Epidural Morphine in Children: Pharmacokinetics and CO_2 Sensitivity

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The effects of epidural morphine (50 $\mu g \cdot kg^{-1}$) after abdominal and urologic surgery were studied in 20 children ranging in age from 2 to 15 yr and weighing between 9 and 54 kg. The onset and the duration of analgesia were 30 ± 12 min and 19.5 ± 8 h, respectively (mean ± SD). Side effects were pruritus (4/20), nausea and vomiting (8/20), and urinary retention (4/14). No apnea was observed. Ventilation control was studied in seven children. No significant change in resting respiratory variables occurred after both surgery and epidural morphine injection. However, the slope of the ventilatory response to CO_2 was significantly ($P < 0.05$) decreased after surgery but before morphine, as compared with its preoperative control value (0.84 ± 0.44 versus 1.51 ± 0.721 $\cdot min^{-1} \cdot mmHg^{-1}$), and remained low for 22 h after epidural morphine (0.90 ± 0.57 $l \cdot min^{-1} \cdot mmHg^{-1}$). Sixty minutes after morphine injection, the plasma morphine concentration was always less than 12 $ng \cdot ml^{-1}$ in the seven children studied. Pharmacokinetic parameters were similar to those observed after epidural injection of morphine in adults, except for a shorter terminal half-life (73.8 ± 41.6 min) attributed to a greater total body clearance of morphine in the children (28.3 ± 3.4 $ml \cdot min^{-1} \cdot kg^{-1}$). It is concluded that epidural morphine provides effective and prolonged analgesia in children after abdominal and urologic surgery and that it is associated with prolonged respiratory depression that requires close monitoring for at least 24 h. (Key words: Analgesics, narcotic: morphine. Anesthesia: pediatric. Anesthetics, intravenous: morphine. Anesthetic techniques: epidural. Pain: postoperative. Pharmacokinetics: epidural morphine. Ventilation: carbon dioxide response.)

EPIDURAL NARCOTICS ARE being used with increasing frequency to provide pain relief in adults[1,2] and in children[3–5] after major surgical procedures. Epidural morphine in adults induces respiratory depression as a result of the rostral spread of morphine in the cerebrospinal fluid (CSF)[6,7] but no information on the respiratory effect of epidural morphine is available in children. The pharmacokinetics of epidural morphine have been re-

ported in adults[8,9] but not in children. The present study evaluates, in children, the pharmacokinetics, duration of analgesia, occurrence of nonrespiratory side effects, and ventilatory response to CO_2 after epidural morphine given for postoperative pain relief.

Methods

PATIENTS

Twenty ASA I or II children, aged 6.4 ± 5.4 yr (mean ± SD) (range 2–15 yr), weighing 21.9 ± 13.9 kg (range 9–54 kg), were studied. No patient had abdominal pain before surgery. None was receiving narcotics before the operation. The investigation was approved by the Human Investigation Committee, and parental consent was obtained. The children were scheduled to undergo elective abdominal or urologic surgery (nephrectomy, pyeloplasty).

PROCEDURE FOR ALL THE PATIENTS STUDIED

All patients had fasted 6 h before anesthesia. They were premedicated orally with diazepam prepared in a liquid form (0.33 $mg \cdot kg^{-1}$ up to 10 mg) 1 h before induction of anesthesia, and with atropine (0.01 $mg \cdot kg^{-1}$) iv in the induction room. A cardiotachometer triggered by the ECG continuously recorded heart rate. Following induction of anesthesia with thiopental (10 $mg \cdot kg^{-1}$) over a 1-min period in order to obtain a prolonged sedation and orotracheal intubation performed after administration of pancuronium bromide (0.1 $mg \cdot kg^{-1}$), a 20 gauge epidural catheter was placed using a midline approach at the L2–L3 (n = 12) or T9–T10 (n = 8) interspace using a 18 gauge Tuohy needle and a loss of resistance technique. After an aspiration test, 1 or 2 ml of 2% lidocaine with epinephrine 1:200,000 was injected to identify an accidental vascular or dural puncture. Luer Lock® adapters with bacteriostatic filters were connected to the free ends of the catheters. A 22 gauge radial artery catheter (inserted in patients with surgery at high risk of rapid blood loss) or automated blood pressure cuff allowed continuous monitoring of arterial pressure. Anesthesia was maintained with 60% N_2O in O_2, isoflurane (1–1.5%) and pancuronium bromide (0.025 $mg \cdot kg^{-1}$ every 90 min). Ventilation was controlled mechanically, and no narcotics were used. The duration of the operation was 138 ± 72 min (range 80–300 min), and the volume of dextrose in

