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Anesthesiology
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High Thoracic Epidural Sufentanil for Post-thoracotomy Pain: Influence of Epinephrine as an Adjuvant—A Double Blind Study

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A previous study in which epinephrine was added to morphine administered epidurally resulted in analgesia of a more intense nature, more rapid in onset, and of longer duration than when plain morphine solutions were used.[1] It was also noted that the adverse effects of pruritus, nausea, vomiting, and difficulty of micturation were intensified by the addition of epinephrine. Furthermore, respiratory depression as reflected by diminished responsiveness to inhaled CO_2 between 6 and 16 h after morphine injection was greater following morphine-epinephrine solution. However, these studies were performed in human volunteers using a poorly lipid soluble drug. Results from three recent studies suggest that epinephrine added to highly lipid soluble opioids for lumbar epidural analgesia not only reduces their unwanted side effects, but also confers a longer duration and intensity of analgesia.[2–4] Sufentanil has a lipid solubility 1000 times greater than morphine, is even more selective than fentanyl for the μ-receptor,[5] and is clinically more potent[6] than fentanyl or morphine. In addition, it has not yet been associated with delayed respiratory depression after epidural administration.[7,8] A previous study in which plain sufentanil was administered for thoracic epidural analgesia revealed a peak plasma level of sufentanil within 10 min of the initial and subsequent injections.[9] Respiratory rate,

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TABLE 1. Demographic Data: Mean (SEM)

	Group 1 (SP)* (n = 12)	Group 2 (SE)* (n = 11)
Age (yr)	46 (6)	51 (6)
Height (cm)	175 (3)	175 (3)
Weight (kg)	67 (4)	71 (3)

* (SP) = sufentanil plain 50 μg in 10 ml saline; (SE) = sufentanil 50 μg in 10 ml saline + epinephrine 5 $\mu g \cdot ml^{-1}$.

as an indicator of respiratory depression, decreased 25% after each injection associated with an increase in Pa_{CO_2} of 12 and 27% 60 min after the first and second injections, respectively. Because of the excellent quality of analgesia obtained, as well as the findings of this and an earlier study,[4] the present investigation was designed to determine whether epinephrine in a dose of 50 μg when added to sufentanil 50 μg in 10 ml saline for high thoracic epidural analgesia materially affects the incidence and severity of unwanted side effects, the duration and intensity of analgesia, the distribution of sufentanyl, and the safety of administration of sufentanil at a high thoracic level.

MATERIALS AND METHODS

Twenty-three patients, ASA physical status 1–3, scheduled for elective pulmonary resection or correction of chest wall deformities were studied. Informed consent and institutional approval for human study was obtained. Selected demographic characteristics of the patients are shown in table 1. All patients received oral diazepam 10 mg 1 h before surgery. After intravenous access had been assured, an epidural catheter was inserted through a 16-gauge Tuohy needle inserted *via* a paramedian approach at T3-4 using the hanging-drop method. The epidural catheter was directed cephalad for a distance of 3–4 cm and the patient was then positioned supine before an initial test dose of 3 ml of lidocaine 2% was injected. When bilateral sensory analgesia had been verified by pin-prick about 15 min after the test dose, a dose consisting of bupivacaine 0.5% with epinephrine 5 $\mu g \cdot ml^{-1}$ in a volume of 6–10 ml was injected.

Induction of anesthesia was achieved with thiopental 5–7 $mg \cdot kg^{-1}$ followed by pancuronium 0.1 $mg \cdot kg^{-1}$ and droperidol 5 mg. After tracheal intubation, anesthesia was maintained with halothane 0.3–0.5% and a N_2O-O_2 mixture with an FI_{O_2} ranging between 0.3 and 0.5. Mechanical ventilation was set to deliver a tidal volume of 10 $ml \cdot kg^{-1}$ and an end-tidal Pa_{CO_2} of 34–38 mmHg was maintained. A radial arterial cannula was inserted to allow for continuous measurement of blood pressure and for serial sampling of blood for plasma sufentanil and blood gas estimations. No opiates were administered before or during the surgical procedure.

