

Pain Relief and Plasma Concentrations from Epidural and Intramuscular Morphine in Post-Cesarean Patients

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In a double-blind study of post-cesarean analgesia, a single dose of 4 mg epidural morphine sulfate (EMS), with and without epinephrine, was compared with an equal dose of intramuscular morphine (IMS). Postoperative pain was assessed by visual analogue scores and the frequency of patient requests for subsequent meperidine injections. Plasma concentrations of morphine base after EMS and IMS were contrasted. Clinically apparent adverse effects were recorded. The stability of the preservative-free morphine preparation was substantiated.

Pain indices after EMS were improved significantly over those after IMS. Pain scores and requests for intramuscular meperidine indicated that the onset of effective EMS analgesia was delayed. The duration of EMS analgesia was about 20 h. No significant difference between the effect of EMS with and without epinephrine was demonstrated. No circulatory or respiratory depression was attributed to the use of 4 mg EMS. The mean peak plasma morphine concentration after 4 mg EMS was significantly lower and later than the mean peak after 4 mg IMS. No correlation was observed between plasma morphine concentration and analgesic effect. These results support the view that epidural administration delivers more of a given dose of morphine directly (rather than via the bloodstream) to the spinal site of action than does intramuscular administration. (Key words: Analgesia: measurement; postoperative. Analgesics: meperidine; morphine. Anesthesia: obstetric. Anesthetic techniques: epidural, lumbar. Anesthetics, local: chloroprocaine. Pharmacology: morphine.)

THE INITIAL OBSERVATIONS of Wang *et al.*¹ and Bahar *et al.*² have led to numerous investigations of pain relief following subarachnoid and epidural administration of narcotics. These investigators have reported on a variety of drugs, doses, dosing schedules, patient populations and definitions of analgesia.³⁻⁵ However, double-blind control observations were not obtained concurrently.

In a controlled, double-blind study, we sought to compare objectively the analgesic efficacy of a single dose of epidural morphine with conventional manage-

ment in a homogenous population. We compared the post-cesarean analgesia produced by 4 mg epidural morphine sulfate (EMS), with and without epinephrine, with that of an equal dose of intramuscular morphine (IMS). Postoperative pain was assessed by visual analogue scores and the frequency of patient requests for subsequent meperidine injections. We examined curves of plasma concentration of morphine base after intramuscular and epidural administration. We also investigated the stability of the special morphine solutions used in the study.

Methods and Materials

DOUBLE-BLIND ANALGESIC STUDY

For elective cesarean section, 35 unmedicated patients received continuous lumbar epidural anesthesia with chloroprocaine (Nesacaine-CE) and no other sedation. The study was approved by the Institutional Review Board for Human Investigation, and informed consent was obtained from each patient.

Patients were randomly assigned to three treatment groups (table 1). Control Group A received 10 ml epidural normal saline (NS) and 4 mg morphine sulfate (MS—4 mg/ml) in saline injected into the anterior thigh. Experimental Group B received 1 ml intramuscular saline and 4 mg epidural morphine (4 mg/10 ml) in saline. Group C was treated the same as Group B, except that epinephrine 1:200,000 was added to the epidural morphine. Injection of these solutions was made 10–20 min after the administration of the last supplemental epidural anesthetic dose. This reference point was considered time zero for all later observations.

As the chloroprocaine anesthesia receded postoperatively, each patient could request intramuscular meperidine. To reflect conventional postoperative management, orders for meperidine (in the range of 50–100 mg q 3–4 h prn) were left to the discretion of the obstetrician. Patients were informed that they could ask for supplemental "pain shots" as they felt the need for relief. The nursing staff was instructed to administer supplemental meperidine injections only on request. Persistence of autonomic, motor, light-touch, or position-sense blockade was assessed during regular post-anesthetic visits. Changes in blood pressure, pulse, and respiratory rate were recorded. The occurrence of nausea, vomiting, or other adverse effects also was noted.

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SUPPLEMENTAL INTRAMUSCULAR MEPERIDINE INJECTIONS

The number of requests for supplemental narcotic doses (SNDs) of intramuscular meperidine were recorded. Differences between groups in the number of SNDs requested were evaluated statistically by the Wilcoxon rank sum test.

