Anesthesiology
67:948–951, 1987

Analgesia and Ventilatory Response to CO_2 Following Epidural Sufentanil in Children

Malik Benlabed, M.D., Claude Ecoffey, M.D.,† Jean-Claude Levron, Ph.D.,‡ Benedicte Flaisler, M.D.,‡ Jeffrey B. Gross, M.D.§*

The authors studied the effects of epidural sufentanil (0.75 $\mu g \cdot kg^{-1}$) after urologic surgery in 15 children ranging in age from 4 to 12 yr, and in weight from 14 to 47 kg. The onset and duration of analgesia were 3.0 ± 0.3 and 198 ± 19 min, respectively (mean ± SEM). Side effects included pruritus (3/15), nausea and vomiting (5/15), drowsiness (10/15), and urinary retention (1/11). No apnea was observed. Periosteal analgesia and ventilation were studied in eight of the children (mean age 8.6 ± 0.8 yr). There was significant periosteal analgesia of the tibia (30, 60, 90, and 120 min after injection) and of the radius (60, 90, and 120 min after injection). Resting respiratory rate and tidal volume did not change during the study. Resting minute-ventilation decreased from 6.3 ± 0.5 $l \cdot min^{-1}$ preoperatively to 5.6 ± 0.6 $l \cdot min^{-1}$ ($P < 0.05$) postoperatively, before epidural sufentanil injection; it did not decrease further after epidural sufentanil. Similarly, end-tidal CO_2 tension increased significantly from 37.2 ± 0.7 mmHg preoperatively to 39.9 ± 1.2 mmHg ($P < 0.05$) postoperatively, before epidural sufentanil; epidural sufentanil did not cause a further significant increase in end-tidal CO_2 tension. The slope of the CO_2 ventilatory response curve decreased significantly from 1.68 ± 0.12 $l \cdot min^{-1} \cdot mmHg^{-1}$ preoperatively to 1.10 ± 0.13 $l \cdot min^{-1} \cdot mmHg^{-1}$ ($P < 0.01$) postoperatively. There were further significant decreases to 0.68 ± 0.10 and 0.89 ± 0.16 $l \cdot min^{-1} \cdot mmHg^{-1}$ 30 and 60 min after epidural sufentanil. By 240 min after sufentanil, the slope had increased to 1.42 ± 0.08 $l \cdot min^{-1} \cdot mmHg^{-1}$, which was significantly greater than the immediate postoperative value. The authors conclude that epidural sufentanil provides rapid and effective analgesia in children; however, the clinical usefulness may be limited because of the relatively short duration of analgesia. Additionally, the significant early respiratory depression following epidural sufentanil mandates close monitoring of these patients for more than 1 h. (Key words: Analgesia: postoperative. Analgesics, narcotic: sufentanil. Anesthesia: pediatric. Anesthetic techniques: epidural. Ventilation: carbon dioxide response.)

EPIDURAL MORPHINE is effective for treatment of postoperative pain in children after major surgical procedures.[1,2] However a major side effect of epidural morphine is delayed and prolonged depression of the ventilatory control,[3] which may be attributed to rostral spread of this water soluble opioid.[4] Epidural administration of sufentanil, a new highly lipophilic opioid, has been proposed for postoperative pain relief in adults.[5–7] No information is available on the efficacy and the possible side effects of epidural sufentanil administration. The aim of this study was to evaluate the efficacy of epidural sufentanil for the relief of postoperative pain in children and to determine its effects on the ventilatory response to CO_2.

Methods

PATIENTS

Fifteen ASA physical status I or II children, aged 7.7 ± 0.9 yr (mean ± SEM) (range 4–12 yr), weighing 27.7 ± 3.0 (range 14–47 kg), were studied. No patient had pain or received narcotics before surgery. This investigation was approved by the Human Investigation Committee, and parental consent was obtained. The children were scheduled to undergo lower urinary tract surgery (*e.g.*, orchidopexy, hypospadias, or ureteral reimplantation).