lactated Ringer's solution infused was 9 ± 4 ml $\cdot$ kg^{-1} $\cdot$ h^{-1}. At the end of surgery, inhalation anesthesia was discontinued and neuromuscular blockade was assessed by the head-lift test and reversed if necessary. The patients were extubated and taken to the recovery room where they remained during the first postoperative day. When grade 2 pain (as defined in table 1) occurred (mean time for the onset of pain was 70 ± 15 min, range 45 min to 2 h), 50 μg $\cdot$ kg^{-1} of preservative-free morphine in 2 ml of isotonic saline solution was injected in the epidural catheter. The children remained in a 30° head-up position and the following data were collected: 1) quality, onset, and duration of analgesia (table 1); and 2) presence of nonrespiratory side effects such as nausea, pruritus, and urinary retention.

PLASMA MORPHINE ANALYSIS

The pharmacokinetics of morphine following epidural administration was studied in seven of the 20 children aged 9.1 ± 4.4 yr, weighing 29.0 ± 13.7 kg, who were free of cardiac, hepatic, or renal disease. Arterial blood gases were measured just before morphine administration. Arterial blood samples (3 ml) were collected before and 2, 10, 15, 30, 60, 120, 180, 240, 300, 360, and 540 min after epidural injection of morphine. Plasma was separated, stored at $-20°$ C and assayed in duplicate by a highly specific radioimmunoassay (RIA) with a sensitivity of 0.1 ng $\cdot$ ml^{-1}.[10] Morphine antisera were raised in goats by immunization with the N-carboxymethylnormophine conjugated to bovine serum albumin as described by Gintzler et al.[10] The carrier protein was conjugated to the nitrogen atom of the opiate alkaloid in order to recognize the phenolic–hydroxy group on C3 and the alcoholic group on C6. The coefficient of variation for reproducibility varied from 7.7 to 12.0% at concentration ranging from 0.1 to 60 ng/ml. The specificity of the RIA was assessed by measuring the percentage of cross-reactivity of various congeners that inhibit labeled hapten–antibody complex at 50%. The cross-reactivity of morphine 3-O-glucuronide and of codeine were below 0.2%. 6-Monoacetylmorphine, an analogue of 6-O-glucuronide, had 0.5% of cross-reactivity. The sensitivity was high: 16 pg of morphine could be reliably assayed with ^{3}H-morphine (60 Ci/mmol)** as labeled antigen. A noncompartmental method was used to compute the pharmacokinetic parameters. Assuming a bioavailability of 100%, terminal rate constant (β), and terminal half-life ($t_{1/2\beta}$) were computed by linear regression of the observed terminal curve. Area under the curve (AUC) was calculated by the trapezoidal rule and extrapolated to infinity. Total body clearance (Clt) was calculated as Clt = dose/AUC and apparent volume of distribution (V_β) as V_β = Dose/

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 morphine to no pain

Duration of analgesia
 Time from onset of analgesia to moderate pain

AUC $\cdot \beta$. Time to maximum concentration (t_{max}) and plasma maximum concentration (C_{max}) were the mean of individual data. Results are expressed as mean $\pm$ SD.