PAIN SCORES

Before beginning our comparative evaluation of postoperative pain scores, we tested two pain intensity scales: McGill and visual analogue (VA). These were administered simultaneously at various intervals during the first eight postoperative hours. Our first 20 patients were studied in this way, and the paired scores were subjected to correlation analysis. A categorical scale of numerically ranked descriptive terms was used for McGill pain score assessment^{6,7}: no pain (0), mild (1), discomforting (2), distressing (3), horrible (4), and excruciating (5). For VA pain score assessment, the patient marked a plain, 10-cm vertical line.⁸ The top of the line was labeled "worst pain ever" and the bottom "no pain." For scoring, we divided the line into five equal zones to correspond to McGill scores 1 through 5. Score zero was represented only by the lower end of the line. Analysis of 64 pairs of scores revealed a significant correlation between these two pain scales (Spearman rank correlation 0.872, $P < 0.01$).

Comparative evaluation of postoperative pain intensity was carried out in the course of studying the last 15 of our 35 patients (five from each group). VA scores only were obtained hourly for the first six postoperative hours. Hourly scores and total six-hour VA scores (sum of six hourly scores) were evaluated statistically by the Wilcoxon rank sum test.

SAMPLING FOR PLASMA CONCENTRATIONS OF MORPHINE BASE

We also examined plasma concentrations of morphine base after EMS and IMS. After injection, blood samples were obtained at 5, 10, 15, 20, 45, 90, 180, 360, and 720 min.

When the code was broken at the conclusion of the double-blind study, we found that the above sampling times were inadequate for describing morphine absorption in the IMS group. Since plasma concentration studies need not be blinded, blood samples were obtained from additional patients in an open study to attain a total of 15 patients (five per group) and assure statistical relevance. Sampling times for the IMS group were shortened to 2, 4, 6, 10, 15, 20, 40, 90, 180, and 240 min. Our final analysis included samples from 5 patients in the double-blind study, and 10 patients in the open study.

TABLE 1. Study Design (MS = Morphine Sulfate;
NS = Normal Saline)

Group	n	IM	Epidural
A	12	4 mg MS	NS
B	12	NS	4 mg MS
C	11	NS	4 mg MS + epi 1:200,000

ANALYSIS OF PLASMA CONCENTRATIONS OF MORPHINE BASE

The venous blood samples for analysis of morphine base were placed in Vacutainers® (Becton-Dickinson, Rutherford, New Jersey 07070) containing disodium edetate, mixed by inversion, and centrifuged. The resulting plasma samples were removed and stored in Teflon®-lined screw-capped, silanized glass culture tubes at -20°C until analyzed.

Analysis of morphine base, using 1-ml plasma aliquots, was performed using pentafluoropropionyl derivatization, gas-liquid chromatographic separation, and electron capture detection. Nalorphine was used as an internal standard. The extraction and derivatization procedures employed were modifications of procedures described by Dahlström and Paalzow⁹ and Wallace *et al.*¹⁰ and entailed the use of silanized glassware throughout the extraction and derivatization sequence, as well as the use of ammonium carbonate to saturate and adjust the final extraction mixture to a pH of 8.6. Recovery studies (using 6-³H-morphine) were done at levels of 3.5 and 14 ng/ml, and showed recovery of morphine base to be $91 \pm 3\%$ at both levels.

Analysis of each patient's samples was accompanied by analysis of a suitable number of plasma morphine standards, the concentrations of which ranged from 0.5 to 20 ng/ml, as well as analysis of both positive and negative quality control samples. Precision studies showed the methodology possessed a day-to-day coefficient of variation of 6.4% at 1.2 ng/ml and 2.7% at 20 ng/ml. Linearity of detection, from 0.6 to 40.0 ng/ml, was found to have a correlation coefficient of 0.9998.

A study of the potential influence of Vacutainer® storage (contact with glass wall and rubber stopper) upon whole blood and plasma concentrations of morphine base revealed that loss was less than 1% (within error of measurement).

We used weighted nonlinear least-squares regression analysis¹¹ to determine a curve of "best fit" for each patient.¹² Composite graphs for each group (A, B, and C) were then appropriately constructed, plotting hourly means and standard errors. The mean maximum plasma morphine concentration ($C_{p\text{max}}$) and the mean time required to reach the peak (T_{max}) were evaluated statistically by two-tailed *t* test.

