VAS at cough and VDS satisfaction scores between the three groups.

Conclusion. Epidural oxycodone was as effective as morphine at the doses investigated, with fewer side-effects.


Keywords: anaesthetic techniques, epidural; analgesia, postoperative; analgesic techniques, extradural; analgesics, opioid, morphine; analgesics, opioid, oxycodone

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Epidural morphine has been widely used for postoperative pain relief.\(^{1,2}\) Although it provides excellent analgesia, the incidence of side-effects such as nausea, vomiting and pruritus is unavoidably high and may limit its application. Pruritus often responds poorly to conventional treatment, especially after Caesarean section;\(^{3}\) nausea and vomiting also occur frequently (30–65%).\(^{1,4,5}\)

Oxycodone is a semi-synthetic opioid derivative that has been in clinical use since 1917. It resembles morphine structurally and has a similar lipid solubility.\(^{6}\) It is thought to induce analgesia by mechanism(s) similar to morphine (mu-opioid receptor agonist).\(^{7}\) Recently, it has been reported that the analgesic action of oxycodone is more rapid in onset than with morphine and is mediated by kappa-opioid receptors in the spinal cord.\(^{8}\) Although systemic administration of oxycodone has been reported to cause fewer side-effects than morphine,\(^{9,10}\) only one study has compared oxycodone with morphine by epidural injection for postoperative pain relief in humans.\(^{11}\) Since epidural administration of morphine has been standard practice for postoperative pain relief, we compared analgesia and side-effects of epidural oxycodone with those of epidural morphine after gynaecological surgery.

Methods

After institutional ethics approval and written informed consent, 75 consenting women (ASA physical status I or II) undergoing gynaecological surgery were studied in a randomized (shuffled, sealed, opaque, numbered envelopes), double-blinded manner. Ninety min before arrival in the operating room (OR), each patient received diazepam 10 mg and famotidine 20 mg orally. After routine monitoring of ECG, arterial pressure and pulse oximetry, a catheter was placed in the epidural space using an 18-gauge Tuohy needle...
through T12/L1 or L1/L2 intervertebral space in the lateral decubitus position. An epidural test dose of lidocaine 1.5%, 3 ml with 1:200 000 epinephrine was injected through the catheter to confirm the catheter was placed in the correct space. No local anaesthetic was administered into the epidural space thereafter during surgery.

General anaesthesia was induced with i.v. thiopental 4–5 mg kg⁻¹ supplemented with fentanyl 3 μg kg⁻¹, and tracheal intubation was facilitated with i.v. vecuronium 0.1–0.2 mg kg⁻¹. Anaesthesia was maintained with inhalation of isoflurane, nitrous oxide (67%) and oxygen and intermittent i.v. fentanyl. The total use of fentanyl was recorded. After tracheal intubation, a nasogastric tube was inserted and the gastric contents aspirated.

On termination of surgery, each of the 75 patients received one of the following: (i) epidural morphine 2 mg bolus with bupivacaine 0.25%, 10 ml before starting the infusion of morphine at 6 mg day⁻¹ for 3 days; (ii) epidural oxycodone 2 mg bolus with bupivacaine 0.25%, 10 ml before starting the infusion of oxycodone at 6 mg day⁻¹ for 3 days; (iii) epidural oxycodone 4 mg bolus with bupivacaine 0.25%, 10 ml before starting the infusion of oxycodone at 12 mg day⁻¹ for 3 days.

All patients received continuous epidural infusion (total volume 36 ml, infusion rate 0.5 ml h⁻¹). Before discharge from the OR, approximately within 2 h after the bolus administration of epidural oxycodone or morphine with bupivacaine, we measured arterial blood gases and pH. (Supplementary oxygen was given by face mask.) Until the day after surgery, patients were given oxygen by nasal canula and oxyhemoglobin saturation (SpO₂) was monitored.

In order to examine the efficacy of the treatment regimens employed, the following values were recorded every 3 h after surgery for 6 h, then once a day for the first days after surgery: (i) pain score at rest and on coughing using a 10 cm visual analogue scale (VAS) (0 mm=no pain; 100 mm=worst unbearable pain); (ii) score on a verbal descriptive scale (VDS) of the fulfillment of the patient’s need for analgesia (0=most satisfactory, 10=worst status); (iii) sedation score (1=awake and no sedation; 5=asleep and difficult to rouse); (iv) nausea score (1=none, 2=slight, 3=mild, 4=moderate, 5=severe); (v) vomiting score (1=none, 2= single vomit, 3=multiple vomiting); (v) pruritus score (1=none, 2=slight, 3=mild, 4=moderate, 5=severe).

