Epidural Morphine:
A Clinical Double-Blind Study of Dosage

Egon Lanz, MD, Eduard Kehrberger, MD, and Dieter Theiss, MD

LANZ E, KEHRBERGER E, THEISS D. Epidural morphine: a clinical double-blind study of dosage. Anesth Analg 1985;64:786–91.

The purpose of this randomized double-blind study was to determine the optimal dose of epidural morphine by establishing a dose–effect relationship. The 139 patients, who had orthopedic operations on the lower extremities, received continuous lumbar epidural anesthesia with bupivacaine, 0.75%, with or without the addition of 1,2,3,4, or 5 mg of morphine hydrochloride. Analgesia and side effects were determined during the first 24 hr postoperatively. In the 12-hr period after epidural anesthesia, arterial blood gas tensions were compared between those patients who received 5 mg morphine (n = 13) and those who received no morphine (n = 14). Patients who received 2 or more mg of morphine were less likely to require the administration of postoperative systemic analgesics (P < 0.05). The addition of 2 or more mg of morphine to bupivacaine, 0.75%, reduced postoperative pain intensity (P < 0.05); 5 mg of morphine reduced pain intensity for the longest time. Frequency of catheterization and pruritus increased dose-dependently. The mean $PaCO_2$ after 5 mg of epidural morphine averaged 5 mm Hg higher than in the control group, indicating minor respiratory depression, better analgesia, or both. The dose of 3 mg of epidural morphine added to the local anesthetic is recommended for postoperative analgesia after surgery of the lower extremity; it is a compromise that provides adequate analgesia with an acceptably low frequency and intensity of side effects.

Key Words: ANALGESICS—morphine. ANESTHETIC TECHNIQUE—epidural. PAIN—postoperative.

Despite the extensive use of epidural morphine for postoperative analgesia, only a few controlled double-blind studies have attempted to define the most appropriate dosage (1–5). These studies suggest that analgesia is not significantly improved when doses larger than 2–5 mg of morphine are employed.

The present study was designed to define which dose of epidural morphine is optimal in providing satisfactory postoperative analgesia with the lowest frequency and intensity of side effects (6,7). We used a randomized double-blind technique in which 0, 1, 2, 3, 4, or 5 mg of morphine were added to epidural bupivacaine given for epidural anesthesia before surgery of the lower extremity.

Methods

After giving informed consent, 139 patients received continuous lumbar epidural anesthesia for orthopedic surgery of the lower extremity. Prior to the study, the patients were randomly assigned to one of six groups. Epidural anesthesia consisted of bupivacaine, 0.75%, to which either 1 mg (n = 23), 2 mg (n = 23), 3 mg (n = 22), 4 mg (n = 22), or 5 mg (n = 25) of morphine hydrochloride (Merck, Darmstadt, Germany) was added. The sixth group was the control and received no morphine. After a test dose of 4 ml bupivacaine, 0.75%, 6–16 ml bupivacaine, 0.75%, were given depending on the age, height, and weight of the patient. All patients were premedicated with 25 mg meperidine and 25 mg promethazine. During surgery, they received by choice either no systemic medication or diazepam for sedation. Only technically satisfactory procedures were included in the study.

After surgery, patients were monitored in the recovery room until the afternoon of the first postoperative day. If the patients complained of pain, they received pentazocine intramuscularly or the pyrazolone derivative dipyrone (Novalgin, Hoechst, Frankfurt, Germany) added to an intravenous sugar–electrolyte solution as analgesics. Ward personnel and the investigator were not aware of the patients' randomized groups. Postoperative data included blood pressure; heart rate; respiratory rate at hourly intervals; subjective pain rating at intervals of 2 hr for 24

Results of the study were evaluated in the doctoral dissertation of E. Kehrberger.

Received from the Department of Anesthesiology of the Johannes Gutenberg-University, Mainz, Federal Republic of Germany. Accepted for publication March 15, 1985.

Address correspondence to Dr. Lanz, Institut für Anaesthesiologie der Johannes Gutenberg-Universität, Langenbeckstrasse 1, D-6500 Mainz, Federal Republic of Germany.

