Anesthesiology
54:210–214, 1981

# *Serum Levels Following Epidural Administration of Morphine and Correlation with Relief of Postsurgical Pain*

*Stephen J. Weddel, M.D., CPT, MC, USA* and Richard R. Ritter, M.D., COL, MC, USA†*

**This study was undertaken to determine the serum levels of free morphine base resulting from the epidural administration of morphine, and to correlate these serum levels with analgesic effect. Results from twenty-one patients are presented. Following major surgery with bupivicaine or lidocaine continuous epidural block as the primary anesthetic, 5 or 10 mg/70 kg body weight of preservative-free morphine sulfate was administered through the epidural catheter when the patient noted the onset of postsurgical pain. Serum morphine levels were determined at intervals between 5 and 240 min post injection using a liquid chromatography technique with electrochemical detection, and analgesic effectiveness was assessed using a linear pain analogue scale and the subjective response of the patient.**

**The mean peak serum level in the patients receiving 5 mg/70 kg was 28.0 ± 20.6 ng/ml with mean serum levels declining to 2.1 ± 1.6 ng/ml over the four-hour post injection period. The patients receiving 10 mg/70 kg had a mean peak serum level of 49.7 ± 35.6 ng/ml with mean serum levels declining to 5.4 ± 4.8 ng/ml over the 4-hour postinjection period. Average onset of significant analgesia was 15 min postinjection. Duration of adequate analgesia varied from 4 hours to several days, the mean being 37.9 hours for those receiving 5 mg/70 kg, and 51.6 hours for those receiving 10 mg/70 kg.**

**Side effects included pruritis, ameliorated with diphenhydramine, and urinary retention. Somnolence and slowing of respiratory rate which developed in one patient were reversed with naloxone without notable effect on the duration or intensity of the analgesic response to the epidural morphine. This study demonstrates the analgesic effectiveness of and the serum morphine levels consequent to the epidural administration of morphine, and supports the concept of a selective spinal analgesic action. (Key words: Analgesia: postoperative. Analgesics, narcotic: morphine. Anesthetic techniques: epidural. Complications: pruritis; urinary retention. Pain: postoperative.)**

THE CONCEPT of direct spinal action of narcotics is being extensively explored and the analgesic effectiveness of subarachnoid and epidural narcotic administration is recognized.[1–6] With the open speculation as to the potential value of subarachnoid or epidural narcotics in various areas, including obstetric analgesia,[3,7] it becomes important to understand the disposition of narcotics administered by this route. The purpose of this study was to determine serum levels of free morphine base resulting from epidural administration of morphine given for postsurgical pain, and to look at the correlation of these serum levels with the analgesic effect of epidural morphine.

## Materials and Methods

This study was approved by the Institutional Review Committee and informed consent was obtained from each patient. Thirty-four patients who were to undergo elective abdominal, perineal, or lower extremity surgery were chosen for the study. The primary anesthetic was continuous epidural block using bupivicaine, 0.5 per cent, in all except two patients (patients 4 and 14) in whom lidocaine, 1.5 per cent, was used. No patient had been given any form of narcotic analgesic within the 48 hours prior to surgery, nor were any narcotics given intraoperatively.

When the patient noted the development of postsurgical pain in the recovery room, preservative-free morphine sulfate in a concentration of 1 mg/ml was administered through the epidural catheter already in place. The epidural catheter was then removed. Eleven patients received 5 mg/70 kg body weight (Group I), and ten patients received 10 mg/70 kg body weight (Group II). Dosages were administered on a body weight basis as they have in most other morphine disposition studies so the results could be more directly compared. Although smaller doses of epidural morphine have been used for pain control, we found from preliminary studies at our institution, that less than 5 mg/70 kg would frequently not relieve severe postoperative pain adequately. Bromage *et al.* have recently reported a similar minimal effective dose.[6]

Blood samples were drawn from an antecubital vein prior to and at 5, 15, and 30 min and 1, 2, and 4 hours after the morphine administration. Each patient's pain relief was evaluated using both a linear

* Resident in Anesthesiology, Brooke Army Medical Center.

† Chief, Anesthesiology & Operative Service, Brooke Army Medical Center.

Received from the Brooke Army Medical Center, Fort Sam Houston, Texas 78234. Accepted for publication September 25, 1980. Presented at the 1980 Society of Obstetric Analgesia and Perinatology Meeting in Cambridge, Massachusetts, May 8–11, 1980, and will be presented at the ASA annual meeting in St. Louis, Missouri, October 12–16, 1980.