VENTILATORY MEASUREMENTS

Ventilation was studied in seven of the 20 children, aged 10.1 ± 2.6 yr, weighing 31.7 ± 8.6 kg. All the children studied had a median upper abdominal incision and a lumbar epidural catheter. Tidal volume (V_T), respiratory rate (RR), and minute ventilation ($\dot{V}_E$) were recorded when they were breathing room air and during CO_2 rebreathing with either a mouthpiece and a nose-clip or a face-mask and a pneumotachograph (Fleisch® n° 1 for children younger than 8 yr, Fleisch® n° 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 (PET_{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 verified to be within 1% using Sholander microanalysis. All signals were recorded on a Gould® ES 1000 recorder using a paper speed of 10 mm $\cdot$ s^{-2}. Linear regression of $\dot{V}_E$ on PET_{CO_2} for each CO_2 response curve yielded a slope ($\dot{V}_E/PET_{CO_2}$). The $\dot{V}_E$ at PET_{CO_2} 55 mmHg ($\dot{V}_E$ 55) was calculated. Duplicate CO_2 response curves were performed the day before surgery and, postoperatively, just before the injection of morphine, when pain grade 1 occurred, and 3, 6, 10, and 22 h after the injection.

STATISTICAL ANALYSIS

All values are expressed as mean $\pm$ SD. Statistical analysis consisted of analysis of variance followed by Newman-

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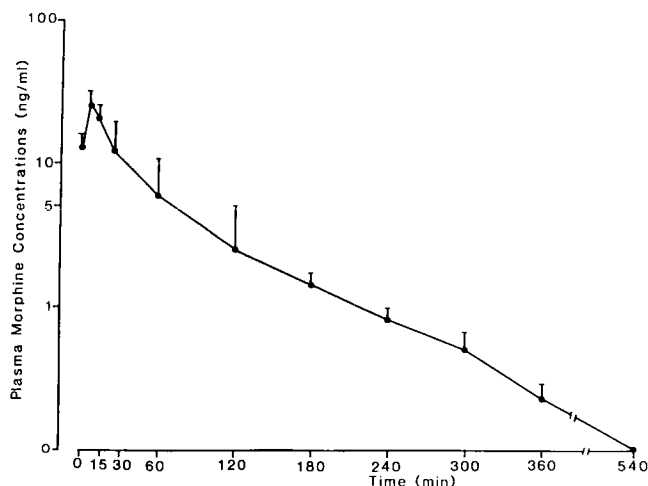** N.E.N., Boston, Massachusetts 02118.

FIG. 1. Mean values (±SD) for plasma morphine following administration of 50 $\mu g \cdot kg^{-1}$ into the epidural space in seven children.

Keul's test. Statistical significance was indicated by $P < 0.05$.

Results

ANALGESIA AND SIDE EFFECTS

The onset of analgesia (defined as the absence of pain) occurred 30 ± 12 min (range 15–40 min) after epidural morphine administration, and its duration was 19.5 ± 8 h (range 5–24 h). No supplemental analgesia was required in any child. The upper level of analgesia was difficult to assess because the pinprick test was unreliable. Pruritus occurred in four of 20 children, with a mean onset of 3 $\pm$ 1 h, was nonsegmental (occurring mainly on the head and trunk), and was never a discomfort for the child. Nausea and vomiting occurred in eight of 20 children, with a mean onset of 6 ± 2.2 h. Urinary retention occurred in four out of 14 children without a bladder catheter; none of them required catheterization of the bladder. No patient had apnea, cyanosis, or an abnormally slow respiratory rate. No complications resulted from the placement of the epidural catheter.

PLASMA PHARMACOKINETICS

Arterial pH and blood gas tensions before epidural morphine injection were within normal limits for all patients (pH 7.38 ± 0.02). Figure 1 shows the mean time course of the plasma morphine concentration, and table 2 summarizes individual pharmacokinetic parameters and mean values $\pm$ SD for the group.

