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Epidural administered buprenorphine in the perioperative period

Purpose: To study the effect of epidural buprenorphine on minimum alveolar concentration (MAC) of volatile anaesthetics, duration of analgesia and respiratory function in the perioperative period.

Methods: One hundred and twenty patients, ASA I–II undergoing gynaecological surgery were randomly divided into three studies. The forty patients in each study were randomly divided into four groups depending on the dosage; Group I (control), Group II ($80 \mu\text{g} \cdot \text{kg}^{-1}$ morphine), Group III ($4 \mu\text{g} \cdot \text{kg}^{-1}$ buprenorphine), Group IV ($8 \mu\text{g} \cdot \text{kg}^{-1}$ buprenorphine). The MAC of halothane was measured following epidural administration of the agents in each group. The duration of analgesia was assessed by the first request for pentazocine. Postoperative analgesic effects were assessed by the total dosage of pentazocine required for the 48 hr after surgery. Respiratory rate (RR), minute volume (MV), and PaCO_2 were measured during surgery and the postoperative period. The MAC of halothane was reduced in Group IV ($P < 0.01$). The duration of analgesia was 10.0 ± 5.1 hr (Mean $\pm$ SE) in Group I, 37.7 ± 4.7 hr in Group II, 27.1 ± 7.1 hr in Group III, and 44.4 ± 4.1 hr in Group IV. Total dosage of pentazocine was lower in Group IV ($P < 0.05$) than in the other groups. The decrease of RR, MV and the increase of PaCO_2 were observed within 60 min in Group III and IV dose dependently.

Conclusion: Epidural buprenorphine administered in a dose of 4 or $8 \mu\text{g} \cdot \text{kg}^{-1}$ provides postoperative analgesia that is no less effective than that of morphine.

Objectif: Évaluer l'influence de la buprénorphine épidurale sur la concentration alvéolaire minimale (MAC) d'anesthésique volatil, la durée de l'anesthésie et la fonction respiratoire à la période périopératoire.

Méthodes: Cent vingt patientes de classe ASA I et II programmées pour une chirurgie gynécologique étaient réparties en trois études. Les 40 patientes de chaque étude étaient divisées aléatoirement en quatre groupes déterminés selon la dose; Groupe I (contrôle), Groupe II (morphine $80 \mu\text{g} \cdot \text{kg}^{-1}$), Groupe III (buprénorphine $4 \mu\text{g} \cdot \text{kg}^{-1}$), Groupe V (buprénorphine $8 \mu\text{g} \cdot \text{kg}^{-1}$). Le MAC de l'halothane était déterminé après l'administration épidurale de l'agent à l'étude dans chaque groupe. Le première demande de pentazocine permettait de préciser la durée de l'analgesie. La dose totale de pentazocine requise pendant les premières 48 h postchirurgicales évaluait les effets analgésiques postopératoires. À la période postopératoire, la fréquence respiratoire (FR), le volume minute (VM) et la PaCO_2 étaient notés. Le MAC de l'halothane diminuait dans le Groupe IV ($P < 0,01$). La durée de l'analgesie était de $10.0 \pm 5,1$ h (moyenne $\pm$ ET) dans le Groupe I, de $37,7 \pm 4,7$ h dans le Groupe II, de $27,1 \pm 7,1$ h dans le Groupe III et de $44,4 \pm 4,1$ h dans le Groupe IV. La dose totale de pentazocine était moins élevée dans le groupe IV ($P < 0,05$) que dans les autres groupes. Une baisse de FR, MV et une augmentation de la PaCO_2 proportionnelles à la dose étaient observées en deçà de 60 min dans les groupes III et IV.

Conclusion: La buprénorphine épidurale administrée à des doses de 4 ou $8 \mu\text{g} \cdot \text{kg}^{-1}$ procure une analgesie postopératoire aussi efficace que celle de la morphine.

Key words

ANAESTHESIA: gynaecology;
ANAESTHETIC TECHNIQUES: epidural;
ANALGESIA: postoperative;
ANALGESICS: buprenorphine morphine.