The opinions or assertations contained herein are the private views of the authors and are not to be construed as reflecting the views of the Department of the Army or the Department of Defense.

Address reprint requests to Dr. Weddel.

0003-3022/81/0300/0210 $00.75 

TABLE 1. Serum Morphine Levels and Analgesic Onset and Duration Consequent to Epidural Morphine Administration. Underlined Values are Peak Serum Morphine Levels.

| Patient Number | Total Dose (mg) | Analgesia Onset (min) | Analgesia Duration (hours) | Procedure | Serum Morphine Levels (ng/ml) 5′ | 15′ | 30′ | 60′ | 120′ | 240′ | 720′ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Group I | | | | | | | | | | | |
| 1 | 7.0 | 15 | 24 | herniorrhaphy | 17.8 | 9.7 | 10.9 | 10.7 | 4.7 | 0 | — |
| 2 | 4.8 | 60 | 28 | laparotomy | 3.8 | 14.2 | 19.4 | 19.0 | 4.3 | 0 | — |
| 3 | 4.7 | 15 | 48 | laparotomy | 38.5 | 47.6 | 37.9 | 32.3 | 21.4 | 5.3 | — |
| 4 | 5.0 | 15 | 48 | herniorrhaphy | 44.2 | 22.7 | 24.0 | 16.5 | 7.5 | 5.3 | — |
| 5 | 5.0 | 30 | 64 | herniorrhaphy | 39.1 | 26.8 | 16.9 | 8.2 | 4.4 | 2.0 | — |
| 6 | 5.0 | 15 | 36 | cholecystectomy | 10.0 | 16.7 | 11.1 | 5.6 | 4.3 | 2.5 | — |
| 7 | 3.7 | 15 | 3.5 | abdominal hysterectomy | 3.1 | 3.7 | 2.9 | 4.4 | 3.4 | 2.4 | — |
| 8 | 4.9 | 30 | 18 | abdominal hysterectomy | 1.4 | 4.6 | 3.4 | 2.5 | 1.5 | 0 | — |
| 9 | 4.2 | 15 | 27 | abdominal hysterectomy | 20.7 | 15.7 | 10.3 | 7.9 | 3.0 | 2.9 | — |
| 10 | 4.7 | 60 | 24 | gastrostomy | 61.1 | 72.2 | 52.4 | 14.6 | 12.7 | 1.9 | — |
| 11 | 6.8 | 30 | 96 | herniorrhaphy | 9.3 | 18.5 | 22.0 | 7.5 | 3.5 | 2.8 | — |
| Mean Serum Morphine Level | | | | | 41.4 | 43.4 | 33.4 | 24.0 | 13.0 | 5.4 | — |
| (SD) | | | | | 33.0 | 31.4 | 24.1 | 18.0 | 8.7 | 4.8 | — |
| Group II | | | | | | | | | | | |
| 12 | 10.0 | 15 | 32 | cholecystectomy | 16.1 | 25.4 | 22.1 | 15.7 | 14.9 | 7.1 | — |
| 13 | 6.5 | 15 | 24 | vaginal hysterectomy | 26.1 | 20.7 | 16.8 | 11.5 | 4.2 | 2.1 | 0 |
| 14 | 10.0 | 30 | 72 | vein strip. | 119.0 | 83.7 | 67.4 | 59.5 | 30.3 | 12.7 | — |
| 15 | 9.0 | 15 | 96 | cesarean section | 66.2 | 98.6 | 77.4 | 50.0 | 24.6 | 12.8 | — |
| 16 | 9.5 | 60 | 36 | cholecystectomy | 33.0 | 50.3 | 20.3 | 14.4 | 12.6 | 9.9 | — |
| 17 | 10.0 | 15 | 40 | cholecystectomy | 12.4 | 7.6 | 19.3 | 12.4 | 8.6 | 2.7 | 0 |
| 18 | 9.1 | 15 | 60 | cholecystectomy | 39.7 | 29.4 | 21.4 | 19.0 | 4.8 | 2.7 | — |
| 19 | 10.0 | 15 | 48 | cholecystectomy | 9.8 | 9.5 | 8.9 | 8.5 | 7.9 | 2.9 | — |
| 20 | 10.0 | 30 | 72 | cesarean section | 58.1 | 68.8 | 56.5 | 35.5 | 15.9 | 0 | — |
| 21 | 11.5 | 15 | 36 | urethroplasty | 33.9 | 39.8 | 23.7 | 13.2 | 6.1 | 1.5 | — |
| Mean Serum Morphine Level | | | | | 22.7 | 23.0 | 19.2 | 11.8 | 6.4 | 2.1 | — |
| (SD) | | | | | 20.5 | 20.3 | 15.0 | 8.5 | 5.8 | 1.6 | — |

pain analogue scale[8] and the subjective response of the patient. The level of pain was documented with each blood sample drawn. The patient was closely observed for at least 20 hours for the development of potential side effects or complications. The patient's position was not controlled and the patient was allowed to lie flat.