VENTILATORY CONTROL

The results are summarized in table 3. Resting RR, V_T, $\dot{V}_E$, and PET_{CO_2} did not change significantly during the study. All of the CO_2 response curves were linear, with a correlation coefficient (r) ranging between 0.92 and 0.98. After surgery, and before epidural morphine, the slope $\dot{V}_E/PET_{CO_2}$ and $\dot{V}_E$ 55 were significantly less than the values obtained the day before the surgery, except for the $\dot{V}_E$ 55 at 22 h after epidural morphine injection; however, epidural morphine administration was not associated with further depression of ventilatory control at any time during the 22-h measurement period.

Discussion

Epidural morphine provides effective and prolonged analgesia in postoperative patients following abdominal and urologic surgery. Although they received no opioids during surgery, none of the children required systemic analgesia during the first postoperative day. The major advantage of this method is the consistent analgesia achieved in contrast to the varying degree of analgesia observed with intermittent intramuscular or subcutaneous narcotic injections. The latency of onset and the individual variability of the duration of analgesia is similar to that observed previously reported in adult[2] and pediatric[3] patients. When analgesia from epidural morphine decreased, our standard analgesia therapy was continued. The fre-

TABLE 2. Pharmacokinetic Parameters of Each Child and Mean Values $\pm$ SD for the Group after Epidural Morphine (50 $\mu g \cdot kg^{-1}$)

Patient	Weight (kg)	Age (yr)	T_{max} (min)	C_{max} (ng·ml⁻¹)	$T_{1/2}\beta$ (min)	$V\beta$ (l·kg⁻¹)	Clt (ml·min⁻¹kg⁻¹)	AUC (ng·min⁻¹ml⁻¹)
1	15	5	10.7	13.1	74.2	3.42	31.9	1190
2	18.4	4.5	10	19.6	77.0	3.45	31.0	1222
3	22.2	6	10.2	34	69.8	2.51	24.9	1509
4	22.2	7.5	10.2	33.6	54.2	2.10	26.9	1398
5	30	12	10	39	65.2	2.36	24.9	1524
6	41	14	10.7	23	70.7	2.05	24.5	1511
7	54	15	10	24.9	104.7	4.69	31	1244
Mean $\pm$ SD	29.0 ± 13.8	9.1 ± 4.4	10.3 ± 0.3	26.7 ± 9.1	73.8 ± 41.6	2.94 ± 0.93	28.3 ± 3.4	1371 ± 148

See text for abbreviations.

TABLE 3. Respiratory Variables the Day before the Surgery, before and after Epidural Morphine (50 $\mu g/kg$)

	Preoperative Values	Before Epidural Morphine	Postoperative Period			
			After Epidural Morphine			
			3 h	6 h	10 h	22 h
Resting RR (breaths/min)	25.1 ± 6.2	21.2 ± 5.7	25.0 ± 4.9	23.3 ± 4.9	23.5 ± 7.3	25.7 ± 7.8
Resting V_T (ml·kg⁻¹)	8.6 ± 2.5	6.5 ± 2.7	7.3 ± 2.2	6.0 ± 1.2	6.7 ± 2.4	7.5 ± 2.2
Resting $\dot{V}_E$ (ml·kg⁻¹·min⁻¹)	187 ± 42	133 ± 49	168 ± 32	155 ± 16	135 ± 42	164 ± 32
Resting $P_{ET_{CO_2}}$ (mmHg)	38.3 ± 5.4	42.1 ± 5.2	42.3 ± 6.5	43.0 ± 7.5	43.8 ± 6.0	0.7 ± 6.7
Slope $\dot{V}_E/P_{ET_{CO_2}}$ (l·min⁻¹·mmHg⁻¹)	1.51 ± 0.72	0.84 ± 0.44*	0.62 ± 0.21*	0.77 ± 0.26*	0.73 ± 0.33*	0.90 ± 0.57*
$\dot{V}_E$ 55 (l·min⁻¹)	18.6 ± 8.6	10.6 ± 4.7*	9.2 ± 3.1*	9.5 ± 6.5*	10.7 ± 4.7*	15.1 ± 5.7

Values are mean ± SD.