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Epidural administration of morphine has been used extensively since the initial positive report.¹ However, compared with the intrathecal route, epidural administration of opioids is complicated by pharmacokinetic aspects related to dural penetration, fat deposition, and systemic absorption. The effect of epidural opioids and analgesics on the onset and duration of analgesia is considered to be strongly correlated with its lipophilicity and hydrophilicity.² The pharmacokinetic behaviour of the agents also influences the incidence of undesirable side effects, particularly early and late respiratory depression, which is often observed with epidural administration of morphine.^{3–5}

Buprenorphine is a relatively new synthetic opioid with both agonistic and antagonistic properties. Unlike morphine, it is a more lipid soluble and less water soluble drug and is less likely to cause late respiratory depression.⁶

Systemic administration of opioids reduces the MAC of volatile anaesthetics, but there have been recent conflicting reports that intrathecal morphine does not reduce MAC, and the subject is still controversial.

This study was designed to evaluate the effects of epidural administration of morphine and buprenorphine, which have different hydro- and lipophilicity on the MAC of halothane, duration of analgesia, postoperative analgesic requirements and the respiratory function during and after surgery.

Methods

Study population

Following approval of the institutional ethical committee, 120 patients undergoing gynaecological surgery of the lower abdomen consented to participate in this study. All subjects were ASA I or II, and aged 25–62 yr. Subjects >70 yr or >70 kg body weight were excluded. All patients underwent hysterectomy or ovariectomy for the removal of a benign tumour excluding laparoscopic surgery.

Anaesthetic technique

Premedication was administered with 0.5 mg atropine sulphate *im* 30 min before induction of anaesthesia. After local anaesthesia, an epidural catheter was inserted at the interspace between L₃ and L₄ and advanced 3 cm cephalad into the epidural space. Morphine or buprenorphine with saline or lidocaine was injected via an epidural catheter according to the protocol. After confirming the level of analgesia by pin-prick 20 min after the injection, anaesthesia was induced with 5 mg·kg⁻¹ thiopentone and tracheal intubation was facilitated with 1 mg·kg⁻¹ succinylcholine chloride *iv* 20 min before the incision.

Study 1, MAC

The patients were randomly divided into four groups of ten subjects.

Group I, 20 ml saline via an epidural catheter;

Group II, 20 ml saline and 80 µg·kg⁻¹ morphine via an epidural catheter;

Group III, 20 ml saline and 4 µg·kg⁻¹ buprenorphine via an epidural catheter;

Group IV, 20 ml saline and 8 µg·kg⁻¹ buprenorphine via an epidural catheter.

The patients breathed spontaneously throughout sur-

gery with 6 L·min⁻¹ oxygen. To determine MAC, the preselected end-tidal halothane concentration was maintained for a minimum of 20 min before the incision. A nerve stimulator was used to ensure no residual paralysis by succinylcholine chloride remained at the time of the incision. The presence or absence of movement was determined by a blinded observer. A positive response was defined as "gross purposeful" movement.⁷ If a patient did not move at incision, the next patient in the same treatment group was tested with a 0.1% lower halothane concentration. If movement was apparent, the halothane concentration was increased by 0.1%. The MAC of halothane for each group was calculated and compared using logistic calculation.⁷

Study 2, Postoperative analgesia

The patients were divided randomly into four groups of ten subjects.

Group I, 20 ml lidocaine 2% (control) via an epidural catheter;

Group II, 20 ml lidocaine 2% and 80 µg·kg⁻¹ morphine via an epidural catheter;

Group III, 20 ml lidocaine 2% and 4 µg·kg⁻¹ buprenorphine via an epidural catheter;

Group IV, 20 ml lidocaine 2% and 8 µg·kg⁻¹ buprenorphine via an epidural catheter.