All blood samples were immediately refrigerated at 6° C. The serum was separated the same day and frozen until analyzed. Serum morphine levels were determined using liquid chromatography with electrochemical detection.[9] This method effectively assays morphine concentrations as low as 1 ng/ml with an acceptable precision (coefficient of variation 11.6 per cent). The precision at higher morphine levels is greater (coefficients of variation less than 6.5 per cent). This technique is also very specific, having no interference from compounds similar in structure to morphine or from the major inactive metabolite, morphine-3-glucuronide. To assure accuracy of this relatively new morphine detection technique, 28 serum samples containing known concentrations of morphine were also analyzed, along with the samples from our patient population.

Data from 21 patients are presented. Thirteen patients were dropped from the study due to inadvertant

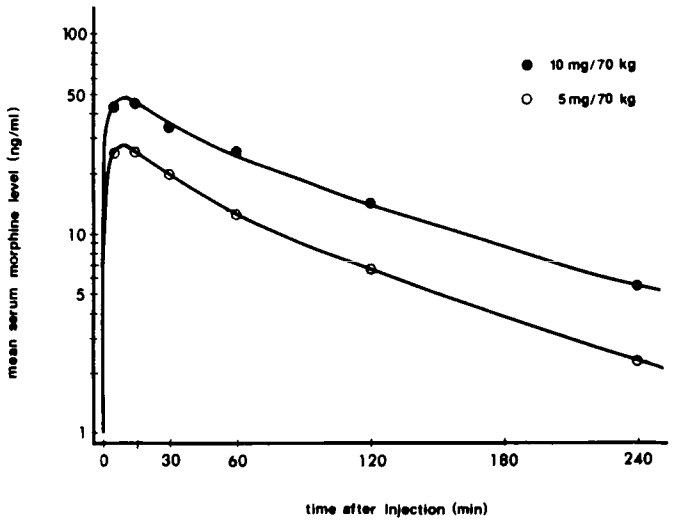


FIG. 1. Mean serum morphine levels (ng/ml) plotted on a log scale *vs.* time (min) following epidural administration of 5 and 10 mg morphine sulfate per 70 kg body weight.

destruction of the serum samples in transit to the laboratory.

## Results

All patients had undetectable serum morphine levels prior to the epidural morphine administration. At any given time after the morphine administration, there was a wide variance in the serum concentration of free morphine among the patients in each of the groups (table I). Peak serum levels occurred between 5 and 30 min postinjection and also varied greatly among patients. The mean of the peak serum concentrations for the group receiving the 5 mg/70 kg dose was 28.0 ± 20.6 ng/ml, and for the group receiving the 10 mg/70 kg dose was 49.7 ± 35.6 ng/ml. However, after the peak serum levels were reached, each patient demonstrated a similar complex nonlogarithmic curve describing the disappearance of morphine from the serum. Serum morphine levels were undetectable at 4 hours postinjection in three patients from Group I and in one patient from Group II. Twelve-hour serum levels measured in two other patients in Group II were also undetectable. Extrapolation of the individual semi-logarithmic curves of serum morphine levels *vs.* time indicated the serum level in each patient declined to less than 1 ng/ml between 4 and 12 hours after epidural injection.

The mean serum morphine concentrations at each sampling time for each group were dose related and are shown in figure 1. For the group receiving the 5 mg/70 kg dose, the mean serum level rose to 23.0 ± 20.0 ng/ml 15 min postadministration and declined to 2.1 ± 1.6 mg/ml over the 4 hours postadministration. The mean serum levels for the group receiving the 10 mg/70 kg dose rose to 43.4 ± 31.4 at 15 min and declined to 5.4 ± 4.8 ng/ml over the 4 hours postadministration. The decline in mean serum morphine concentration was not exponential in either group.

