Anesthesiology
71:48–52, 1989

The Dose Response of Caudal Morphine in Children

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The authors compared the duration of analgesia and the frequency of side effects of three doses of caudal epidural morphine in children aged 1.2–7.9 yr. Caudal catheters were inserted in 32 children, randomly assigned to receive 0.033 mg·kg^{-1}, 0.067 mg·kg^{-1}, or 0.10 mg·kg^{-1} of preservative-free morphine for analgesia after major surgical procedures below the diaphragm. The first dose of caudal morphine was mixed with 0.25 ml·kg^{-1} of 1% lidocaine to confirm correct caudal catheter placement. By assessment of periodic pain scores and the time intervals between administration of caudal morphine and the recurrence of pain, the authors found that the mean (±SD) duration of analgesia was significantly longer after 0.10 mg·kg^{-1} (13.3 ± 4.7 h) than after either 0.033 mg·kg^{-1} or 0.067 mg·kg^{-1} (10.0 ± 3.3 and 10.4 ± 4.2 h, respectively) ($P < 0.02$). The frequency of vomiting, pruritus, and urinary retention was similar in each group. Vomiting was less common in patients who had nasogastric drainage than in patients who were fed soon after surgery ($P < 0.05$). Delayed respiratory depression occurred in one child after 0.10 mg·kg^{-1} of caudal morphine. Caudal morphine, 0.033–0.10 mg·kg^{-1}, provided prolonged analgesia in children. The authors recommend 0.033 mg·kg^{-1} of caudal morphine as an initial dose for children. (Key words: Analgesia, postoperative. Anesthesia: pediatric. Anesthetics, epidural: morphine. Anesthetic techniques, caudal: morphine.)

THE USE OF CAUDAL preservative-free morphine for treatment of postoperative pain in children has increased in popularity since first described by Jensen.[1] Subsequent reports have shown that caudal or lumbar epidural morphine, when used in doses between 0.05 and 0.10 mg·kg^{-1}, provides prolonged analgesia compared with that provided by conventional methods, with an acceptable incidence of side effects.[2–4] The purpose of this study was to establish a dose-response of caudal morphine in children following major abdominal, urogenital, or lower extremity orthopedic operations. We thus determined the duration of analgesia, and the frequency of side effects following 0.033 mg·kg^{-1}, 0.067 mg·kg^{-1}, or 0.10 mg·kg^{-1} morphine injected into the caudal canal.

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Received from the Departments of Anesthesiology and Pediatrics, University of Washington School of Medicine, Seattle, Washington; and the Department of Anesthesia, Children's Hospital and Medical Center, Seattle, Washington. Accepted for publication February 23, 1989. Supported by NIH Grant 507 RR 05655-16. Presented in part at the 1st International Symposium on Pediatric Pain, July, 1988, Seattle, Washington, and to the American Society of Anesthesiologists, October, 1988, San Francisco, California.
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Methods

STUDY PROTOCOL

Institutional Review Board approval and informed consent from parents or guardians were obtained. Children, ages 1.2–7.9 yr, ASA physical status I–III, who were scheduled for lower extremity orthopedic operations requiring osteotomy or bone resection, major abdominal operations, or major genitourinary procedures, were randomly assigned to receive 0.033 mg·kg^{-1}, 0.067 mg·kg^{-1}, or 0.10 mg·kg^{-1} of caudal preservative-free morphine (Astramorph™) postoperatively.

General anesthesia consisted of either inhalation or barbiturate induction, followed by inhalation of halothane or isoflurane with or without nitrous oxide. Perioperative opioids were not administered to any patient. At the conclusion of surgery before discontinuation of general anesthesia, a 20-gauge epidural catheter (Burron®) was inserted into the caudal epidural space. In three instances, the caudal catheter was inserted after induction of general anesthesia prior to surgery, because of planned spica cast application. Epidural catheters were inserted 3–4 cm through either an 18-gauge Crawford needle, or an 18-gauge vascular catheter. Sterile transparent dressings (Tegaderm™, 3M) were applied over the caudal catheters to allow postoperative inspection of the skin site. Children under 3 yr of age also had the lower back draped with a sterile plastic sheet (SteriDrape™, 3M) to isolate the catheter site from potential fecal contamination. The assigned dose of morphine in a concentration of 1.0 mg·ml^{-1} was mixed with lidocaine (1.0% without epinephrine) 0.25 mg·kg^{-1}, and injected *via* the caudal catheter. The lidocaine was of sufficient dosage to serve to confirm correct catheter placement by producing transient anesthesia in the sacral dermatomes.[5] At the conclusion of surgery, patients were taken to the recovery room to awaken.