The patients' lungs were mechanically ventilated using pancronium bromide with a mixture of N₂O (4 L·min⁻¹) and O₂ (2 L·min⁻¹) throughout surgery. In the postoperative period, when analgesia was requested, 15 mg pentazocine was injected *im*. For further analgesia, the dose was repeated. The exact time and dose of pentazocine was recorded in the chart for 48 hr after surgery. No other analgesics were administered during the postoperative period. The duration of analgesia was defined as the period from the epidural administration of the agents to the first request for analgesia. The effect of analgesia by epidural morphine or buprenorphine was assessed by the total dose of pentazocine required for 48 hr after surgery.

Study 3, Respiratory function

The patients were divided randomly into four groups of ten subjects in the same way as in study 2. The patients breathed spontaneously throughout surgery with a mixture of N₂O (4 L·min⁻¹) and O₂ (2 L·min⁻¹). Respiratory rate (RR), Minute Volume (MV) and PaCO₂ were measured continuously during surgery. The RR and MV were also measured at 6 and 12 hr after the administration of morphine or buprenorphine.

Information regarding side effects such as nausea, vomiting, pruritus, and urinary retention was obtained

from the chart in the recovery room. Any complaints of dyspnoea were also recorded every three hours.

Data were analyzed using unpaired Student *t* test. *P* < 0.05 was considered statistically significant. Data are presented as mean values $\pm$ SD or SE.

Results

One hundred and twenty patients were investigated. Their mean age was 41.2 ± 2.6 yr (mean $\pm$ SD), and body weight was 59.9 ± 9.8 kg (mean $\pm$ SD). The duration of surgery was 118 ± 29 min. (mean $\pm$ SD).

Study 1

MAC OF HALOTHANE

The MAC of halothane was $0.79 \pm 0.03\%$ (mean $\pm$ SE) in Group I, $0.62 \pm 0.03\%$ in Group II, $0.61 \pm 0.02\%$ in Group III, and $0.40 \pm 0.02\%$ in Group IV. The MAC of halothane in Group IV was lower than that in the others. (*P* < 0.01) (Figure 1).

Study 2

DURATION OF ANALGESIA

The time from the epidural administration of the agents until the first request for pentazocine for postoperative pain relief was 10.0 ± 5.1 hr (mean $\pm$ SE) in Group I, 37.7 ± 4.7 hr in Group II, 27.1 ± 7.1 hr in Group III, and 44.4 ± 4.1 hr in Group IV. The duration of analgesia in Groups II, III and IV was longer than that of Group I (*P* < 0.05). There were no differences between Group II, III, and IV (Figure 2).

POSTOPERATIVE ANALGESIA

The total dose of pentazocine during the 48 hr after surgery in Group I was 15.0 ± 6 mg (mean $\pm$ SE), 6.7 ± 4 mg in Group II, 6.0 ± 3 mg in Group III, and 2.5 ± 2 mg in Group IV. The dose in Group IV was lower than that of the other groups. (*P* < 0.05) (Figure 3).

Study 3

RESPIRATORY RATE (RR)

Sixty minutes after the administration of morphine or buprenorphine, RR remained within the normal range (15 to $20 \cdot \text{min}^{-1}$) in Group I. Compared with Group I, RR decreased by 15% in Groups II and III, and decreased by approximately 50% 60 min after the administration of $8 \mu\text{g} \cdot \text{kg}^{-1}$ buprenorphine in Group IV (*P* < 0.05) (Figure 4).

MINUTE VOLUME (MV)

Sixty minutes after the administration of morphine or

FIGURE 1 Change of the minimum alveolar concentration (MAC) of halothane. MAC of halothane decreased in Group IV compared with Group I (*P* < 0.01).

FIGURE 2 Duration of analgesia. The duration of analgesia in Group II, Group III, and Group IV was longer than that in Group I (*P* < 0.05).

buprenorphine, MV decreased to $3.8 \pm 0.41 \text{ L} \cdot \text{min}^{-1}$ (mean $\pm$ SE) in Group II and $4.1 \pm 0.88 \text{ L} \cdot \text{min}^{-1}$ in Group III. In Group IV, MV decreased sharply to $3.4 \pm 0.61 \text{ L} \cdot \text{min}^{-1}$ 30 min after the administration (*P* < 0.01, compared with Group I) and $3.6 \pm 0.85 \text{ L} \cdot \text{min}^{-1}$ 60 min after the administration (Figure 5).