Table 2. Supplementation with Systemic Analgesics and Quality of Sleep during First Postoperative Night

	Epidural morphine dose (mg)					
	0 (n = 24)	1 (n = 23)	2 (n = 23)	3 (n = 22)	4 (n = 22)	5 (n = 25)
Request for additional analgesics during 24 hr after surgery (n patients)	21	15	12[a]	12[a]	12[a]	10[a]
Pentazocine						
Administered to n patients	17	10	7[a]	9[a]	8[a]	7[a]
Total dose per group (mg)	760	540	270	390	270	240
Dipyrone						
Administered to n patients	13	9	10	6[a]	5[a]	6[a]
Total dose per group (g)	27.5	19.0	13.4	7.0	7.4	9.4
Sleep during first postoperative night (n patients)						
Good	5	4	12[a]	8	9	18[a]
Moderate	7	9	4[a]	8	5	2[a]
Bad	12	10	7[a]	6	8	5[a]

[a] $P < 0.05$ comparing various morphine doses with 0 mg (χ^2-test).

tered to significantly fewer patients given 3–5 mg morphine than no epidural morphine ($P < 0.05$); the total doses of dipyrone were lower for the patient group given 3–5 mg morphine than for the control group. Sleep during the first postoperative night was rated better for patients who received 2 and 5 mg morphine than for those who received no morphine ($P < 0.05$).

In the control group there was almost complete analgesia for 4 hr after the start of epidural anesthesia; thereafter mean intensity of pain increased until the twelfth hr and then remained rather constant (Fig. 1). The mean intensity of pain in the group given 1 mg epidural morphine did not differ from that of the control group. After 2 mg epidural morphine, the mean intensity of pain was less than that in the control group at the twelfth hour ($P < 0.05$). The epidural injection of 3 mg resulted in less pain intensity compared to that of the control group 8 ($P = 0.05$), 10, and 12 hr ($P < 0.05$) after injection. Four mg epidural morphine did not further decrease pain intensity, and 5 mg decreased pain intensity at the fourteenth and sixteenth hours as compared to the control group ($P < 0.05$). The epidural injection of 4 mg morphine resulted in a pain course over the entire 24 hr that was almost identical to that associated with 3 mg epidural morphine. A dose of 5 mg epidural morphine resulted in a pain course that until 12 hr was very similar to that of 3 mg and thereafter was less (not statistically significant). Pain intensity at the twelfth hr was independent of age, sex, body weight, height, site, type and duration of surgery, as well as dose of bupivacaine.

Side Effects

First postoperative micturition was delayed after 1 mg or more of epidural morphine compared to the control group ($P < 0.05$) (Table 3). Spontaneous micturition decreased linearly with increasing doses of morphine ($P < 0.05$); reciprocally, the need for catheterization increased from about 12% of the patients in the control group to almost 50% of the patients receiving 5 mg morphine ($P < 0.05$).

Pruritus, mainly in the face or the trunk, also increased linearly with increasing doses of morphine ($P < 0.05$). It did not occur without morphine; it occurred in more than half of the patients given 4 and 5 mg ($P < 0.05$). Nausea and vomiting, in most cases single occurrences of short duration, as well as headache were independent of the administration or dose of morphine.

Blood Gases

In the control group, mean $PaCO_2$ increased 2 mm Hg within the first 1.5 hr after administration of the local anesthetic ($P < 0.05$), then gradually returned to the starting values until the sixth hr, and thereafter decreased continuously until 35 mm Hg in the twelfth hr (Fig. 2). After the epidural injection of 5 mg morphine, the mean $PaCO_2$ increased 0.5 hr after the administration of morphine, remained significantly ($P < 0.05$) elevated above starting values for 6 hr, and thereafter gradually returned to the starting values by 12 hr. From 2.5 to 12 hr, the $PaCO_2$ values in the 5 mg morphine group averaged 5 mm Hg higher than those of the control group ($P < 0.05$). The highest individual value was 57 mm Hg at 2.5 hr after epidural morphine. PaO_2 and base excess were similar in both groups.

Discussion

We administered morphine together with the local anesthetic for the following reasons: the initial epi-