When the child was awake in the recovery room, the presence or absence of the anal wink reflex was assessed by one of the study investigators. Patients with an anal wink reflex present were assumed to have incorrect catheter placements, and were removed from the study.

Five-point pain scores[2] were used as a nominal index of the presence or absence of pain, and were assigned every 15 min in the recovery room by a nurse unaware of the morphine dose administered, and thereafter every 2 h by ward nurses, also unaware of the treatment group assignment. When the pain score was 4 or 5 (indicating moderate to severe pain), the assigned dose of caudal

morphine (1.0 mg · ml^{-1}) was repeated. In patients in whom the duration of analgesia was less than 6 h, the next dose and all subsequent doses of caudal morphine were increased to the next higher dose, to a maximum of 0.10 mg · kg^{-1}. Subsequent data from these patients were then included with the data from the higher dose group of patients. Catheters were left in place for 48–72 h, until postoperative pain could be managed with oral analgesics. The catheter site was inspected daily through the transparent dressing, and at the time of catheter removal.

Naloxone, oxygen, and an anesthesia bag with an appropriately sized face mask were available at each bedside. Patients were cared for on a pediatric surgical ward by nurses who had been trained by the investigators regarding the care of epidural catheters and the risks of spinal opioids.

All patients were monitored for delayed respiratory depression with a cardiorespiratory monitor until 24 h after the last dose of caudal morphine. Arousability was determined by nursing staff hourly for the first postoperative 24 h by gently stimulating the child during sleep, until the child aroused, moved on command, or answered a question, as was appropriate to the child's age.

A nurse recorded the occurrence of vomiting, pruritus, urinary retention, respiratory depression, or other side effects and complications in a bedside log. Metoclopramide (0.1 mg · kg^{-1}) was used to treat vomiting; naloxone (5 μg · kg^{-1}) was used to treat severe pruritus. Urinary retention was relieved by intermittent bladder catheterization.

Statistical Analysis

The ages and weights of children were compared with a one-way analysis of variance. Analgesia of the three treatment groups were analyzed by pooling the durations of analgesia for each dose of caudal morphine, then applying one-way analysis of variance, and Student's t tests with Bonferroni corrections. The frequencies of side effects were compared using Fisher's exact test. Data are reported as mean ± SD. $P \leq 0.05$ was considered statistically significant.

Results

Analgesia

Thirty-two children were studied; five were eliminated from analysis because they did not have demonstrable sacral dermatome anesthesia in the recovery room, and one because he was treated with naloxone by continuous infusion for delayed respiratory depression (see below). Therefore, data from 26 children were the basis of this study. There were no significant demographic differences between the treatment groups (table 1).