Treatment for postoperative pain and side-effects was at the patient’s request and was recorded. Analgesia was provided with diclofenac sodium 25 mg (first choice) or pentazocine 15 mg at intervals of 3 h, as required. Nausea and vomiting was treated with i.v. metoclopramide 10 mg at intervals of 3 h, as required. Pruritus was treated with diphenhydramine ointment on request. Arterial pressure (AP), heart rate (HR) and respiratory rate (RR) were also recorded over the same time period.

Statistical analysis
In order to have 80% power of detecting a 35% reduction in VAS pain scores with a significance level of 0.05 (two tailed), and using the method described by Motulsky,¹² we required 25 subjects in each group.

All data are expressed either as the mean (SD) (parametric values) or as the median and 95th percentile (non-parametric values) unless stated otherwise. Patient characteristics were analysed using one-way ANOVA. AP and HR after surgery were analysed using repeated-measures ANOVA. Quantitative non-parametric data were compared using the Kruskal–Wallis test. If a significant result was obtained, post hoc analysis was performed using Bonferroni test for multiple comparisons. Significance was set at P<0.05.

Results
Seventy-five women were enrolled in the study and the three patient groups were comparable in terms of age, height and body weight (Table 1). No significant differences existed between the groups with respect to the amount of fentanyl administered intraoperatively and the duration of surgery and anaesthesia time. VAS pain scores at rest were significantly lower in patients who received epidural morphine compared with those who received epidural oxycodone 6 mg day⁻¹ at 6 h (P=0.01) and on the first postoperative day (P=0.004) and were significantly higher in patients who received epidural oxycodone 6 mg day⁻¹ compared with those who received epidural oxycodone 12 mg day⁻¹ one the first postoperative day (P=0.002) (Fig. 1). VAS pain scores at rest at 0 h in patients who received oxycodone 12 mg day⁻¹ were as follows: 80% (n=20) scored 0; the rest scored 14, 25, 50, 66 and 80. Therefore the median VAS pain score at 0 h was 0.

There was no significant difference between the groups in VAS pain score on coughing (Fig. 1). No significant difference was seen in AP and HR (data not shown). There was no

| Table 1 Patient characteristics and clinical data. Values are mean (range) for age, or mean (SD). SAP, systolic arterial pressure |
|-----------------------------|-----------------------------|-----------------------------|
| Age (yr)                    | Morphin 6 mg day⁻¹         | Oxycodone 6 mg day⁻¹         | Oxycodone 12 mg day⁻¹ |
| Height (cm)                 | 51 (22–69)                 | 49 (24–67)                  | 45 (20–69)             |
| Weight (kg)                 | 56 (11)                    | 52 (10)                     | 54 (7)                 |
| SAP (mm Hg)                 | 122 (14)                   | 116 (17)                    | 106 (14)               |
| Heart rate (beats min⁻¹)    | 74 (10)                    | 78 (11)                     | 71 (12)                |
| Fentanyl used (μg)          | 200 (71)                   | 200 (51)                    | 200 (47)               |
| Duration of surgery (min)   | 130 (75)                   | 115 (52)                    | 135 (72)               |
| Duration of anaesthesia (min)| 210 (80)                   | 180 (66)                    | 205 (81)               |
The total number of additional analgesics given was 23 in the morphine group, 28 in the oxycodone 6 mg day\(^{-1}\) group, and 26 in the oxycodone 12 mg day\(^{-1}\) group (not significant). The number of anti-emetics given was significantly lower in patients who received oxycodone 12 mg day\(^{-1}\) than in patients who received morphine or oxycodone 6 mg per day (8). Two patients in the morphine group, one in the oxycodone 6 mg day\(^{-1}\) group, and none in the oxycodone 12 mg day\(^{-1}\) group required medication to relieve pruritus.

