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COMPARISON OF EXTRADURAL ADMINISTRATION OF SUFENTANIL, MORPHINE AND SUFENTANIL–MORPHINE COMBINATION AFTER CAESAREAN SECTION

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SUMMARY

We have studied postoperative analgesia and unwanted side effects of a single dose of a mixture of morphine and sufentanil administered extradurally with the effects produced by extradural injection of each opioid alone in 64 patients after Caesarean delivery. The patients were allocated randomly to receive morphine 4 mg (n = 21), sufentanil 50 μg (n = 22) or morphine 2 mg with sufentanil 25 μg (n = 21) via an extradural catheter in a double-blind design. Intensity of pain was measured using a linear visual analogue scale. Compared with the effect produced by morphine alone, the morphine–sufentanil combination produced more rapid onset of pain relief (19 (SD 5) min vs 79 (23) min for a 75% reduction of pain; P < 0.01), whereas the duration and quality of analgesia assessed during 12 h was similar for these two groups. In contrast, patients receiving sufentanil alone required significantly more supplementary analgesia 4 h after administration than with morphine alone or morphine combined with sufentanil. There were no significant changes in cardiorespiratory variables in any group. Side effects consisted mainly of pruritus and nausea and did not differ between groups, with the exception of early and transient dizziness which was observed only in patients given sufentanil either alone or in combination with morphine. We conclude that a single extradural injection of morphine and sufentanil combines the short onset time produced by sufentanil and the long duration of analgesia attributable to morphine, thus providing excellent and prolonged analgesia after Caesarean delivery.

KEY WORDS

Analgesics: morphine, sufentanil. Anaesthetic techniques: extradural. Pain: postoperative. Surgery: Caesarean delivery.

Continuous administration of opioids via an extradural catheter is being used increasingly for analgesia after Caesarean section. Morphine remains the reference substance among the agents used in this situation [1–4]. While the quality of analgesia with this opioid is excellent, the onset of pain reduction, which ranges from 45 to 90 min, is late, thus usually necessitating concomitant parenteral injection of another opioid. Unwanted side effects of extradural morphine include nausea, vomiting, pruritus, excessive sedation, urinary retention and early or delayed respiratory depression. These problems limit the widespread routine use of this mode of administration. In particular, reports of delayed, profound and prolonged respiratory depression impose the need for continuous surveillance over many hours after extradural morphine has been administered [5–9].

Sufentanil is a lipophilic opioid belonging to the fentanyl derivatives, with physicochemical and pharmacodynamic characteristics distinct from those of morphine derivatives. It is five to seven times more potent than fentanyl, highly lipophilic, and has a high affinity for spinal cord mu opioid receptors. As a result, sufentanil possesses a rapid onset of action with excellent analgesic properties [10]. However, the duration of action of sufentanil administered by the extradural route is less than 4 h [10–12]. Adequate postoperative analgesia with this drug therefore requires either continuous administration or repeated i.v. bolus injections.

Because of their different pharmacokinetic and pharmacodynamic characteristics, administration of morphine and sufentanil as a single combined injection via an extradural catheter at 50% of the dose used for each agent alone should allow advantageous combination of the short onset time of sufentanil and the long duration of analgesia of morphine. In addition, it may be possible to reduce the incidence of side effects observed with each agent alone.

The present study was undertaken to evaluate, after Caesarean delivery, the time course of postoperative analgesia using a mixture of morphine and sufentanil injected extradurally. In addition, we wished to compare the observed effects of this combination with those produced by extradural injection of each opioid alone.

PATIENTS AND METHODS

Sixty-four ASA I or II patients undergoing elective Caesarean delivery gave informed consent to participate to the study, which was approved by the Ethics Committee for Human Research of our institution. Drug-dependent patients or those who had received parenteral injection of a benzodiazepine

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or an analgesic in the postoperative period were excluded. No medication was administered to the parturient during the study, other than the two opioids investigated, the local anaesthetics used for delivery by Caesarean section, and ephedrine administered when there was a decrease in mean arterial pressure of more than 25% of baseline.

Before operation, a large i.v. cannula was inserted into a peripheral arm vein and patients received balanced electrolyte solution 10 ml kg^{-1}. An extradural catheter was introduced at the L2–3 or L3–4 interspace and advanced 5 cm cephalad. A mixture of equal volumes of 0.5% bupivacaine and 2% lignocaine was injected in incremental doses into the extradural space to produce a sensory anaesthesia to T4 dermatome. In addition, the bladder was catheterized.