Following completion of surgery, all patients were allowed to resume spontaneous breathing, and following tracheal extubation they were transferred to an adjacent unit where they remained under continuous observation for the next 3 days. The severity of postoperative pain was assessed at 5, 15, and 30 min and thereafter each 30 min by means of the inverse visual analog scale (IVAS), where 0 is the most severe pain and 10 is no pain. A coded ampule containing sufentanil 50 μg in 10 ml of saline, with or without epinephrine 5 $\mu g \cdot ml^{-1}$ was administered *via* the epidural catheter on request of the patient.

Plasma sufentanil measurements were made on 10 ml arterial samples drawn at 0, 3, 5, 10, 20, 30, 60, 120, and 180 min following injection. After extraction, all samples were subjected to duplicate ratio-immune assay having a detection limit of 0.01 $ng \cdot ml^{-1}$ and a coefficient of variation of 18%.[10] Maximum observed plasma sufentanil concentration (C_{peak}) and the time at which it occurred (T_{peak}) were noted for all patients. Areas under the plasma concentration-time curve for 0–15 min (AUC_{0-15}) were noted visually and from 0–180 min (AUC_{0-180}) were calculated by trapezoidal summation. Blood gas measurements were made at 0, 15, 30, and 60 min and each hour thereafter until analgesia had regressed to that level at which the patient requested a second dose. Following the second epidural injection of sufentanil (of the same composition as the first injection), the same sequence of arterial blood sampling was repeated.

Duration of analgesia was defined as the time elapsed between the epidural injection of sufentanil and the request of the patient for a repeat injection. Throughout the entire study, arterial blood pressure, electrocardiogram, and respiratory rate were monitored continuously. By observation and direct questioning, the side effects of pruritus, nausea, vomiting, somnolence, and urinary retention were noted. A physician was notified if the respiratory rate fell below 10 $breaths \cdot min^{-1}$ or the Pa_{CO_2} increased above 60 mmHg. All patients received at least two consecutive injections of epidural sufentanil with or without epinephrine 5 $\mu g \cdot ml^{-1}$, in accordance with their group.

Statistical analysis of the data was performed by both the nonparametric Wilcoxon and Mann-Whitney P-tests; $P < 0.05$ was considered significant. Data are expressed as mean with standard error of the mean in parentheses. In addition, the plasma sufentanil data were subjected to a two-tailed Student's *t* test. All tests were performed using the SAS statistical procedures.

RESULTS

Analgesia. Evidence of pain relief—slowing of the pulse and respiratory rate—were noted within 3 min following sufentanil administration. Analgesia as determined by the

IVAS had reached an average score of 7.8 (SEM = 0.9) in the SP group and 8.6 (SEM = 0.5) in the SE group by 15 min. By 30 min, these scores were 9.8 (SEM = 0.2) and 9.5 (SEM = 0.3), respectively, for SP and SE. Analgesia following the second sufentanil injection was nearly the same as that following the first injection, as illustrated in figure 1. Clinically relevant is the fact that the quality of analgesia allowed intensive pulmonary physical therapy to be employed without obvious discomfort for the patient.

Mean duration of analgesia after the first injection was 270 (SEM = 35) min for patients in the SP group and 316 (SEM = 30) min for those in the SE group. After the second injection, however, the sufentanil-epinephrine solution significantly prolonged analgesia duration by about 33% to 367 (SEM = 53) min compared with 271 (SEM = 19) min in the SE group.