PaCO₂

The mean value of PaCO₂ in Group I was 39.5 ± 1.7 mmHg. (mean $\pm$ SE). The PaCO₂ in Group IV at 60 min was 47.0 ± 1.4 mmHg which was higher than that of

FIGURE 3 Postoperative analgesia. The total dose of pentazocine 48 hr after surgery in Group IV was less than that in the other groups ($P < 0.05$).

FIGURE 4 Change of the respiratory rate. Sixty minutes after the administration of morphine or buprenorphine, the respiratory rate (RR) decreased by 15% in Group II and Group III, 50% in Group IV ($\bullet - \bullet$) ($P < 0.05$) compared with Group I.

Group I ($P < 0.05$). There were no changes in PaCO_2 in Group I, II, and III (Figure 6).

Side effects

There were no serious side effects requiring treatment in any patient. No undesirable side effects such as pruritus, or urinary retention were observed except in two patients in Group II who experienced nausea. There was

FIGURE 5 Change of the minute volume (MV). The MV decreased in Group II, Group III and Group IV 60 min after the administration of morphine ($\circ - \circ$). In Group IV ($\bullet - \bullet$), MV had decreased 30 min after the administration of buprenorphine ($P < 0.01$).

FIGURE 6 Change of PaCO_2 . The PaCO_2 in Group IV ($\bullet - \bullet$) had increased 60 min after the administration of buprenorphine ($P < 0.05$, compared with Group I).

no correlation between dose and side effects in epidural administration of buprenorphine in Groups III or IV.

Discussion

The transmission of pain is not a simple passive process but is produced by messages between neuronal systems at many levels of the central nervous system which converge on the spinal cord.^{8,9} It is well known that wind-up and NMDA receptor activation can be induced with electrical, mechanical, and inflammatory C-fibre

stimulation. These events are likely to occur during surgical procedures even in the presence of anaesthesia.¹⁰

Recent work has revealed that pre-emptive analgesia is relevant for postoperative pain relief by suppressing hypersensitivity of neurons and blocking abnormal exaggerated pathways.¹⁰⁻¹² Opioids and local anaesthetics exert their antinociceptive effects in the spinal cord by a different mechanism and opioids prolong the duration of local anaesthetic-induced sensory blockade. A combination of these agents may offer a theoretical advantage for postoperative pain relief.¹³

Postoperative analgesia by epidural opioids has been tested in numerous studies and is now widely used in clinical practice. Although morphine has been the most commonly used opioid, it can cause side effects such as: pruritus, nausea, vomiting, urinary retention, and respiratory depression.¹⁴⁻¹⁶

Buprenorphine is a relatively new synthetic opioid with both agonist and antagonist properties, and has a high receptor affinity and lipid solubility⁶ with less physical dependence.¹⁷ Unlike morphine, the more lipid soluble and less water soluble drugs, such as buprenorphine and fentanyl are less likely to cause late respiratory depression unless an extremely large dose is used. It may be preferable to morphine when used perioperatively as a pre-emptive agent.

Systemic administration of opioids reduces the MAC of volatile anaesthetics by 20 to 60% in animals and humans, depending on the dosage and route of administration.¹⁸⁻²² However, a conflicting report has recently emerged suggesting that intrathecal morphine does not reduce MAC.²³

In our study, the MAC of halothane in the control group corresponded to previously published values,²⁴ while epidural administration of morphine reduced the MAC of halothane by 22%, and buprenorphine reduced it by 23% after administration of $4 \mu\text{g} \cdot \text{kg}^{-1}$ and 49% after $8 \mu\text{g} \cdot \text{kg}^{-1}$ respectively. This reduction probably resulted from impairment of rostral transmission of nociceptive impulses by binding of spinal opioid receptors as well as activation of supraspinal opioid sensitive sites. Opioids produced analgesic effects both during and after surgery, and the analgesic effect of buprenorphine was dose-dependent.