The time of onset of satisfactory postoperative analgesia did not significantly vary with the dose of morphine and ranged from 5 to 60 min, most patients noting significant relief in 15 min (table I). Duration of adequate analgesia, as subjectively determined by the patients noting increased pain, varied from 18 hours to several days, the mean being 37.9 hours for those in Group I and 51.6 hours for those in Group II (fig. 2). The one exception occurred in the patient receiving 3.7 mg (5 mg/70 kg), this being the smallest mass of drug given to any patient. Her analgesia lasted only 3.5 hours. All patients, however, were very satisfied with the completeness of their pain relief while it lasted and were observed to be remarkably relaxed and comfortable.

Generalized itching occurred in five patients (Patients 11, 12, 14, 19, and 21) from 2 to 12 hours post epidural morphine administration. The pruritis resolved within 15 min with the administration of diphenhydramine, 25 mg, im, and 25 mg, iv. All but one patient had postoperative urinary retention lasting 12 to 24 hours post injection and necessitating catheterization.

Analysis of the serum samples containing known concentrations of morphine revealed an excellent correlation of the measured to the known serum levels of free morphine base (coefficient of determination $r^2 = .96$), lending support to the validity of this detection technique.

## Discussion

Consideration of the use of epidural morphine for analgesic relief in various clinical situations requires knowledge of its disposition to better understand its mechanism of action and its potential side effects. There is general agreement that 10 mg morphine/70 kg body weight, im, is an optimal analgesic dose,[10,11] and that such a dose given im results in peak serum levels of 80 ± 6 ng/ml occurring 30 min post injection, with mean serum levels declining to about 11 ng/ml over the 4 hours postinjection.[12] Previous data gathered at our institution using liquid chromatography with electrochemical detection to measure serum morphine levels have supported these figures. Mean serum levels from 10 mg morphine/70 kg, im,

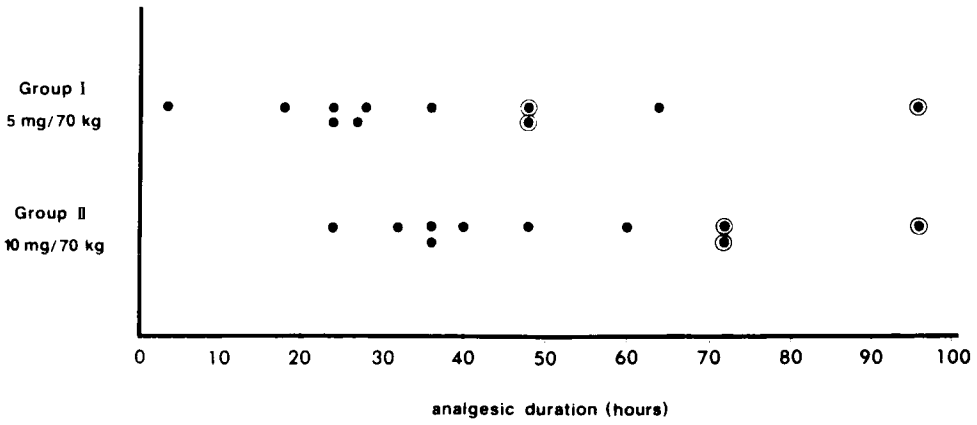


FIG. 2. Correlation of analgesic duration (hours) to epidural administration of 5 and 10 mg doses of morphine sulfate for postsurgical pain. Circled points (⊙) indicate patients discharged from the hospital having experienced no increase in postsurgical pain.

peaked at 61.6 ± 31.3 ng/ml between 15 and 30 min postinjection and declined to 7.15 ± 5.0 ng/ml over the 4 hours postadministration.

Serum morphine levels following epidural administration of morphine sulfate varied widely from patient to patient. The levels were dose dependent, with the serum levels resulting from the 10 mg/70 kg dose correlating closely with those levels resulting from 10 mg/70 kg, im. The serum levels of all patients studied were below 13 ng/ml after 4 hours and were calculated to fall below 1 ng/ml between 4 and 12 hours post administration. The onset, duration, or intensity of analgesia did not correlate well with serum morphine levels. The duration of profound analgesia lasted from 18 hours to several days in all but one patient. The intensity of analgesic response also empirically seemed greater than that obtained by iv or im analgesics, the patients being universally satisfied with the pain relief and being notably more relaxed and comfortable than patients receiving im or iv narcotic analgesics for postsurgical pain from similar surgical procedures. Residual analgesia from the local anesthetic administered epidurally for the surgical procedure was not considered by us to be a significant factor in this extended analgesic response. These results, demonstrating a longer and more intense analgesic response from epidural morphine as compared with the analgesia resulting from iv or im morphine, lend further support to the idea of a direct spinal action of epidural morphine.[1,2,13,14]

Notable side effects in this study were generalized pruritis, easily ameliorated with diphenhydramine, and urinary retention. Although a definite cause-and-effect statement cannot be made about urinary retention in these patients, as the sample size was small and they all received epidural anesthesia, it seemed to be a consistent and significant side effect, lasting up to 24 hours postinjection.