TABLE 1. Types of Surgery, Patient Ages, Weights, and Genders

Dose	Operation	Age (yr)	Weight (kg)	Sex
0.033 mg · kg^{-1}	Pemberton osteotomy	3.8	22.4	M
	Nephrectomy	2.5	13.9	F
	Trochanteric osteotomy	7.0	29.0	F
	Ureteral reimplant	1.2	11.7	F
	Duhamel procedure	4.3	10.1	M
	Ureteral reimplant	5.9	19.5	M
	Ureteral reimplant	6.0	21.8	F
	Nephrectomy	2.3	11.2	F
	Colectomy/colostomy	5.8	18	M
	Mean	4.3	17.5	4M:5F
0.067 mg · kg^{-1}	Pyeloplasty	5.7	19.4	F
	Anoplasty	3.3	8.1	M
	Pyeloplasty	7.9	28.5	M
	Cholecystectomy	6.7	25.8	M
	Nephrectomy	3.9	12.0	F
	Nephrectomy	1.3	11.0	F
	Duhamel procedure	1.7	12.5	M
	Ureteral reimplant	4.4	17.0	F
	Nephrectomy	4.4	19.0	F
	Mean	3.9	17.6	4M:5F
0.10 mg · kg^{-1}	Hypospadias repair	3.2	15.0	M
	Ureteral reimplant	1.8	9.7	M
	Bladder augmentation	4.7	15.0	F
	Pemberton osteotomy	3.1	13.0	F
	Bilat. nephrectomy	3.1	12.5	M
	Pyeloplasty	5.4	22.0	F
	Duhamel procedure	1.7	9.6	M
	Salter osteotomy	2.3	10.6	M
	Mean	3.1	13.4	5M:3F

The ranges and mean durations of analgesia are presented in table 2. One child who received 0.033 mg · kg^{-1} and two children who received 0.067 mg · kg^{-1} obtained less than 6 h of analgesia, and crossed over to the next highest dose group. The crossovers occurred after the first dose of caudal morphine; all doses after the first dose resulted in greater than 6 h of analgesia. One child in the 0.10 mg · kg^{-1} group obtained less than 6 h of analgesia after the first dose, but satisfactory durations after subsequent doses.

After both 0.033 or 0.067 mg · kg^{-1}, approximately 75% of doses produced analgesia of greater than 8 h duration, and 30% of doses were followed by analgesia of greater than 12 h. After 0.10 mg · kg^{-1} only one dose was followed by less than 8 h of analgesia, while 60% were followed by analgesia of greater than 12 h.

There was no difference in the duration of analgesia after 0.033 or 0.067 mg · kg^{-1}. The duration of analgesia following 0.10 mg · kg^{-1} of caudal morphine was statistically greater than that following 0.033 or 0.067 mg · kg^{-1} ($P < 0.02$).

The duration of analgesia did not significantly increase or decrease between the first and fourth administrations of the three doses studied (fig. 1), demonstrating the absence of development of either short-term tolerance or

TABLE 2. Duration of Analgesia following Caudal Morphine, With and Without Concomitant Naloxone Therapy (5 $\mu g \cdot kg^{-1}$) Given to Treat Severe Pruritus

		Duration of Analgesia								
		All Doses			No Naloxone			Naloxone		
Dose ($mg \cdot kg^{-1}$)	N*	N (doses)	Range (h)	Mean ± SD (h)	N (doses)	Range (h)	Mean ± SD (h)	N (doses)	Range (h)	Mean ± SD (h)
0.033	9	23	4.0–18.6	10.0 ± 3.3	19	4.0–18.6	10.3 ± 3.3	4	6.0–13.4	8.9 ± 3.4
0.067	9 (1)	30	3.8–24.2	10.4 ± 4.2	29	3.8–24.2	10.6 ± 4.2	1	6.2	6.2
0.10	8 (2)	27	5.7–26.0	13.3 ± 4.7†	22	5.7–26.0	12.9 ± 4.7†	5	12.2–23.8	14.9 ± 5.0†

* Numbers in parentheses refer to the additional number of children who crossed over into the dose group from the lower dose group, one patient from 0.033 $mg \cdot kg^{-1}$ to 0.067 $mg \cdot kg^{-1}$, and two patients from 0.067 $mg \cdot kg^{-1}$ to 0.10 $mg \cdot kg^{-1}$ (see text for explanation).
† $P < 0.02$ compared to lower doses.

sensitivity to the analgesic effects of caudal morphine in children.

Side Effects

Side effects that occurred were vomiting, pruritus, urinary retention, delayed respiratory depression, and dysphoria. No catheter-related infectious complications occurred.