After delivery of the infant, the patient was transferred to the recovery room. When the patient first requested pain relief she was asked to rate her level of pain intensity on a 10-cm linear visual analogue scale (VAS) (0 = no pain; 10 = worst pain) [13, 14]. Baseline arterial pressure, heart rate and ventilatory frequency were noted. The anaesthetist then injected through the extradural catheter in a randomized and double-blind manner one of three preparations: group 1 = sufentanil 50 μg; group 2 = morphine 4 mg; group 3 = sufentanil 25 μg + morphine 2 mg. Each preparation consisted of two syringes (in order to avoid mixing morphine and sufentanil) with the opioid diluted in 0.9% sodium chloride 5 ml, to produce a total injected volume of 10 ml. The original blinded vials containing the drugs were prepared and provided by Janssen Pharmaceuticals.

After the extradural injection of the opioid, the following variables were recorded, first at 5-min intervals during the first 15 min, then every 15 min during the subsequent 2 h and then at 1-h intervals to the end of the study (12 h): pain intensity as estimated by VAS score; heart rate and rhythm using a standard Hewlett–Packard monitor; mean arterial pressure using a non-invasive automatic pressure monitor (Dinamap, Criticon, U.S.A.); ventilatory frequency by counting ventilations; and oxygen haemoglobin saturation by pulse oximetry (Satlite, Datex Instrumentarium, Helsinki, Finland).

Side effects such as pruritus, nausea, vomiting, drowsiness and respiratory depression were recorded during the investigation by the nursing staff. If necessary, these side effects were treated with promethazine (pruritus), metoclopramide (nausea and vomiting) or naloxone (respiratory depression).

The patients remained in the recovery room for at least 12 h after the first extradural injection of opioid. They were instructed to ask for additional parenteral pain medication (morphine, pethidine) when they began to experience pain and the time interval between extradural and parenteral administration of opioid was recorded.

Statistical analysis

Numeric data were expressed as means (SD) and compared between groups with one-way analysis of variance followed by Student's *t* test using Bonferroni's correction. Non-parametric data were compared using chi-square analysis. The mean time interval in each treatment group corresponding to a decrease of the VAS pain score to 50% or 25% of baseline, respectively, was obtained by linear regression analysis of individual VAS scores over the initial time period.

RESULTS

There were no significant differences between the three groups of patients in the number of parturients entered in each group, age, height, weight or parity (table I).

Time to the onset of pain relief was similar in the sufentanil and morphine–sufentanil groups, but statistically longer in the morphine group (fig. 1). A 50% decrease in pain score from baseline was observed within 7 (0.2) min in the sufentanil group and within 13 (3) min in the morphine–sufentanil group, but was not observed until 53 (15) min after morphine administration ($P < 0.01$ compared with the other two groups). Similarly, a 75% reduction in pain score was observed after 10 (0.3) min in the sufentanil group, 19 (5) min in the morphine–sufentanil group and 79 (23) min in the morphine group ($P < 0.01$).

From 60 min after extradural drug injection until the end of the 12-h study, the VAS score was no longer significantly different between patients who received morphine and those who received the morphine–sufentanil combination. In patients given sufentanil alone, the VAS score was smaller at first

TABLE I. *Patient data (mean (SD)). No statistically significant differences between groups*

	Sufentanil ($n = 22$)	Morphine ($n = 21$)	Morphine–sufentanil ($n = 21$)
Weight (kg)	76 (12)	71 (11)	70 (11)
Height (cm)	160 (5)	161 (7)	158 (6)
Age (yr)	31 (15–40)	30 (20–41)	32 (24–42)

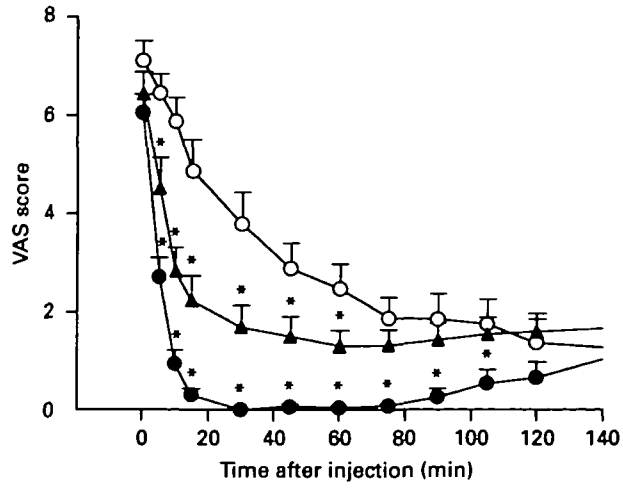

FIG. 1. Pain, as measured by visual analogue scale (VAS), before and after the first 120 min of extradural administration of morphine 4 mg (○) ($n = 21$), sufentanil 50 μg (●) ($n = 22$) or the combination of morphine 2 mg and sufentanil 25 μg (▲) ($n = 21$) (mean + SE). *$P < 0.05$ compared with time-matched data points for morphine administration.