Early and late respiratory depression is a major complication when opioids are administered into the intrathecal or epidural space. In our study, early respiratory depression occurred within 60 min, indicated by the decrease of RR and MV, and increase of PaCO_2 , after epidural buprenorphine. Respiratory depression was most remarkable in the patients of Group IV ($8 \mu\text{g} \cdot \text{kg}^{-1}$ buprenorphine) but they recovered without treatment. This early respiratory depression probably reflects the

absorption via epidural veins and rapid distribution to the brain as suggested by Cousin *et al.*²⁵ and it may be explained by its lipophilicity which also induces the rapid onset and medium duration of analgesia of epidural buprenorphine. Compared with morphine, which tends to linger in the water phase in the cerebrospinal fluid (CSF) and spread more widely and rostrally²⁶ in the spinal canal due to its hydrophilicity, buprenorphine can reach the brain more quickly due to the rapid uptake into the epidural veins, as Moore *et al.* suggested.²⁷ The high lipophilicity and relatively small molecular weight of buprenorphine lead to rapid vascular removal. Late respiratory depression was not recorded in the 48 hr after surgery in any group, probably because epidural administration of morphine $80 \mu\text{g} \cdot \text{kg}^{-1}$ was not a large enough dose to cause late respiratory depression in relatively healthy middle-aged patients.

Postoperative analgesia was obtained in both groups receiving epidural morphine and buprenorphine. Duration of analgesia, evaluated by the first request for pentazocine after surgery, was longer in both groups of buprenorphine and morphine than in the control group, and was dependent on the dose of buprenorphine. The effect of morphine $80 \mu\text{g} \cdot \text{kg}^{-1}$ on the duration of analgesia was similar to that of buprenorphine $8 \mu\text{g} \cdot \text{kg}^{-1}$. The total dose of pentazocine during the 48 hr after surgery was lower in the group receiving buprenorphine $8 \mu\text{g} \cdot \text{kg}^{-1}$ than in the control group. Thus, the epidural administration of opioids caused prolonged analgesia when used as a supplement to local anesthesia. There was no difference between morphine and buprenorphine in our study although the effectiveness of buprenorphine could have been dose-dependent.

The ideal dose of buprenorphine to add to the intrathecal space suggested by Valenti was $3 \mu\text{g} \cdot \text{kg}^{-1}$, which produced the same duration of analgesia as $7 \mu\text{g} \cdot \text{kg}^{-1}$ of morphine, but with fewer side effects.²⁸ Raudomanska *et al.* showed that epidural administration of 0.3 mg buprenorphine was safe and effective for postoperative pain relief.²⁹ In contrast, Wolff reported that 0.3 mg buprenorphine administered epidurally provided similar analgesia to 4 mg morphine, and did not offer any advantages over morphine following orthopaedic surgery. However a high incidence of pruritus and urinary retention was reported with the administration of morphine.³⁰

We studied two different doses of buprenorphine, 4 and $8 \mu\text{g} \cdot \text{kg}^{-1}$. Increasing the dose of buprenorphine did extend the duration of analgesia but increased the respiratory depression within 60 min in the case of the $8 \mu\text{g} \cdot \text{kg}^{-1}$ buprenorphine although this recovered without treatment. In our investigation no high risk patients were studied and no serious side effects occurred following

gynaecological surgery. Therefore the "risk profile" must be taken into account when deciding on dose.

It is uncertain whether epidural buprenorphine offers any benefits compared with morphine, because the effectiveness of analgesia and incidence of complications may depend on the dose, the patient's physical and mental condition, and the type of surgery. However epidural administration of buprenorphine has the possibility of being used widely in clinical practice in the same way as morphine to prolong the duration of analgesia, and produce less undesirable side effects such as late respiratory depression due to its high lipid solubility.

In conclusion, epidural buprenorphine administration of 4 or 8 $\mu\text{g} \cdot \text{kg}^{-1}$ provided prolonged analgesia when used as a pre-emptive analgesia and resulted in dose-dependent reductions of anaesthesia during surgery and analgesics in the postoperative period.

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