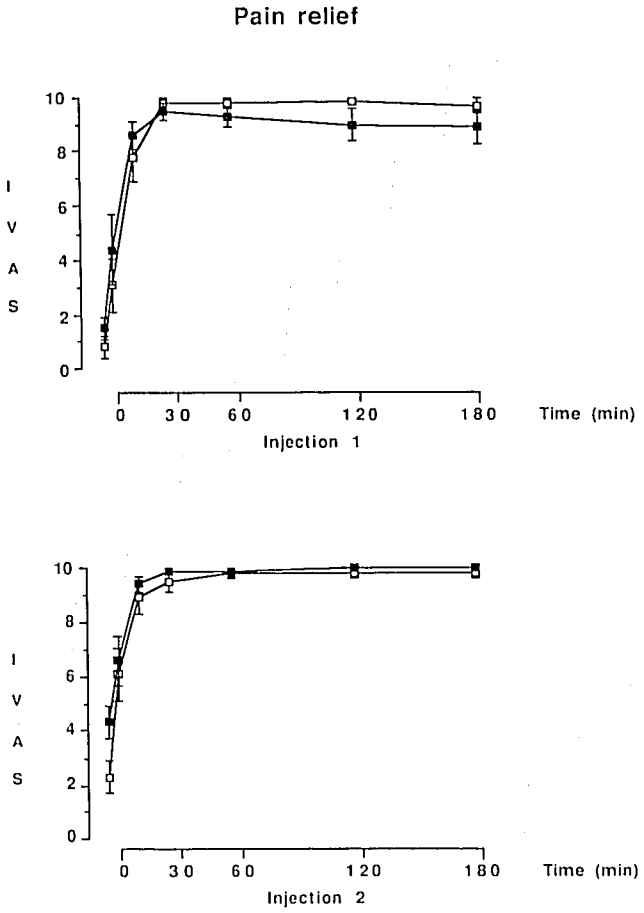

FIG. 1. Pain-relief scores after sufentanil or sufentanil-epinephrine assessed by means of the inverse visual analogue scale (IVAS) where 0 = maximum pain and 10 = no pain, plotted against time for 180 min after the first and second injections (n = 23). Mean values ± SEM. There are no significant differences at any point. □ = plain sufentanil; ■ = sufentanil + epinephrine.

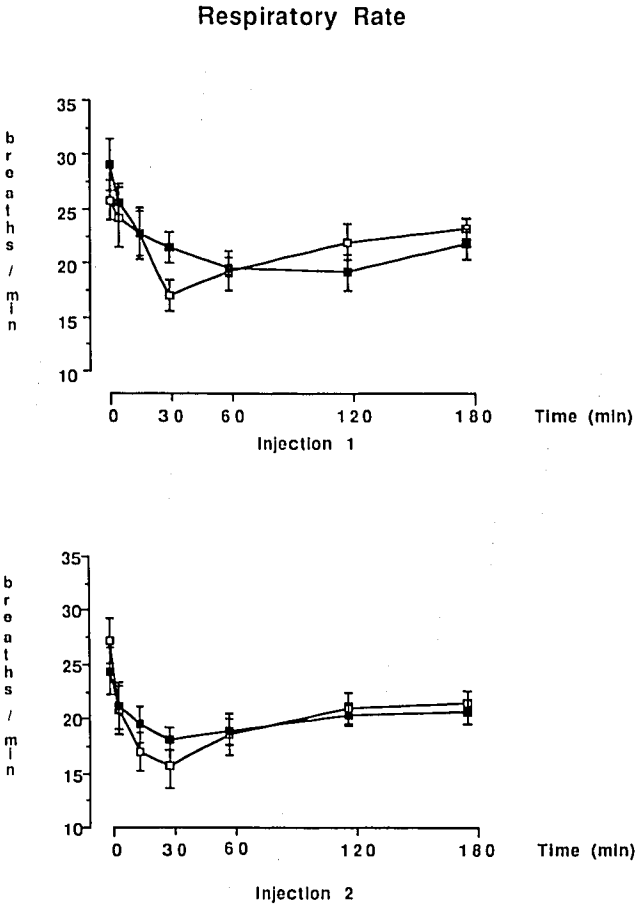

FIG. 2. Changes in respiratory rate (breaths · min^{-1}) after the first (n = 23) and second epidural injections (n = 21). Mean values ± SEM. Significant differences were not observed at any of the sample points. □ = plain sufentanil; ■ = sufentanil + epinephrine.