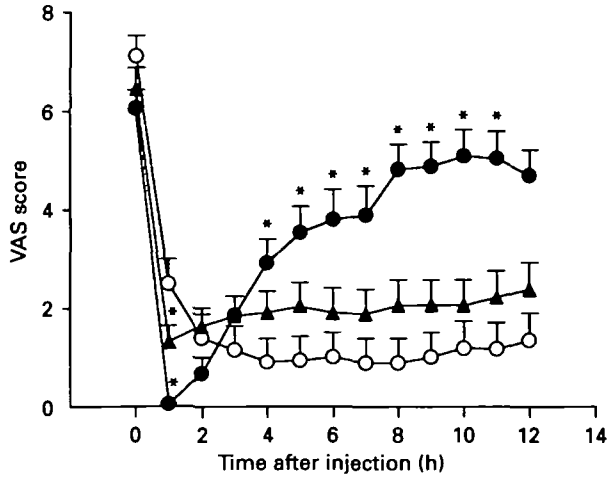

FIG. 2. Pain, as measured by visual analogue scale (VAS), before and after extradural administration of morphine 4 mg (○) ($n = 21$), sufentanil 50 μg (●) ($n = 22$) or the combination of morphine 2 mg and sufentanil 25 μg (▲) ($n = 21$) (mean + SE). *$P < 0.05$ compared with time-matched data points for morphine administration.

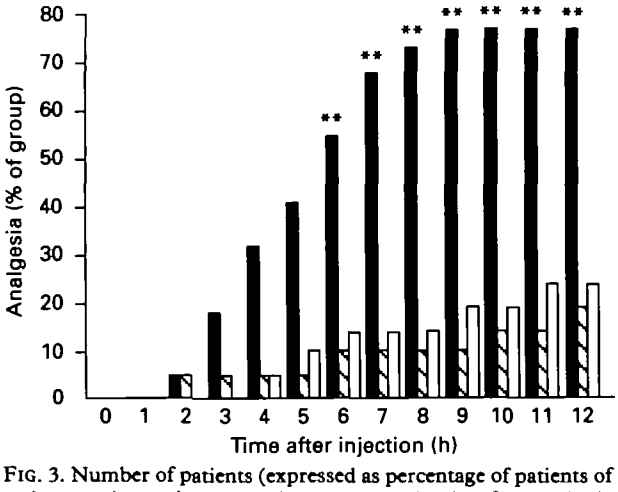

FIG. 3. Number of patients (expressed as percentage of patients of each group) requiring supplementary analgesia after a single extradural administration of morphine 4 mg (▨) ($n = 21$), sufentanil 50 μg (■) ($n = 22$) or the combination of morphine 2 mg and sufentanil 25 μg (□) ($n = 21$). **$P < 0.01$ compared with time-matched data points for morphine administration.

TABLE II. *Respiratory variables (mean (SD) [range]) and patients (No. (%)) with side effects after extradural sufentanil, morphine or morphine–sufentanil combination.* *P < *0.05 compared with morphine*

	Sufentanil ($n = 22$)	Morphine ($n = 21$)	Morphine–sufentanil ($n = 21$)
Ventilatory frequency (b.p.m.)	17.1 (2.2) [9–24]	18.5 (3.2) [10–28]	17.1 (1.9) [12–24]
O_2 haemoglobin saturation (%)	96.0 (1.4) [90–100]	96.7 (1.2) [92–99]	96.5 (1.2) [91–99]
Pruritus	9 (41)	10 (48)	9 (43)
Nausea or vomiting	3 (14)	2 (10)	2 (10)
Dizziness	3 (14)*	0 (0)	6 (29)*

(between 75 and 105 min) (fig. 1); thereafter it was significantly greater (between 4 and 11 h) than in the two other groups (fig. 2).

The need for supplementary analgesia appeared at 105 min in the sufentanil group and became and remained significantly different from that in the other two groups between 6 and 12 h of the study (fig. 3). There were no significant differences between the two other groups in this respect. At 12 h, 77% of patients in the sufentanil group had requested additional pain medication, whereas only 24% (morphine–sufentanil group) and 19% (morphine group) requested analgesia in the other two groups.