The incidence of vomiting was greatest after the first dose of caudal morphine (33–56%), and thereafter diminished, so that only one child vomited after the third administration of caudal morphine, and no children after the fourth administration of caudal morphine ($P < 0.05$ 1st *vs.* third or fourth administration, Fisher's exact test) (fig. 2). It is uncertain whether this observation represents the superimposition of postanesthetic vomiting, the cumulative effect of earlier antiemetic therapy in some patients, or patient tolerance to the emetic effects of epidural morphine. The incidence of vomiting was similar following each of the three doses that we evaluated.

Vomiting occurred more frequently (9/20 patients) in orthopedic and urologic surgery patients who were fed within 8–24 h of surgery, than in general surgery patients (0/6 patients) who were fasted and had nasogastric drainage for 48–72 h following surgery ($P < 0.05$, Fisher's exact test).

The incidence of pruritus varied from 22% to 57% (fig. 3). There was no difference in the occurrence of pruritus between the three doses of caudal morphine. Pruritus was usually facial in distribution, and was most often no more than an annoyance in those children who were old enough to describe their symptoms. However, five children had pruritus of sufficient severity (as evidenced by excoriation of the skin from scratching) to warrant therapy with naloxone (5 $\mu g \cdot kg^{-1}$). Pruritus re-

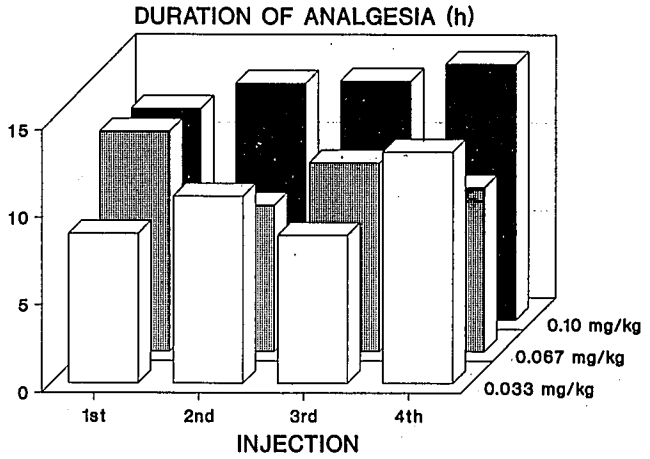

FIG. 1. Durations of analgesia associated with the first through fourth administration of three doses of caudal morphine, 0.033 $mg \cdot kg^{-1}$ (white bars), 0.067 $mg \cdot kg^{-1}$ (gray bars), and 0.10 $mg \cdot kg^{-1}$ (black bars). There is no demonstrable tendency toward the development of short-term sensitivity or tolerance to the analgesic effect of caudal morphine.

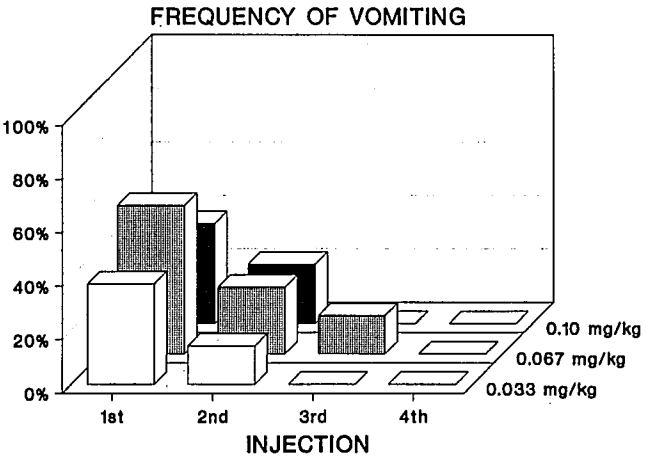

FIG. 2. Frequency of vomiting associated with the first through fourth administration of three doses of caudal morphine, 0.033 $mg \cdot kg^{-1}$ (white bars), 0.067 $mg \cdot kg^{-1}$ (gray bars), and 0.10 $mg \cdot kg^{-1}$ (black bars). The incidence of vomiting decreased between the first and third administration ($P < 0.05$). There is no difference in the frequency of vomiting among the three doses of caudal morphine.

solved in each instance following naloxone, but recurred in two children after subsequent doses of caudal morphine, requiring additional naloxone therapy.