Table 1. Clinical Data

	Epidural morphine dose (mg)					
	0 (n = 24)	1 (n = 23)	2 (n = 23)	3 (n = 22)	4 (n = 22)	5 (n = 25)
Age ($\bar{x}$ ± SD years)	51 ± 19	43 ± 22	47 ± 20	51 ± 20	46 ± 20	50 ± 20
Sex						
Female (n)	9	17	15	17	15	18
Male (n)	15	6	8	5	7	7
Height ($\bar{x}$ ± SD cm)	169 ± 7	166 ± 12	170 ± 10	163 ± 11	170 ± 12	163 ± 9
Weight ($\bar{x}$ ± SD kg)	71 ± 11	66 ± 12	70 ± 15	65 ± 12	70 ± 15	63 ± 9
Site of operation (n patients)						
Hip	12	7	8	8	10	11
Thigh	1	1	2	1	1	2
Knee	8	7	11	10	6	7
Calf	1	3	1	0	2	0
Foot	2	5	1	3	3	5
Type of operation (n patients)						
Total hip replacement	8	6	6	7	6	9
Total knee replacement	4	2	6	6	3	3
Arthrotomy	3	3	2	4	2	3
Osteotomy	2	2	1	1	2	1
Removal of metal	3	1	1	0	1	1
Other	4	9	7	4	8	8
Duration of operation ($\bar{x}$ ± SD hr)	2.7 ± 0.9	2.9 ± 1.3	2.8 ± 0.7	2.6 ± 0.7	2.4 ± 0.7	3.1 ± 1.2
Bupivacaine 0.75% ($\bar{x}$ ± SD ml)	16 ± 3	17 ± 4	17 ± 3	16 ± 3	18 ± 4	16 ± 3
Diazepam intraoperatively						
(n patients)	17	22	17	15	19	18
($\bar{x}$ ± SD mg)	9.0 ± 5.5	8.9 ± 3.2	8.8 ± 4.5	7.4 ± 3.8	9.0 ± 5.2	8.0 ± 3.6

Not significant (χ^2-test, Kruskal–Wallis test, Mann–Whitney–Wilcoxon test).

hr after the end of surgery (1, no pain; 2, mild pain; 3, moderate pain; 4, severe pain; 5, very severe pain); time of onset of severe postoperative pain; additionally requested systemic analgesics (dose and time of administration); subjective sleep rating during the first postoperative night (good, moderate, bad); and side effects such as disturbed micturition (spontaneous or catheterization), pruritus, nausea, vomiting, fatigue, headache.

After receiving additional information and giving consent, 27 patients gave arterial blood samples obtained from a catheter placed into the radial artery. Fourteen had received bupivacaine, 0.75%, without addition of morphine, and 13 patients had received 5 mg morphine added to the local anesthetic. Gas tensions in these samples were determined with an ABL 2 (Radiometer, Copenhagen) before as well as 0.5, 1.5, 2.5, 3.5, 4.5, 6.0, 7.5, 9.0, 10.5, and 12 hr after the start of epidural anesthesia. The presence of the radial artery catheter did not identify a patient's group, as the investigator was excluded from the final decision of which groups to sample.

In addition to calculation of frequency distributions of data, statistical significance of comparisons among all groups was determined using the Kruskal–Wallis test and χ^2-test, and between any two groups using the Mann–Whitney–Wilcoxon test and χ^2-test. Differences were accepted as statistically significant at an error probability of $P < 0.05$.

Results

Patients in each of the six groups were similar in age, male/female ratio, body height and weight, site, type and duration of surgery, volume and dosage of bupivacaine and intraoperative sedation (Table 1), premedication (25 mg meperidine, 25 mg promethazine), and extent of epidural blockade (mean ± SD, T8 ± 2.7 segments). During the intra- and postoperative periods there were no differences among the groups with regard to ventilation as determined by respiratory rate and hemodynamics as determined by blood pressure and heart rate.

Analgesia

Patients who received 2–5 mg epidural morphine requested additional systemic analgesics significantly less frequently than the control group within 24 hr after surgery ($P < 0.05$) (Table 2). Pentazocine was administered to significantly fewer patients given 2–5 mg epidural morphine than no epidural morphine ($P < 0.05$); the total doses of pentazocine were lower for the patient groups given 2–5 mg morphine than for the control group. Similarly, dipyrone was adminis-