TABLE 2. Median Numbers of Supplemental Intramuscular Meperidine Injections Requested Postoperatively

Group	n	MS dose (mg)	0-8 h	8-20 h	0-20 h	20-24 h
A	12	4 im	2.5	2.0	5.0	1.0
BC	23	4 epidural	1.0*	0.0*	1.0*	1.0

* $P < 0.001$, Wilcoxon rank sum test.

ANALYSIS OF MORPHINE SULFATE SOLUTIONS

All morphine sulfate solutions used in this study were freshly prepared in normal saline, sterilized by filtration, and administered within 1-6 h after preparation. Solutions contained 0.1% sodium bisulfite antioxidant and were otherwise preservative-free.

The addition of sodium bisulfite antioxidant to epidural local anesthetic solutions is not a new practice. At low (10 mg) doses, no adverse reactions have been shown to date. Since the solutions were unavailable commercially and information concerning the stability of morphine is lacking, it was deemed necessary to determine the concentration and stability of the morphine sulfate solutions experimentally.

Concentration was assessed by analysis of 15 preparations (five from each of the study Groups A, B, and C) with the aid of an electrochemical detector coupled to a high-pressure liquid chromatograph. Stability was assessed at 25°C by serially analyzing triplicate samples of the three types of preparations over a six-hour period.

Results

CLINICAL OBSERVATIONS

We found no differences among Groups A, B, and C with respect to absence of circulatory or respiratory depression, nausea and vomiting, or persistence of autonomic, motor, or sensory (other than pain) blockade. All patients had a urinary bladder catheter for up to 24 h. In no instance was it necessary to reinsert the catheter because of urinary retention. Two patients in Group B and one in Group A complained of generalized itching without rash.

SUPPLEMENTAL INTRAMUSCULAR MEPERIDINE INJECTIONS

The median number of requested SNDs are presented in table 2. (Note that these data are nonpara-

metric because the measurement scale is ordinal rather than interval. Though the number of SNDs allows ranking of each patient's demand for analgesia, the differences between scores cannot be quantified precisely. Under these circumstances, the appropriate measurement of central tendency is the median.)

The median number of injections (0-20 hours) for both Group B and Group C was one. Since neither a statistical nor a clinical difference could be demonstrated, data for the two groups were combined (Group BC). For the first 20 h postoperatively, patients in Group BC requested significantly fewer SNDs than those in Group A ($P < 0.001$).

Table 3 contains hourly SND data. In the first three hours, 100% of Group A and 61% of Group BC patients requested at least one SND. After this early peak, the SND rate for Group BC fell rapidly and remained low. Seventy-four per cent of Group BC patients experienced a pain-free interval of at least 12 h. No patient in Group A remained similarly pain-free.

Of the 17 Group BC patients experiencing a pain-free interval of at least 12 h, five requested no further intramuscular dosing during their hospital stays. The remaining 12 patients experienced a return of incisional pain and resumed intramuscular dosing. The median time from EMS injection to the intramuscular injection marking the end of the pain-free interval and resumption of supplemental intramuscular dosing for these Group BC patients was 21 h. The number of SNDs requested by Group BC in the postoperative interval from 20 to 24 h was not statistically different from that requested by Group A. (Analysis of narcotic requirements after 24 h was not undertaken since dosing regimens were no longer comparable. At this time, many patients, predominantly in Group BC, were converted to oral dosing.)

PAIN SCORES

Table 4 presents median hourly (MHVA) and median of total six-hour (MTVA) VA scores for the first six postoperative hours (15 patients, five in Group A and 10 in Group BC). (The MTVA for Group B was 7 and for Group C, 5. A significant difference was not demonstrated and the groups were again combined.) For the first two hours, the median scores in Group BC were not statistically different from those in Group A. Significant differences in VA scores, however, were observed between Groups A and BC for hours 3 and 4

TABLE 3. Hourly SNDs

Group	n	Hour																							
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
A	12	4	7	3	2	6	2	2	3	3	1	4	2	2	3	1	0	6	0	2	1	2	3	0	1
BC	23	5	7	2	1	2	0	2	0	2	1	0	0	0	3	1	1	1	0	3	1	3	6	5	2

($P < 0.05$) and for hours 5 and 6 ($P < 0.01$). The MTVA was 19 for Group A and 7 for Group BC ($P < 0.01$). Group BC consistently registered lower median VA scores after the second hour.