Considerable concern has developed over the possibility of significant respiratory depression secondary to subarachnoid or epidural narcotic administration.[15–17] Significant somnolence accompanied by a slowing of respiratory rate occurred in one patient, a 70-year-old female postcholecystectomy among those patients not presented in table 1. Six hours after receiving 8.4 mg morphine sulfate (10 mg/70 kg) through her epidural catheter, she became difficult to arouse and her respiratory rate decreased from 12 to 6 breaths/min. Naloxone, in a dose of 0.1 mg, iv, and 0.3 mg, im, improved her mental status and increased her respiratory rate back to 12/min. Recurrence of her symptoms necessitated repeating the dose of naloxone 2, 4, and 6 hours later. In spite of the use of a narcotic antagonist, her postsurgical analgesia from the epidural morphine administration persisted for 36 hours postinjection. Naloxone administration having no notable effect on the patient's analgesic response is in concurrence with previous findings.[16,17]

In summary, epidural administration of morphine sulfate resulted in serum levels of free morphine corresponding closely to serum levels resulting from similar doses of morphine given im. All patients had serum morphine levels of less than 13 ng/ml 4 hours postadministration. The analgesic effect correlated poorly with serum morphine levels and remained remarkably profound for 18 hours to several days. This study demonstrates the analgesic effectiveness of epidural morphine and supports the concept of a direct spinal action.

The authors thank Drs. Robert Watson and L. Jack Hempling for helping initiate the study, Dr. Jack E. Wallace for performing the morphine assay, and the A. H. Robins Co. for providing the preservative-free morphine sulfate for epidural administration and the morphine containing serum samples for verification of the accuracy of the technique of analysis.

## References


1. Behar M, Magora F, Olshwang D, et al: Epidural morphine in the treatment of pain. Lancet 8115:527–529, 1979
2. Cousins MJ, Mather LE, Glynn CJ, et al: Selective spinal analgesia. Lancet 8126:1141–1142, 1979
3. Wang JK, Nauss LA, Thomas JE: Pain relief by intrathecally applied morphine in man. ANESTHESIOLOGY 50:149–151, 1979
4. Wolfe MJ, Nicholas ADG: Selective epidural analgesia. Lancet 8134:150–151, 1979
5. Leslie J, Camporesi E, Urban B, et al: Selective epidural analgesia. Lancet 8134:151, 1979
6. Bromage PR, Camporesi E, Chestnut D: Epidural narcotics for postoperative analgesia. Anesth Analg (Cleve) 59: 473–480, 1980
7. Alper MH: Intrathecal morphine: A new method of obstetric analgesia. ANESTHESIOLOGY 51:378–379, 1979
8. Revill SI, Robinson JO, Rosen M, et al: The reliability of a linear analogue for evaluating pain. Anaesthesia 31:1191–1198, 1976
9. Wallace JE, Harris SC, Peek MW: Determination of morphine by liquid chromatography with electrochemical detection. Anal Chem (in press)
10. Smith GM, Lowenstein E, Hubbard JH, et al: Experimental pain produced by the submaximum effort tourniquet technique: Further evidence of validity. J Pharmacol Exp Ther 463:468–474, 1968
11. Lasagna L, Beecher HK: The optimal dose of morphine. JAMA 156:220–234, 1954
12. Brunk SF, Delle MS: Morphine metabolism in man. Clin Pharmacol Ther 16:51–57, 1974
13. Yaksh TL, Rudy TA: Studies on the direct spinal action of narcotics in the production of analgesia in the rat. J Pharmacol Exp Ther 202:411–428, 1977
14. Samaii K, Feret J, Harari A, et al: Selective spinal analgesia. Lancet 8126:1142, 1979
15. Liolios A, Andersen, FH: Selective spinal analgesia. Lancet 8138:357, 1979
16. Glynn CO, Mather LE, Cousins MJ, et al: Spinal narcotics and respiratory depression. Lancet 8138:356–357, 1979
17. Scott DB, McClure J: Selective epidural analgesia. Lancet 8131:1410, 1979