Administration of naloxone had no immediate antianalgesic effect that was evident to observers. However, the duration of analgesia following naloxone when 0.033 mg · kg^{-1} or 0.067 mg · kg^{-1} of caudal morphine had been administered tended to be shorter compared with when naloxone had not been given (table 2). This difference was not statistically significant.

The majority of children in each group had routine postoperative bladder catheterization, leaving too few children to statistically compare the incidence of urinary retention. The approximate overall incidence was 27%, comparable to our earlier results and the observations of Attia *et al.*[2,3]

Delayed respiratory depression occurred in one child who received 0.10 mg · kg^{-1} of caudal morphine; the case is described in detail elsewhere.[6] Naloxone was administered by continuous infusion and caudal morphine was discontinued.

Transient dysphoria and disorientation occurred in a second child within 1 h of the first two doses of caudal morphine, prompting discontinuation of this form of analgesia. However, dysphoria recurred following subsequent intravenous administration of morphine.

Discussion

Caudal morphine, 0.033–0.10 mg · kg^{-1}, produces prolonged analgesia in children following surgical procedures below the diaphragm. The mean duration of analgesia is lengthened and the proportion of children with prolonged analgesia (>8 h) is greater following 0.10 mg · kg^{-1} of caudal morphine. Nevertheless, analgesia of more than 8 h duration is seen in most children who receive as little as 0.033 mg · kg^{-1} of caudal morphine.

The increase in analgesic duration after 0.10 mg · kg^{-1} caudal morphine was not associated with a measurable increase in the incidence of vomiting or pruritus. It is interesting to note the absence of vomiting in patients who were fasted and had nasogastric drainage, from which we infer that oral intake within the first 24–48 h following surgery may increase the incidence of vomiting in children who receive caudal morphine. We observed nonrespiratory side effects with a frequency similar to that reported in adults who receive lumbar epidural morphine,[7–9] and in children treated with either caudal or lumbar epidural morphine.[2,3]

The presence of a dose response for analgesia and the absence of a dose response for nonrespiratory side effects seems paradoxical, but is similar to the findings of Martin *et al.*,[10] who found longer durations of analgesia after 2.0–8.0 mg of lumbar epidural morphine compared with that following 0.5–1.0 mg of epidural morphine in adults, but no statistically significant difference in the frequency of itching, urinary retention, or respiratory depression after 0.5–8.0 mg, and no difference in nausea after 0.5–6.0 mg.

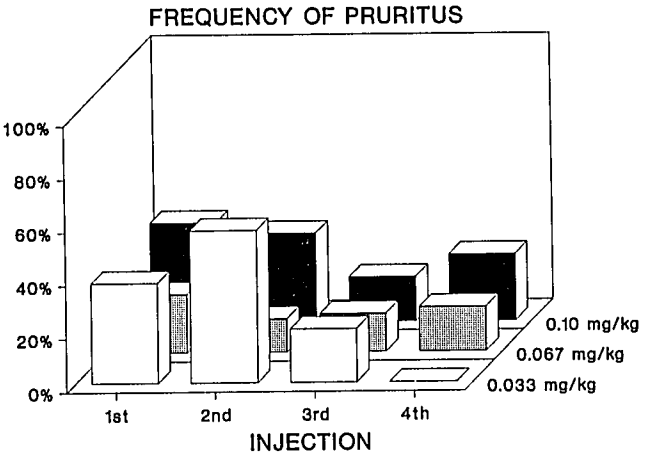

FIG. 3. The frequency of pruritus associated with the first through fourth administration of three doses of caudal morphine, 0.033 mg · kg^{-1} (white bars), 0.067 mg · kg^{-1} (gray bars), and 0.10 mg · kg^{-1} (black bars). There was no significant difference in the frequency of pruritus between the three doses of caudal morphine, nor decreasing incidence of pruritus with time.