RR = respiratory frequency; VT = tidal volume; $\dot{V}E$ = minute ventilation; $P_{ET_{CO_2}}$ = end-tidal tension CO_2; $\dot{V}E$ 55 = minute ventilation at $P_{ET_{CO_2}}$ 55 mmHg.

* $P < 0.05$ statistical significance from preoperative values.

quency of nonrespiratory side effects was similar to that previously reported in adults.[11] Urinary retention was the most disturbing side effect, occurring in 30% of the patients who did not have a catheter inserted preoperatively.

The pharmacokinetic study employed an RIA method that may suffer from a lack of specificity.[10] Of the specific RIA methods reported,[10,12] the most specific uses antiserum against N-carboxymethylmorphine.[10,12,13] The specificity of our antiserum is very high as proved by the study of cross-reactivity according to Abraham's definition.[14] Morphine was rapidly absorbed from the epidural space, which is in agreement with previous studies in adults.[8,9] The average terminal half-life of morphine in our patients was shorter than reported in adults[9] and similar to that reported after intravenous administration in children.[15] The shorter half-life in children may be because of their greater total body clearance compared with adults.[9] This greater total body clearance may be related to increased hepatic mass relative to body weight or to an absolute increase in hepatic microsomial activity.[16] These mechanisms have been previously invoked to explain accelerated elimination of other drugs in children, such as theophylline[17] and thiopental[18] in children. Our pharmacokinetic data suggest two arguments in favor of a nonsystemic analgesic effect of epidural morphine in children: 1) the long duration of analgesia was similar to that observed in adults, despite a shorter plasma half-life of epidural morphine in children; and 2) the effective analgesia observed 1 h after epidural morphine was concommitant with a plasma morphine level always less than 12 ng·ml⁻¹ (fig. 1), a level considered necessary for systemic analgesia in children.[19]

We did not observe apnea after epidural morphine in the 20 children studied. However, both slope $\dot{V}_E/P_{ET_{CO_2}}$ and $\dot{V}_E$ 55 decreased postoperatively from their preoperative values and remained depressed for 22 and 10 h, respectively. First, the relatively high respiratory variables values can be the result of the anxiety of the

children. The decrease in the ventilatory response to CO_2 after surgery and before epidural morphine may be due to the residual effect of anesthetic drugs such as diazepam[20] or isoflurane,[21] or to the site of surgery and to the pain. However Bedford and Wollman[22] and Clergue et al.[23] have shown that 24 h after cardiac and upper abdominal surgery, respectively, the ventilatory response to CO_2 was not affected by surgery, and the response to airway of occlusion during CO_2 breathing was increased.[23] Therefore, following epidural morphine the failure of the ventilatory response to CO_2 to return to its control value was probably due to the respiratory depression induced by epidural morphine. Depression of ventilation has been reported after epidural morphine in adults[6,24] and is probably due to the rostral spread of morphine into the CSF.[7] The delayed occurrence of side effects such as pruritus and nausea have been considered as additional arguments in favor of this hypothesis.[11]

In conclusion, epidural morphine provides prompt, effective, and prolonged analgesia after abdominal and urologic surgery in children; this is not primarily a systemic effect of the drug. Delayed nonrespiratory side effects occur in a significant fraction of the patients. Additionally, the ventilatory response to CO_2 remains depressed for at least 22 h, indicating that pediatric patients should be closely monitored (measurement of respiratory rate by impedance pneumography or oxygen saturation by pulse oximetry) for the first postoperative day in an intensive care unit.

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