PROCEDURE FOR ALL CHILDREN STUDIED

All children had fasted 6 h before anesthesia. They were premedicated orally with diazepam (0.33 $mg \cdot kg^{-1}$ up to 10 mg) 1 h before induction. A cardiotachometer triggered by the ECG continuously recorded heart rate, and an automated blood pressure cuff allowed continuous monitoring of arterial pressure. Anesthesia was induced with thiopental (5 $mg \cdot kg^{-1}$) and maintained with 60% N_2O in O_2, and isoflurane (1–1.5%) administered by face mask. No muscle relaxants or narcotics were used. After the induction of anesthesia, a 20-gauge epidural catheter was inserted *via* L3–L4 interspace using an 18-gauge Tuohy needle and a loss of resistance technique. After aspiration, a test dose 0.075 $ml \cdot kg^{-1}$ of 2% lidocaine with epinephrine 1:200,000 was injected to identify an accidental vascular or dural puncture. At the end of surgery (mean duration 72 ± 19 min), inhalation anesthesia was discontinued. When grade 2 pain (as defined in table 1) occurred (mean time for the onset of pain was 50 ± 3

* Resident in Anesthesiology, Hôpital Bicêtre, Kremlin-Bicêtre.

† Assistant Professor of Anesthesiology, Hôpital Bicêtre, Kremlin-Bicêtre.

‡ Laboratoires Janssen, 75116 Paris, France.

§ Associate Professor of Anesthesiology, Philadelphia Veterans Administration Medical Center.

Received from the Department of Anesthesiology, Bicêtre Hospital, Université Paris-Sud, 94275 Kremlin Bicêtre Cédex—France; and the Department of Anesthesiology, Philadelphia Veterans Administration Medical Center, University of Pennsylvania, Philadelphia, Pennsylvania. Accepted for publication July 22, 1987.

Address reprint requests to Dr. Ecoffey: Département d'Anesthésiologie, Hôpital Bicêtre, 94275 Kremlin Bicêtre Cédex, France.

min, range 30–90 min), 0.75 $\mu g \cdot kg^{-1}$ of preservative-free sufentanil in 2 ml of isotonic saline solution was injected through the epidural catheter. The children remained in a 30° head-up position and were kept in the recovery room for 12 h. At the end of the study period, the children received conventional supplementory analgesics as necessary.

Clinical Effects

In each child, the following data were collected: 1) quality, onset, and duration of analgesia (table 1); and 2) presence of non-respiratory side effects, such as nausea, pruritus, urinary retention, and drowsiness. In addition, analgesia assessed by maximum tolerance to periosteal pressure was studied in eight of the 15 children, aged 8.6 ± 0.8 yr, weighing 31.6 ± 2.7 kg. The maximum tolerance to periosteal pressure was assessed over the distal end of the tibia and of the radius as determined by the average of three readings made with a calibrated spring-loaded rod.[8] Assessment of maximum tolerance to periosteal pressure was recorded immediately before and 30, 60, 90, 120, and 240 min after epidural sufentanil injection. These same eight children also underwent the following study of ventilatory control.

Ventilatory Measurements

Tidal volume (VT), respiratory rate (RR), and minute-ventilation ($\dot{V}E$) were recorded when subjects were breathing room air and during CO_2 rebreathing with either a mouth piece and nose clip or a face-mask, a pneumotachograph (Fleisch no. 1 for children younger than 8 yr, Fleisch no. 2 for children equal to or older than 8 yr), and a Rudolph nonrebreathing valve. Instrument dead space was 45 ml in the children younger than 8 yr and 70 ml in the children older than 8 yr. Ventilatory response to CO_2 was assessed by rebreathing for 4–5 min from a 3–5-l spirometer filled with a mixture of CO_2 (7%) in oxygen. Volume was measured by electronically integrating the flow signal obtained from a Godart 17212 differential pressure transducer (Bilthoven, Holland) connected to the pneumotachograph, which was previously calibrated with a 1-l syringe of air. End-tidal CO_2 tension ($P_{ET_{CO_2}}$) was measured with a Godart capnograph (Bilthoven, Holland) calibrated before and after each measurement with 5% and 7% CO_2 in O_2. Calibration gases were verified to be within 1% using Scholander microanalysis. Pneumotachograph and capnograph outputs were interfaced to a CBM SX64 computer with an analog-to-digital converter.[9] After converting ventilatory variables to BTPS, linear regression equations were computed from $\dot{V}E$ and $P_{ET_{CO_2}}$ for each challenge curve. All responses were linear, with correlation coefficients ranging from 0.94 to 0.98. We performed CO_2 response curve measurements preoperatively (½ h before induction of anesthesia), postoperatively (just before the injection of sufentanil), and 30, 60, 120, and 240 min after the injection of sufentanil.