PLASMA CONCENTRATIONS OF MORPHINE BASE

Due to extremely rapid absorption, the regression analysis could not adequately characterize the absorption kinetics of intramuscular morphine administration in this population. Consequently, the means and standard errors of the observed data are presented in figure 1, graph A. Composite graphs, appropriately derived from the individual patients' computer-fitted curves, are presented for both epidural groups (graphs B and C). Table 5 shows the mean peak plasma concentration of morphine base ($C_{p_{max}}$) as well as the mean time required to reach this level (T_{max}). The peak plasma morphine concentration for graph A (24.8 ± 1.7 ng/ml, declining to 6.3 ± 0.3 ng/ml after 4 h) corresponds to the peak levels reported by others¹³ after intramuscular morphine administration. It is, however, significantly ($P < 0.001$) higher than the peak plasma morphine concentrations from epidural administration of the same milligram dose depicted in graphs B (12.5 ± 0.5 ng/ml, declining to 5.0 ± 0.1 ng/ml after 4 h and 2.1 ± 0.1 ng/ml after 12 h) and C (13.1 ± 0.6 ng/ml, declining to 4.9 ± 0.1 ng/ml after 4 h and 2.1 ± 0.2 ng/ml after 12 h). The time to peak for graph A is significantly shorter than for either graph B or C ($P < 0.001$, $P < 0.01$, respectively).

CONCENTRATION AND STABILITY OF MORPHINE SULFATE SOLUTIONS

Analysis of five morphine sulfate (MS) preparations from each group produced the following results with respect to mean morphine sulfate concentration, standard deviation, and coefficient of variation: A, 3.99 ± 0.12 mg MS/ml NS (CV = 3.0%); B, 4.14 ± 0.08 mg MS/10 ml NS (CV = 1.9%); and C, 4.10 ± 0.12 mg MS/10 ml NS (CV = 2.9%). Analysis of the stability of triplicate morphine sulfate preparations for each group produced the following results after six hours at 25°C: A, 3.97 ± 0.11 mg MS/ml NS (CV = 2.8%); B, 3.98 ± 0.10 mg MS/10 ml NS (CV = 2.5%); and C, 4.05 ± 0.12 mg MS/10 ml NS (CV = 2.9%).

Discussion

In a controlled, double-blind study we sought to compare objectively the analgesic efficacy of a single dose of epidural morphine with conventional management in a homogeneous population. We found that the postcesarean analgesia after 4 mg epidural morphine sulfate (EMS), as compared to an equal dose of intramuscular morphine (IMS), was more profound and prolonged,

TABLE 4. Median of Hourly and of Total Six-hour Visual Analogue Pain Scores

Group	n	MS dose mg	Hour						Total
			1	2	3	4	5	6	
A	5	4 im	4	3	3	4	4	3	19
BC	10	4 epidural	2	1	1*	1*	1†	1†	7†

* $P < 0.05$; † $P < 0.01$, Wilcoxon rank sum test.

though its onset was delayed. The peak plasma morphine concentration after EMS was significantly lower than after IMS. We did not identify autonomic, motor, or sensory (other than pain) blockade, or circulatory or respiratory depression in association with 4 mg EMS. This is consistent with a previous report.⁵ No patient experienced nausea or vomiting. Because our patients were catheterized, the incidence of urinary retention in the first 24 h could not be determined. None was observed thereafter. Three patients (one in Group A and two in Group B) complained of transient generalized itching without rash. Itching does not appear to be an important drawback in the use of low-dose EMS (4 mg).

The number of requests for SNDs represented one method of assessing postoperative pain. A request early in the postoperative course (within 3 h) was interpreted as signaling loss of effective chloroprocaine epidural anesthesia and inadequate or delayed morphine analgesia. All patients in control Group A requested an early SND. These requests reflected recession of chloroprocaine anesthesia and inadequate analgesia from 4 mg intramuscular morphine. In Group BC, 61% of patients requested an early SND. These requests reflected recession of chloroprocaine anesthesia and a probable delay in onset of effective epidural morphine analgesia. This assumption is supported by the fact that 74% of Group BC patients experienced a pain-free interval (without an SND) of at least 12 h. No Group A patient remained similarly pain-free. Finally, resumption of requests for SNDs by Group BC patients at a median time of 21 h suggests a 20-h duration of action for 4 mg epidural morphine in this population.