Heart rate and mean arterial pressure were similar in the three groups and did not change significantly in any group. Similarly, ventilatory frequency and oxygen haemoglobin saturation were unchanged during the whole study; the slowest ventilatory frequency (9 b.p.m.) was noted in one patient at 30 min, associated with an oxygen haemoglobin saturation of 90% and was not accompanied by clinical signs of respiratory depression (table II).

Pruritus and nausea or vomiting were observed in similar proportions in all three groups (table II), with 25% (sufentanil–morphine group) to 50% (morphine group) of patients requiring treatment with either promethazine or metoclopramide. Dizziness was present in 14% of parturients in the sufentanil group and in 28% of the sufentanil–morphine group, but was absent in all patients receiving morphine alone (table II). This side effect was rated mild by the parturients, lasted only a few minutes, and had disappeared completely within 30 min of injection, without treatment.

After the 12-h follow-up study, the patients remained under close monitoring, including pulse oximetry and frequent observation by the ward nurses. There were no complications during the subsequent 12 h.

DISCUSSION

Extradural morphine or sufentanil has been reported to be effective for post-Caesarean pain control [1–4, 10–12]. Our results with both morphine or sufentanil alone confirm previous studies. With morphine, the quality of analgesia was judged excellent and lasted at least 12 h. Side effects consisted mainly of pruritus (47%) and nausea (9%); there was no clinically significant decrease in ventilatory frequency or oxygen haemoglobin saturation. In contrast, extradural injection of sufentanil 50 μg produced very rapid pain relief that was effective but of short duration (~ 4 h), while producing an identical incidence of side effects. Fourteen per cent of patients in this group also presented some degree of mild dizziness which disappeared spontaneously within 15 min. This has been reported also by Klepper and colleagues in human volunteers [15], whereas others did not report this side effect [10–12].

Injection of a combination of these two opioids at 50% of the dose used alone (morphine 2 mg, sufentanil 25 μg) produced rapid onset of analgesia (within 19 min), of excellent quality, and of prolonged duration (> 12 h). During the first minutes, the quality and onset time of pain relief were comparable to those observed with sufentanil alone, and over the 12 h studied the quality and duration of

analgesia were comparable to that observed with morphine administration. Furthermore, the need for supplementary analgesics did not differ between patients receiving the sufentanil–morphine combination and those given morphine alone (24% and 19%, respectively).

The doses of morphine used in this combination have been reported to be insufficient as a single dose [2, 16]. In the present study, we were able to show that this dose was nevertheless sufficient for prolonged analgesia when combined with sufentanil. These results indicate further that competition at spinal cord mu opioid receptors did not seem to occur, and effects were sequential and partly additive. This mode of opioid administration allowed reduction in the amount of opioid injected into the extradural space, thus reducing the incidence of possible side effects caused by excess morphine in the cerebrospinal fluid. The greater lipophilicity of sufentanil provided rapid diffusion of the drug into the cerebrospinal space, where it is bound very strongly to mu opioid receptors [17]. The combination of these two properties, lipid solubility and affinity for mu receptors, explains its rapid and potent analgesic effect. In contrast, the more hydrophilic morphine diffuses more slowly into the intrathecal space, which accounts for its delayed onset but prolonged duration of action [18]. With the exception of dizziness, which was noted only in presence of sufentanil, either alone or in combination with morphine, the other classical side effects noted with opioids were similar in the three groups, indicating that, in spite of the reduced amount of each opioid alone, their combination in a single injection did not significantly diminish the incidence of side effects produced by each drug separately. The transient sensation of dizziness may possibly be explained by sufentanil reaching the equilibrium centres in the central nervous system via diffusion into the intravascular space.

Haemodynamic and respiratory variables did not change significantly in the groups. However, our results do not exclude subclinical respiratory depression. Ventilatory response to carbon dioxide was not measured in this study, and the relatively small number of patients in each group is insufficient to evaluate a complication that has an incidence of 0.09–0.90% [9, 16]. Nevertheless, it is likely that the risk of delayed respiratory depression is attenuated with this mode of combined opioid administration, as this potentially disastrous complication appears to occur most frequently with poorly lipid-soluble drugs, such as morphine [19].

In summary, we have demonstrated that the simultaneous injection of sufentanil and morphine into the extradural space for postoperative analgesia after Caesarean delivery combined the advantages of both drugs administered alone—rapid onset of action produced by sufentanil, together with a long duration of action produced by morphine.

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