Table 1. Criteria for Analgesia

Assessment of pain	
	Grade 0: calm, no pain expressed verbally
	Grade 1: pain expressed if questioned, but appeared to be comfortable
	Grade 2: pain expressed verbally spontaneously, with crying or restlessness
Onset of analgesia	
	Time from epidural sufentanil to no pain
Duration of analgesia	
	Time from onset of analgesia to moderate pain requiring an analgesic.

Plasma Sufentanil Analysis

Plasma sufentanil levels were assayed from venous blood samples taken 30, 60, 120, and 240 min after the injection of sufentanil, just before each CO_2 rebreathing test. Plasma was separated by centrifugation at −4° C, stored at −20° C, and was assayed in duplicate by radioimmunoassay which measured sufentanil with a minimum detectable level of 0.03 ng/ml and a coefficient of variation of less than 5% from 0.07 to 1.6 ng/ml.[10]

Statistical Analysis

Differences in analgesia and respiratory variables were tested using ANOVA followed by the use of the *t* test for paired data. Differences were considered significant when $P < 0.05$. All values are expressed as mean ± SEM.

Results

Analgesia and Side Effects

The onset of analgesia (defined as the absence of pain) occurred 3.0 ± 0.3 min (range 1–5 min) after epidural sufentanil injection; its duration was 198 ± 19 min (range 90–240 min). In addition, we observed significant periosteal analgesia of the tibia at 30, 60, 90, and 120 min, and of the radius at 60, 90, and 120 min (fig. 1). Pruritus occurred in three of the 15 children at 30 min after injection. Nausea and vomiting beginning 60–120 min after injection occurred in five of the 15 children. Drowsiness occurred in ten of the 15 children, beginning 30–60 min after injection and lasting from 30–60 min. One child of the 11 without a bladder cath-

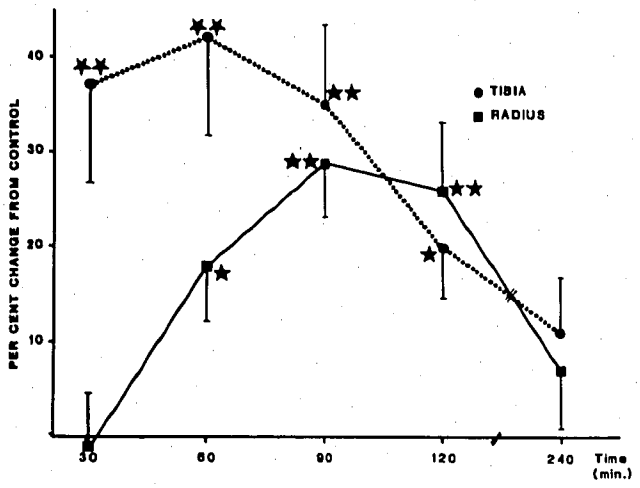

FIG. 1. Percent change in maximum tolerance to periosteal pressure following epidural sufentanil injection. Mean values ± SEM. *$P < 0.05$; **$P < 0.01$ from control value.

eter had urinary retention; however, he did not require catheterization of the bladder. No child had apnea, cyanosis, or an abnormally slow respiratory rate. No complications resulted from the placement of the epidural catheter.

VENTILATORY CONTROL AND PLASMA SUFENTANIL CONCENTRATION

The results are summarized in table 2. Resting RR and VT did not change significantly during the study. Postoperatively, resting $\dot{V}E$ decreased and $P_{ET}CO_2$ increased significantly from preoperatively values both before and after epidural sufentanil. However, epidural sufentanil did not cause a further significant change in these variables. The slope $\dot{V}E/P_{ET}CO_2$ decreased significantly from the pre- to postoperative periods. Compared with postoperative preepidural values, the slope $\dot{V}E/P_{ET}CO_2$ decreased significantly 30 and 60 min after epidural sufentanil, and increased significantly at 240 min after epidural sufentanil. Plasma sufentanil concentrations are also summarized in table 2. The maximum plasma levels were observed in the first sample obtained at 30 min after epidural sufentanil.