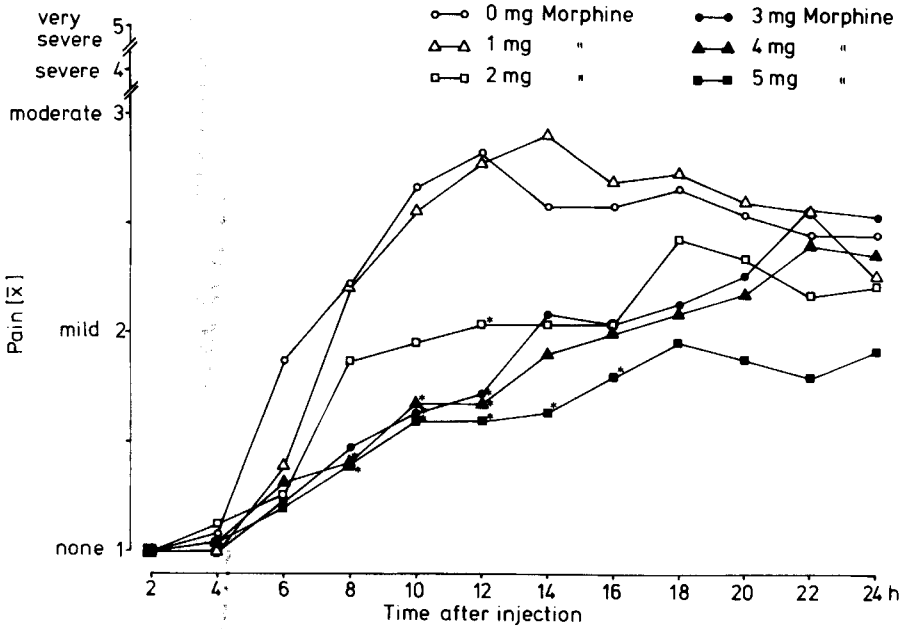

Figure 1. Mean subjective ratings of pain intensity for 24 hr after epidural anesthesia with bupivacaine, 0.75%, with 0 mg (n = 24, control group), 1 mg (n = 23), 2 mg (n = 23), 3 mg (n = 22), 4 mg (n = 22), and 5 mg (n = 25) epidural morphine hydrochloride. For clarity the standard deviations are omitted. Symbols: *P <0.05 comparing various morphine groups with control group; P = 0.05 comparing 3 mg with control group; not significant comparing 4 or 5 mg with 3 mg (Mann–Whitney–Wilcoxon test).

dural spread of morphine could be evaluated by the analgesic level of epidural anesthesia; there was no painful interval after surgery; the efficacy of epidural morphine is increased if morphine is given before the onset of pain (8); adding morphine to the local anesthetic injected epidurally permits use of a single injection epidural technique; and the combination of morphine and local anesthetic does not interfere with testing the efficacy and duration of epidural morphine because the analgesia of bupivacaine, 0.75%, completely wears off after 320 min (9) and because the duration of analgesia is the same when morphine is dissolved in either bupivacaine or saline (2).

Due to ethical reasons, our patients were not refused an analgesic when pain occurred. We administered the peripherally acting pyrazolone derivative dipyrone or the centrally acting opioid pentazocine. Like other investigators (10), we used pentazocine, an agonist–antagonist, which reverses possible respiratory depression induced by morphine (11) without reversing the analgesic effect of morphine, an effect also observed after naloxone (12).

Due to supplementation with systemic analgesics, we were not able to quantitate the analgesic effect of epidural morphine alone. Patients who received 0–1 mg morphine were more likely to require systemic analgesics than those who received higher doses of morphine, consequently diminishing the differences in pain intensity between these groups. If we had not used supplementary analgesics, these differences would have become more marked.

Our methods of measuring postoperative analgesia were of different reliability. The supplementation with systemic analgesics not only reflects pain intensity but also the attitude of patients and nursing personnel towards pain and its therapy with analgesics. We preferred the pain assessment made by the patient him or herself rather than observer assessment, as the former is more reliable (13). The simple 5-graded verbal scale of pain intensity correlates well with the visual analogue pain scale (14). Pain is only one of many factors determining sleep quality during the first postoperative night.

Our results show the following relationships between epidural morphine dose and postoperative analgesia: when 2–3 mg and more morphine was administered, fewer patients required systemic analgesics. Postoperative pain intensity was significantly less with 2 mg epidural morphine than it was when no epidural morphine was given. The decrease in pain intensity was even more marked and longer after 3 mg than after 2 mg, and lasted still longer after 5 mg.

Two side effects showed a linear relationship with the dose of epidural morphine: catheterization and pruritus. The need for catheterization was more frequent by patients who received 5 mg morphine than by those in the control group (P <0.05), and the occurrence of pruritus was more frequent in those who received 3 mg (P <0.05). The first spontaneous micturition was delayed after doses of 1 mg and more of morphine. After doses of up to 5 mg epidural morphine, nausea and vomiting were no more frequent than they were when no morphine was given. These side effects appear to be more frequent after doses of 8 mg (3) and 10 mg (6).