Visual analogue pain scores represented another method of assessing postoperative pain. To test the reliability of this method, VA scores were compared to simultaneously obtained McGill scores in our first 20 patients. A highly significant correlation was demonstrated between these two pain scales. Thereafter, we used VA scores only for six postoperative hours to comparatively evaluate pain intensity in the 15 remaining patients. For Group A, VA scores remained moderately high throughout the first six hours, despite rather frequent requests for SNDs. This is in agreement with the findings of other investigators^{14,15} that conventional regimens of intermittent narcotic administration provide poor control of postoperative pain. By comparison,

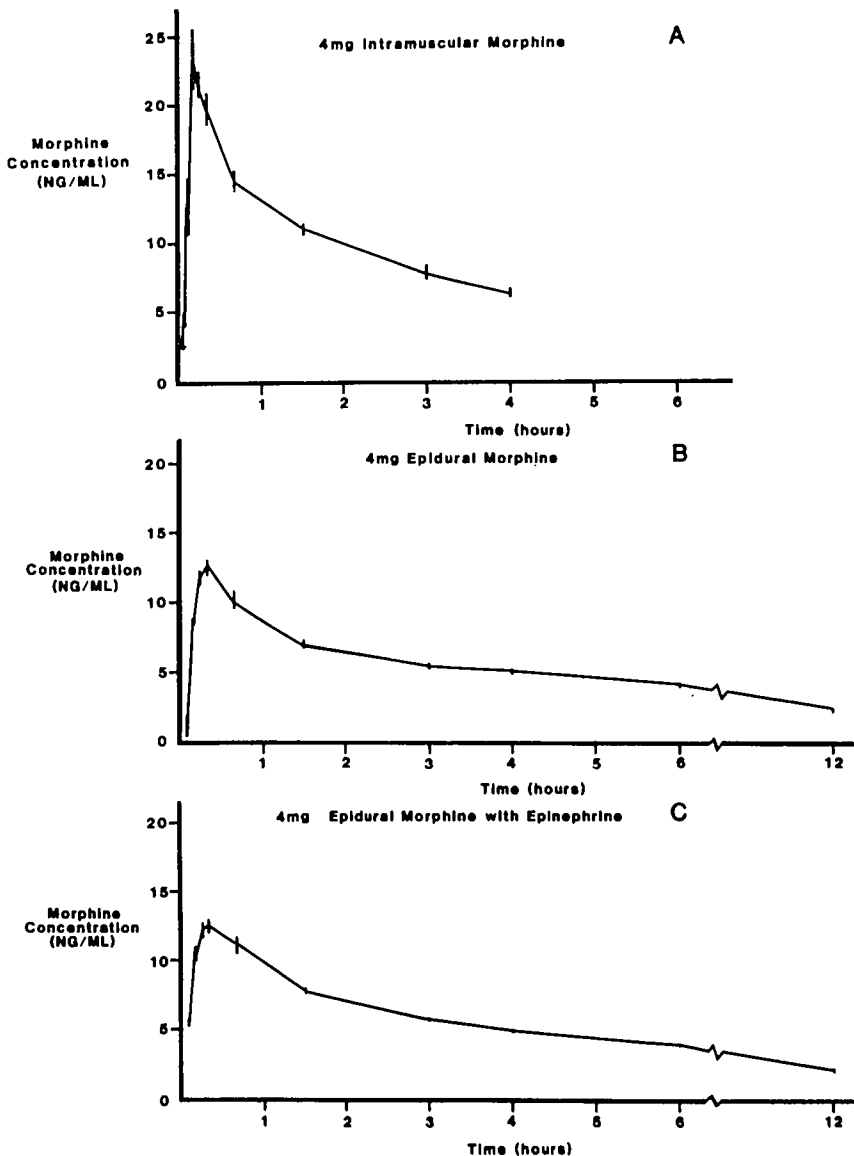


FIG. 1. Plasma concentration of morphine base vs. time following administration of 4 mg morphine sulfate by the intramuscular (A) and epidural [with (C) and without (B) epinephrine] routes. The standard errors, most of them so small that they do not show, are represented by vertical lines intersecting the curves.