The frequency of nausea on the first and second postoperative days was significantly lower in patients who received epidural oxycodone 6 mg day\(^{-1}\) and oxycodone 12 mg day\(^{-1}\) than in patients who received epidural morphine. The frequency of vomiting at 0 h after surgery and on the first postoperative day was significantly lower in patients who had received epidural oxycodone 6 mg day\(^{-1}\), and on the first and second postoperative days was significantly lower in patients who received epidural oxycodone 12 mg day\(^{-1}\) compared with patients who received epidural morphine.
The frequency of pruritus at 6 h and on the first and second postoperative days was significantly lower in patients who received epidural oxycodone 6 mg day$^{-1}$ and 12 mg day$^{-1}$ than in patients who received epidural morphine (Table 2). There were no significant differences between the groups in pHa and arterial blood gas analysis within approximately 2 h after the bolus administration of epidural morphine or oxycodone, except $P_{O_2}$ which was higher in the oxycodone 12 mg day$^{-1}$ group than in the oxycodone 6 mg day$^{-1}$ group (Table 3). In no patients did RR decrease to 10 bpm after surgery. Two patients who received epidural morphine and none who received epidural oxycodone complained of headache. One patient in the epidural morphine group and one in the epidural oxycodone 6 mg day$^{-1}$ group had urinary retention after surgery. $S_pO_2$ exceeded 95% in all patients. There were no significant differences in sedation scores.

**Discussion**

Our data indicate that when compared with epidural morphine 2 mg bolus plus 6 mg day$^{-1}$ for 3 days, epidural oxycodone 2 mg bolus and continuous infusion of 6 mg day$^{-1}$ for 3 days is less effective for pain relief at 6 h.
and on the first postoperative day; however, oxycodone 4 mg bolus plus 12 mg day−1 for 3 days is as effective as morphine. The incidence of side-effects in patients given epidural oxycodone 6 mg day−1 and 12 mg day−1 was significantly lower than in those who received epidural morphine. Although respiratory depression is the most feared side-effect of epidural opioids, no respiratory depression was seen in any patient in the present study. Patient satisfaction and VAS pain scores on coughing were similar. It is well known that the effects of opioids differ with age, sex, preanaesthetic medication, anesthetic agent used, surgical site, duration of surgery, and other factors, such as metabolism. These factors were comparable for the three groups of patients. Although the present results indicate that epidural oxycodone is as effective as morphine at twice the dose, in the epidural space, a large degree of interpatient variability necessitates further comparative study.

The antinociceptive potency of oxycodone seems to depend on the route of administration. Systemic oxycodone has been reported to be 0.7–1.3 times more potent than morphine given i.v. When i.v. patient-controlled analgesia administration was used, patients requested a dose of oxycodone that was equal to that of morphine for postoperative analgesia after mastectomy; the total consumption of each opioid was approximately 60 mg over 24 h. However, in contrast to i.m., subcutaneous and rectal administration, intrathecal or epidural oxycodone is associated with variable analgesic effects. Kalso and colleagues examined the spinal antinociceptive effect of oxycodone, and found that intrathecal oxycodone was more than 14 times less potent than morphine in rats. For epidural administration, Backlund and colleagues found that oxycodone was 10 times less potent than morphine in patients after abdominal surgery. Our results also indicated a wide individual variability for both VAS and VDS satisfaction score, with epidural oxycodone similar to epidural morphine. Since we have found that oxycodone administered into the brainstem medial pontine reticular formation in rats did not produce any antinociceptive effects, the reduced potency and individual variability observed in patients who received epidural oxycodone might be attributable to lack of a supraspinal action.

Un desirable side-effects such as pruritus and nausea are common with epidural morphine and are believed to be caused via mu-opioid receptor stimulation at the supraspinal level. It is not clear why the need for anti-emetics was significantly less in those who received epidural oxycodone 12 mg day−1 in our study. Since patient characteristics were similar between the three groups, it may be that oxycodone, when administered in the epidural space, is less emetogenic than morphine. Although oxycodone has effects at both mu and kappa-opioid receptors, the affinity of oxycodone for the mu-opioid receptor has been reported to be one-tenth that of morphine. This may account for the fewer side-effects and less analgesia when compared with the same dose of epidural morphine.

In conclusion, our data indicate that epidural oxycodone is as effective as morphine when given at twice the dose, perhaps with fewer side-effects. However, a large degree of interpatient variability suggests the need for further comparative study.

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