Discussion

Epidural sufentanil provided rapid and effective analgesia in children following urologic surgery. The short latency of onset and the individual variability of the duration of analgesia is similar to that previously reported in adult patients.[6] Because of the short duration of action, when analgesia from epidural sufentanil decreased, we use standard analgesia therapy. The frequency of non respiratory side effects was similar to that previously reported in adults.[5-7] The main side effect was drowsiness, which was observed in 70% of our patients, and has been previously reported following the use in adults. The frequency of other side effects, such as pruritus, nausea, and urinary retention, was low, and similar to that observed following epidural morphine.[3]

We did not observe apnea after epidural sufentanil in the 15 children studied. However, a major finding of this study is that, despite its high lipid solubility and opiate receptor affinity,[11] epidural sufentanil causes respiratory depression for 1 h after administration. The control resting RR, VT, and $\dot{V}E$ values of the children studied were higher than the normal values for their age.[12] This was probably related to their anxiety, as

TABLE 2. Respiratory Variables and Plasma Sufentanil Concentrations Before and After Epidural Sufentanil

	Postoperative Period					
			After Epidural Sufentanil			
	Preoperative Values	Before Epidural Sufentanil	30 min	60 min	120 min	240 min
Resting RR (breaths/min)	23.7 ± 1.6	23.5 ± 1.3	20.2 ± 1.7	20.4 ± 2.1	20.7 ± 2.0	24.0 ± 2.1
Resting VT (ml)	257 ± 7	227 ± 16	192 ± 27	206 ± 12	221 ± 15	221 ± 11
Resting $\dot{V}E$ ($l \cdot min^{-1}$)	6.3 ± 0.5	5.6* ± 0.6	4.2* ± 0.6	4.2* ± 0.5	4.6* ± 0.6	5.4 ± 0.5
Resting $P_{ET}CO_2$ (mmHg)	37.2 ± 0.7	39.9* ± 1.2	42.5* ± 1.2	41.1* ± 1.3	39.8 ± 1.7	39.2 ± 1.3
Slope $\dot{V}E/P_{ET}CO_2$ ($l \cdot min^{-1} \cdot mmHg^{-1}$)	1.68 ± 0.12	1.10* ± 0.13	0.68† ± 0.10‡	0.89† ± 0.16‡	1.07† ± 0.07	1.42‡ ± 0.08
Plasma sufentanil concentrations ($ng \cdot ml^{-1}$)	—	—	0.10 ± 0.01	0.09 ± 0.01	0.08 ± 0.01	0.08 ± 0.01

Values are mean ± SEM. RR = respiratory rate; VT = tidal volume; $\dot{V}E$ = minute ventilation; $P_{ET}CO_2$ = end-tidal CO_2 tension.
*$P < 0.05$; †$P < 0.01$ statistical significance from preoperative value.
‡$P < 0.05$ statistical significance from postoperative value before epidural sufentanil.

suggested by the low $P_{ET_{CO_2}}$. Thus, the changes in these variables observed after surgery, but before epidural sufentanil, may be partially explained by a decrease in this psychological variable. Another mechanism which could explain these changes is the residual effect of anesthetic drugs, such as diazepam[13] or isoflurane.[14] However there was a further significant decrease of the slope $\dot{V}E/P_{ET_{CO_2}}$, after epidural sufentanil, suggesting further respiratory depression induced by the epidural sufentanil per se. Epidural sufentanil induces a respiratory depression which may be due to one or more of the following mechanisms: 1) a systemic effect, 2) a rostral spread in the CSF, and 3) a rostral spread *via* a direct perimedullary vascular channel.[15] The low plasma sufentanil concentrations as compared to the levels considered necessary for systemic analgesia in children scheduled for surgery[16] suggests that systemic absorption is not the main cause of respiratory depression following epidural sufentanil. Furthermore, the spread of periosteal analgesia in a rostral direction suggests a rostral spread of sufentanil in the neuraxis, either in the CSF or *via* direct perimedullary vascular channel. Indeed, our result confirms the respiratory depression observed with fentanyl, a lipid-soluble opioid, following epidural administration in adults.[17] However, we cannot establish the precise mechanism of the respiratory depression following epidural sufentanil injection.