VA scores for Group BC were highest or most variable in the first two hours, and accompanied by relatively frequent requests for SNDs. Thereafter, both pain scores and requests for SNDs fell dramatically and remained low as compared with the control group. Thus, pain intensity in Group BC was significantly and continuously reduced after two hours, to a degree that conventional intermittent dosing of intramuscular meper-

idine was unable to achieve in Group A. Presumably, this represented the onset of effective epidural morphine analgesia.

We report a mean peak plasma concentration of morphine base after 4 mg epidural morphine sulfate nearly 50% lower (and ten minutes later) than that after 4 mg intramuscular morphine. The mean peak plasma concentration found by Rawal *et al.*⁵ after 4 mg epidural morphine (about 28 ng/ml) is substantially higher than ours. In fact, it is more than five times higher than the mean peak reported by the same authors after 2 mg epidural morphine (about 5.2 ng/ml). Large standard deviations (observed peaks ranged from 14 to 37 ng/ml) and limited observations (two in the first 30 min after injection) make their pharmacokinetic deductions very difficult to evaluate. Weddel and Ritter⁴ report a mean peak plasma concentration after 5 mg/70 kg EMS of 28.0 ± 20.6 ng/ml. Again, early observations were

TABLE 5. Mean Peak Plasma Morphine Concentration (C_{pmax}) and Time to Peak (T_{max}) after Intramuscular and Epidural Morphine Administration (\pm SE)

Graph	n	MS dose (mg)	C_{pmax} (ng/ml)	T_{max} (min)
A	5	4 im	24.8 ± 1.7	11.3 ± 0.9
B	5	4 epid	$12.5 \pm 0.5^*$	$20.8 \pm 0.6^*$
C	5	4 epid + epi	$13.1 \pm 0.6^*$	$20.4 \pm 2.3^\dagger$

* $P < 0.001$; $^\dagger P < 0.01$, two-tailed *t* test.

limited and standard deviations were large. Dosing on a mg/kg basis and in an inhomogeneous surgical population may have contributed to this variability.

Our observations of a delay in the onset of effective epidural morphine analgesia of 2 to 3 h and a duration of effect of about 20 h correspond to results reported by Yaksh and Reddy¹⁶ after intrathecal injection of macaque monkeys with morphine sulfate. They observed a gradual increase in the level of electrical shock tolerated over a 3-h period after 160 μ g intrathecal morphine. The mean time for the titration threshold to return to baseline after 1.2 mg intrathecal morphine was 21 ± 2 h. The justification for comparing these two routes of administration is supported by the observations of Jørgensen *et al.*¹⁷ These investigators compared CSF and plasma morphine concentrations after intrathecal and epidural morphine administration in humans. After each route of administration, morphine concentration in the CSF was found to increase higher and remain elevated longer than plasma concentrations. The observed peak in CSF concentration after epidural administration occurred at 2 h. After six hours the CSF concentration remained well above the plasma concentration. It should be noted, however, that the morphine concentrations in plasma (but not CSF) reported by Jørgensen were probably spuriously high as a consequence of the radioimmunoassay technique employed.¹⁸

Current evidence indicates that there is no simple correlation between plasma concentration of morphine and analgesic effect.¹⁹ The absence of such a correlation after epidural administration has been reported previously⁴ and is also suggested by our results. The analgesic effects of morphine are believed to correlate more closely with morphine concentrations in the CNS than in plasma.²⁰ Our results in humans support the view of Yaksh and Reddy¹⁶: "the effectiveness of epidural morphine at doses which are inactive systemically, clearly suggests that the drug is diffusing directly to morphine-sensitive sites in the cord and not by a redistribution from blood."

In summary, a single dose of 4 mg epidural morphine sulfate, as compared with the same dose given intramuscularly, provided more profound and prolonged analgesia after cesarean section, though the onset of effect was delayed. The mean peak plasma concentration of morphine base was significantly lower after epidural morphine than after intramuscular morphine. Addition of epinephrine to epidural solutions did not significantly influence either analgesia or plasma morphine concentration. No correlation was observed between plasma morphine concentration and analgesic effect. This study supports the view that epidural ad-

ministration delivers more of a given dose of morphine directly (rather than via the bloodstream) to the spinal site of action than does intramuscular administration.

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