Respiratory and Non Respiratory Side Effects. There were no significant differences in respiratory rate between the patients receiving plain or epinephrine containing solutions of sufentanil following both the first and second injections. The average lowest respiratory rate for patients in the SP group was 17.0 (SEM = 1.5) breaths · min^{-1} at 30 min and 19.2 (SEM = 1.7) breaths · min^{-1} after 120 min in those in the SE group after the first injection (fig. 2). After the second injection, the mean lowest rate in the SP group was 15.7 (SEM = 2.1) breaths · min^{-1} at 30 min.

However, one patient who became apneic for 15 s, 5 min after receiving plain sufentanil, has a gradual increase in respiratory rate to 10 breaths per minute by the end of the first hour. His Pa_{CO_2} increased to 84 mmHg at 15 min and gradually returned to the normal range during the next 45 min. In two other patients receiving sufentanil plain, the respiratory rate decreased below 10 breaths · min^{-1} within the first 30 min after the second injection with corresponding Pa_{CO_2} is of 60 mmHg.

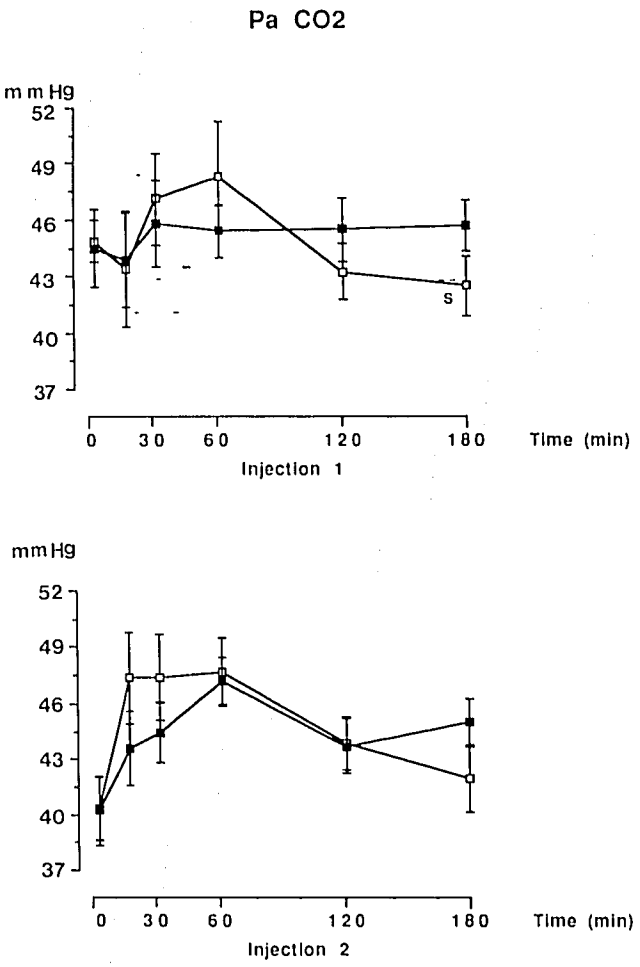

FIG. 3. Changes in Pa_{CO_2} after the first (n = 23) and the second (n = 21) epidural injections. Means ± SEM. There are no significant differences at any point. □ plain sufentanil; ■ = sufentanil + epinephrine.

These values returned to control without clinical assistance. The time course of the Pa_{CO_2} for patients in the plain sufentanil and sufentanil-epinephrine groups after both injections are depicted in figure 3. No significant differences were noted. The Pa_{CO_2} following the first injection peaks slightly in the SP group at 60 min, being 51.6 (SEM = 3.6) mmHg, while such a peak is absent in the SE group.

The incidence of nausea, vomiting, and itching was about 10%, occuring equally in each group. Sedation was noted in two patients of each group and urinary retention occurred in nine of 12 patients of the SP group and in six of 11 patients in the SE group (P = NS).

Plasma Concentration of Sufentanil. Mean plasma sufentanil concentrations after the first and second injections are shown in figure 4. Three was a significant reduction in AUC_{0-15} for patients in the sufentanil-epinephrine group compared with those receiving sufentanil plain after both injections. The influence of epinephrine, however, was not sustained; the reduction in AUC_{0-180} by epinephrine was not significant. Peak plasma sufentanil levels were reached at 3 min in the SP group and at 15 min in the SE group after the first injection. The mean plasma concentrations after the first and second injections are listed in table 2.