The doses we evaluated are larger relative to patient weight than those reported by Martin *et al.*[10] The explanation for this discrepancy may be that we utilized the caudal epidural space rather than the lumbar epidural space, and therefore a larger epidural volume was present in the sacral than in the lumbar space into which the morphine is dispersed prior to transfer to the subarachnoid space. Furthermore, there is, on a per kilogram basis, a greater volume of cerebrospinal fluid present in children into which morphine injected into the epidural space must dissolve prior to uptake into the spinal cord, or rostral conduction to higher brainstem nuclei.[1,11]

Dysphoria, which occurred in one patient, is a previously unreported side effect of spinal opioids, but is a well-recognized side effect of conventionally administered parenteral opioids. Dysphoria occurred hours before rostral circulation of morphine in cerebrospinal fluid to the brain is expected.[9] But the occurrence of dysphoria coincided with when peak serum levels of morphine that are sufficient to produce systemic analgesia or mental status changes are expected.[3,12] We conclude that systemic absorption was the mechanism for this phenomenon.

The overall risk of delayed respiratory depression in children following epidural injection of morphine is unknown, but is probably small. There is, to date, only one report of this complication in a child,[5] yet the number of children who have received lumbar or caudal epidural

morphine, both at our institution and elsewhere, is large. Nevertheless, measurable depression of respiratory control after administration of epidural morphine in children[3] and the frequency of nonrespiratory side effects suggest the spread of morphine to areas near the brainstem[9] and indicate that certain precautions must be taken to detect delayed respiratory depression. Detection of delayed respiratory depression by an apnea monitor alone is, in our view, inadequate; the experience in adults[13] and our episode of delayed respiratory depression[5] demonstrate that life-threatening hypoventilation occurs without frank apnea. Nasal capnography has, in our hands, also been of limited value in children, because many children are mouth breathers, while many others experience facial pruritus and refuse to wear nasal prongs, associating them with the nasal itching. There remains, therefore, a need for an effective noninvasive monitor of respiratory status in children receiving spinal opioids.

Extrapolating from the observations of Ready *et al.* that oversedation is associated with respiratory depression and hypercarbia,[13] and that, without exception, all reported cases of respiratory depression have occurred within the first 24 h after starting epidural narcotics,[14] we have adopted a practice of assessing arousability on an hourly basis for the first 24 postoperative hours. This practice, as well as ward nurses trained by the Pain Service, the 24-hourly availability of a pain consultant, and in-house anesthesiologists have been essential components of our ability to care for children treated with spinal opioids out of an intensive care environment.

Although studies in adults have not consistently demonstrated a dose dependence of the respiratory effects of epidural morphine,[10,15] it seems prudent to assume that a respiratory dose response for caudal or lumbar epidural morphine may exist in children. Therefore, we recommend selecting the lowest effective morphine dose in children having insertion of caudal epidural catheters for postoperative analgesia, and increasing the dose in small increments if analgesia of insufficient quality or duration results.

In summary, caudal epidural morphine, 0.033, 0.067, and 0.10 $mg \cdot kg^{-1}$, provided prolonged postoperative analgesia in children who had undergone major surgical procedures below the diaphragm. The duration of analgesia was greatest in children who received 0.10 $mg \cdot kg^{-1}$, but one child in this group developed delayed respiratory depression. Analgesia was greater than 8 h in most children who received 0.033 $mg \cdot kg^{-1}$. Doses smaller than 0.033 $mg \cdot kg^{-1}$ may also be effective in producing prolonged analgesia; future dose-response studies will be required to extend the range of doses studied to below 0.033 $mg \cdot kg^{-1}$, in order to determine the minimum effective dose that produces prolonged analgesia in children. We recommend that 0.033 $mg \cdot kg^{-1}$ or less of caudal morphine be administered as the initial dose to children following abdominal, urological, or lower extremity orthopedic surgery, and that the dose be incrementally increased if needed to produce a greater duration of analgesia.

The authors wish to thank Drs. Anne Lynn and Gregory Sorensen, and Ms. Maureen Pomietto, R.N., M.S.N., for their expertise, and Drs. Robert K. Crone and Thomas F. Hornbein for review of the manuscript.

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