In conclusion, epidural sufentanil rapidly induces effective analgesia after urologic surgery in children; however, the clinical usefulness of a single epidural injection of sufentanil for postoperative analgesia is questionable because of its short duration of action. In this regard, it may be more appropriate to use a continuous epidural sufentanil infusion, as previously reported with fentanyl.[18] In addition, depression of ventilatory control occurs during the first hour after epidural sufentanil administration; it is, therefore, necessary to closely monitor children receiving epidural sufentanil for more than 1 h. Finally, we studied only the effect of 0.75 μg/kg sufentanil on analgesia and ventilatory control. Additional studies are needed to determine if adequate analgesia and less respiratory depression can be obtained with a lower dose of epidural sufentanil.

The authors thank Janssen Laboratory for sufentanil plasma levels measurements, and Miss Guylaine Rosine for secretarial assistance.

References

1. Shapiro LA, Jedeikin RJ, Shalev D: Epidural morphine in children. ANESTHESIOLOGY 61:210–212, 1984
2. Glenski JA, Warner MA, Dawson B, Kaufman B: Postoperative use of epiduraly administered morphine in children and adolescents. Mayo Clin Proc 59:530–533, 1984
3. Attia J, Ecoffey C, Sandouk P, Gross JB, Samii K: Epidural morphine in children: Pharmacokinetics and CO_2 sensitivity. ANESTHESIOLOGY 65:590–594, 1986
4. Bromage PR, Camporesi EM, Durant PA, Nielsen CH: Rostral spread of epidural morphine. ANESTHESIOLOGY 56:431–436, 1982
5. Donadoni R, Rolly G, Noorduin H, Vanden Bussche G: Epidural sufentanil for postoperative pain relief. Anaesthesia 40:634–638, 1986
6. Verborgh C, Van Der Auwera D, Van Droogenbrock E, Camu F: Epidural sufentanil for postsurgical pain relief. Eur J Anaesth 3:313–320, 1986
7. Tan S, Cohen SE, White PF: Sufentanil for analgesia after cesarean section: Intravenous versus epidural administration (abstract). Anesth Analg 65 (suppl) 1:S158, 1986
8. Bromage PR, Camporesi EM, Leslie J: Epidural narcotics in volunteers: Sensitivity to pain and to carbon dioxide. Pain 9:145–160, 1980
9. Gross JB, Caldwell CB, Shaw LM, Laucks SO: The effect of lidocaine on the ventilatory response to carbon dioxide. ANESTHESIOLOGY 59:521–525, 1983
10. Michiels M, Hendricks R, Heykants J: Radioimmunoassay of the new opiate analgesic alfentanil and sufentanil. Preliminary pharmacokinetic profile in men. J Pharm Pharmacol 35:86–89, 1983
11. Leysen JE, Gommeren W, Niemegeers CJE: (3H*) sufentanil, a superior ligand for μ-opiate receptors: Binding properties and regional distribution in rat brain and spinal cord. Eur J Pharmacol 87:209–225, 1983
12. Crone RK: The respiratory system, Pediatric Anesthesia. Edited by Gregory GA. New York, Churchill Livingstone, 1983, pp 35–62
13. Clergue F, Desmonts JM, Duvaldestin P, Delavault E, Saumon G: Depression of respiratory drive by diazepam as premedication. Br J Anaesth 53:1059–1063, 1981
14. Murat I, Beydon L, Chaussain M, Levy J: Ventilatory changes during nitrous oxide isoflurane anesthesia in children. Eur J Anaesth 3:403–411, 1986
15. Cousins MJ, Mather LE: Intrathecal and epidural administration of opioids. ANESTHESIOLOGY 61:276–310, 1984
16. Greeley WJ, De Bruijn NP, Davis DP: Pharmacokinetics of sufentanil in pediatric patients (abstract). ANESTHESIOLOGY 65:A422, 1986
17. Negre I, Gueneron JP, Ecoffey C, Gross JB, Levron JC, Samii K: CO_2 sensitivity after epidural fentanyl (abstract). ANESTHESIOLOGY 63:A507, 1985
18. Renaud B, Brichant JF, Clergue F, Chauvin M, Levron JC, Viars P: Continuous epidural fentanyl: Ventilatory effects and plasma kinetics (abstract). ANESTHESIOLOGY 63:A234, 1985