Discussion

We speculated that the addition of epinephrine to lipophilic narcotics might reduce their vascular uptake and as a consequence, their systemically mediated side effects. In addition, a greater mass of drug will therefore be available for its local action on neuraxial structures.[1,11] That this hypothesis is correct has been demonstrated for fentanyl,[12] for diacetylmorphine,[3] and in volunteers with sufentanil.[4]

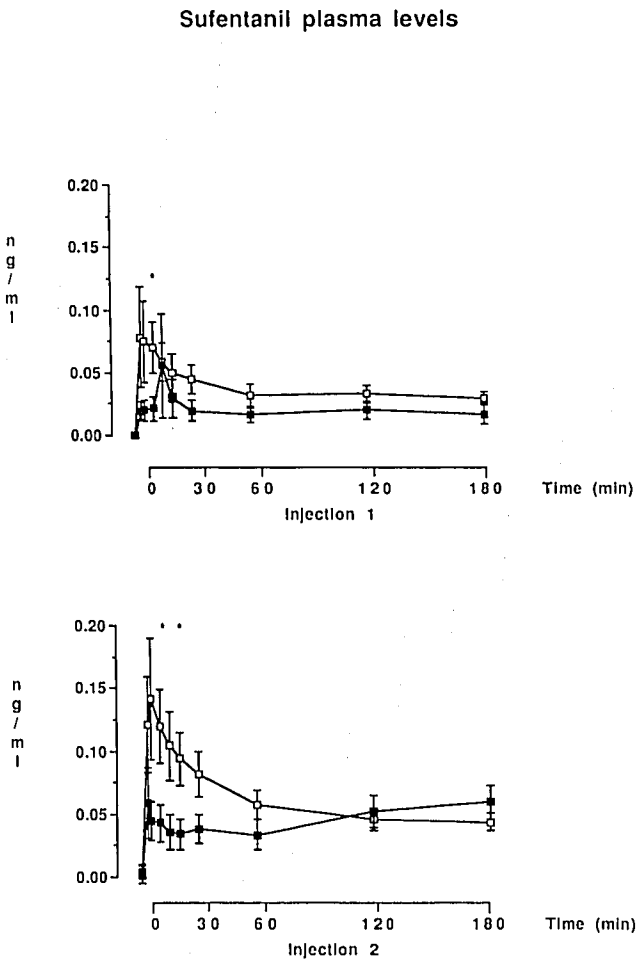

FIG. 4. Sufentanil plasma levels plotted in $ng \cdot ml^{-1}$ after the first (n = 22) and second injections (n = 20) of 50 μg epidural sufentanil (detection limit 0.01 $ng \cdot ml^{-1}$). Mean values ± SEM. *Difference between values ($P < 0.05$). □ = plain sufentanil; ■ = sufentanil + epinephrine.

TABLE 2. Sufentanil Plasma Levels: Mean (SEM)

Time (Min)	Sufentanil Plain ($ng \cdot ml^{-1}$)	Sufentanil + Epinephrine 5 $\mu g \cdot ml^{-1}$ ($ng \cdot ml^{-1}$)
Injection 1		
0	0.0 (0)	0.0 (0)
3	0.078 (0.040)	0.019 (0.007)
5	0.075 (0.033)	0.020 (0.008)
10	0.070 (0.021)	0.021 (0.010)
15	0.059 (0.016)	0.056 (0.041)
20	0.049 (0.016)	0.029 (0.016)
30	0.044 (0.011)	0.020 (0.008)
60	0.032 (0.090)	0.016 (0.006)
120	0.033 (0.007)	0.020 (0.007)
180	0.030 (0.004)	0.017 (0.085)
Injection 2		
0	0.020 (0.006)	0.019 (0.007)
3	0.137 (0.038)	0.075 (0.028)
5	0.158 (0.048)	0.061 (0.016)
10	0.137 (0.029)	0.060 (0.015)
15	0.121 (0.028)	0.052 (0.014)
20	0.111 (0.021)	0.051 (0.012)
30	0.098 (0.018)	0.055 (0.011)
60	0.074 (0.012)	0.050 (0.012)
120	0.062 (0.009)	0.068 (0.013)
180	0.060 (0.007)	0.076 (0.013)

Many factors influence the quality and duration of analgesia. These include the surgical site and type of surgery; the dose, volume, and criteria for narcotic administration; whether intraoperative local anesthetics were used; and the indefinable variables arising from the patient's clinical status that have a bearing on drug kinetics in the epidural space. The 50-μg dose of sufentanil chosen for this study has been shown in dose-response studies to provide the optimum duration of analgesia with minimal side effects when administered as a bolus.[7,8,13] Although the mean duration of 271 min for plain sufentanil recorded in this study is shorter than the 330 min observed in a previous study that was conducted under identical circumstances, the difference is explained by the end point of analgesia selected.[9] Supplemental sufentanil injections in that study were given when the IVAS score had regressed to 4 or less rather than upon patient's request as in this study. The numerical differences in duration of analgesia between the plain and the sufentanil-epinephrine solutions, while not statistically significant after the first injection (15% longer), did reach significance after the second injection for which a 33% increase in duration was achieved. These results compare favorably with those obtained after lumbar epidural administration for abdominal surgery,[7,14] orthopedic surgery,[8] and experimental pain in volunteers.[4] The common opioid side effects of pruritus, nausea, and urinary retention were not exaggerated by the addition of epinephrine. In fact, the incidence of urinary retention was very close to the rate at which it occurred in a number of similar studies performed in this clinic.[9,15,16]

The differences in respiratory depression as expressed in respiratory rate and Pa_{CO_2} were not statistically significant. However, in our previous study[9] with plain sufentanil (in one patient) and in the present study in the SP group (one patient), an apnea of at least 15 s developed about 3–5 min of the injection of the drug. Plasma sufentanil levels in this group reached their maximum value at this time. This clinically important event could not be translated in terms of statistical significance mainly because of small number of patients in each group, but also because of the sampling scheme. Since respiratory rate was noted only at 0, 5, and 15 min after injection while the first arterial blood sample was taken at 15 min, our methods during the first 15 min are not sensitive enough to detect significant differences. The Pa_{CO_2} at 15 min of the apneic patient increased to 84 mmHg and may have been even higher before that time. Such a clinical event is a good example of the extremely rapid vascular uptake of a highly lipid soluble opioid, such as sufentanil, that can take place from the epidural space.

No significant differences in respiratory rate nor in Pa_{CO_2} as indices of respiratory depression were observed between the two groups. Because the time course of any step decrease in ventilation, as might be expected from the rapid vascular uptake of sufentanil, is not necessarily mirrored by a corresponding rapid increase in Pa_{CO_2}, the respiratory rate is a more sensitive index of early, acute changes of ventilation; in fact, Nunn has drawn attention to the very slow increase of Pa_{CO_2} following a step decrease in ventilation.[17] The steep negative slope of respiratory rate within 15 min of injection in contrast to the

rapid increase of plasma sufentanil is consonant with a systemically mediated respiratory depression rather than the cephalad neuraxial spread of the narcotic. There are presently no data of CSF-uptake following epidural injection of the highly lipid soluble opioids, but it is doubtful, given their affinity to fat, that cephalad neuraxial transportation will have any clinically measurable effect. Obviously unknown is the possible axial spread in the vertebro-cranial venous system. An extreme example of such rapid vascular uptake is the case mentioned in the results where the patient became apneic for 15 s within 5 min after receiving plain sufentanil.

The present study demonstrates the epidural sufentanil, 50 μg in 10 ml saline, provides effective analgesia when administered at a high thoracic level. The results indicate that epinephrine 5 $\mu g \cdot ml^{-1}$ when added to epidural sufentanil reduces the overall and peak plasma sufentanil levels, thereby diminishing the potential for early respiratory depression caused by systemic uptake of the drug. The addition of epinephrine also prolongs the duration of analgesia.

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