None of our patients had obvious clinical signs of

Table 3. Side Effects

	Epidural morphine dose (mg)					
	0 (n = 24)	1 (n = 23)	2 (n = 23)	3 (n = 22)	4 (n = 22)	5 (n = 25)
Disturbances of micturition						
1st micturition ($\bar{x}$ ± SD hr after epidural anesthesia)	9.8 ± 2.7	13.3 ± 3.2[a]	13.0 ± 3.5[a]	13.8 ± 3.6[a]	14.0 ± 4.4[a]	13.5 ± 3.9[a]
Spontaneous micturition[c] (n patients)	21	18	16	15	17	13[b]
Catheterization[c] (n)	3	5	7	7	5	12[b]
Pruritus[c] (n)	0	4	5	7[b]	13[b]	14[b]
Nausea (n)	7	8	8	10	6	8
Vomiting (n)	5	4	6	6	3	6
Headache (n)	5	2	5	1	4	4

[a] $P < 0.05$ comparing 1–5 mg morphine with 0 mg (Mann–Whitney–Wilcoxon test).
[b] $P < 0.05$ comparing 3, 4, and 5 mg with 0 mg (χ^2-test).
[c] Linear regression: for spontaneous micturition $r = 0.975$, $P < 0.005$; for catheterization $r = 0.802$, $P < 0.025$; for pruritus $r = 0.965$, $P < 0.001$ (2 × K table for trend).

respiratory depression for 24 hr after epidural morphine. We examined the $PaCO_2$ values only in the control group and in the group receiving our study's highest dose of 5 mg, because the greatest differences were expected here. We measured $PaCO_2$ for only the first 12 hr to avoid any possible complications that might be associated with leaving the arterial cannula in place for 24 hr. The mean $PaCO_2$ after epidural morphine was 5 mm Hg above the values of the control group from the second hr until the end of measurements at 12 hr. This finding can be ascribed, at least during the time of complete analgesia from the local anesthetic, to respiratory depression associated with the anesthetic technique. After the epidural anesthesia had worn off, the higher $PaCO_2$ values associated with epidural morphine may be explained either by respiratory depression, better analgesia, or both. It is questionable whether the respiratory depression we observed is dangerous, as it is in the range of $PaCO_2$ observed during physiologic sleep (15). However, respiratory depression may become a risk with additional and repeated systemic administration of opiates and sedatives, especially in older patients and when using thoracic epidural narcotics (16). Our study gave no evidence of delayed respiratory depression.

The relationships between morphine dose and analgesia on the one hand and side effects on the other hand suggest that the optimal dose of epidural morphine for surgery of the lower extremities is 3 mg for the following reasons. First, the need for systemic supplementation and the time of its administration were comparable for 3- and 5-mg doses. Also, although 5 mg produced longer duration of analgesia, the intensity of postoperative pain after 12 hr was not significantly different between the 3-mg and the 5-mg dose of epidural morphine. The curves of pain intensity after the different doses of morphine indicate that doses greater than 3 mg do not appreciably improve postoperative analgesia, a ceiling effect perhaps explained by rather complete occupation of the opiate receptors by morphine with 3-mg doses. Second, the side effects, urinary retention with the need for catheterization as well as pruritus, were dose-dependent. The frequency of catheterization decreased from 48 to 32% when the dose was decreased from 5 to 3 mg epidural morphine. Finally, the increased $PaCO_2$ values with 5 mg epidural morphine and the reported dose-dependent respiratory depression after epidural morphine (17) also suggest that a dose reduction to 3 mg may be associated with greater patient safety.

Our recommendation of 3 mg morphine corresponds well with the results of other investigators who compared postoperative analgesia after surgery of the lower extremities after different doses of morphine and who found no differences in analgesia between 2 and 4 mg (2); among 2, 4, and 8 mg (3); or between 3 and 5 mg (4) of epidural morphine. The analgesia produced by epidural morphine is, however, less complete than that associated with epidural local anesthetics. The former does not always offer complete analgesia but almost always markedly reduces postoperative pain. The common experience with epidural opiate analgesia also indicates a marked variability of intensity and duration of analgesia; incomplete analgesia may be encountered even after high doses, which cannot be recommended due to their higher rates of complications.

The dose of 3 mg epidural morphine appears to us an optimal compromise for postoperative analgesia after surgery of the lower extremities. This dose offers

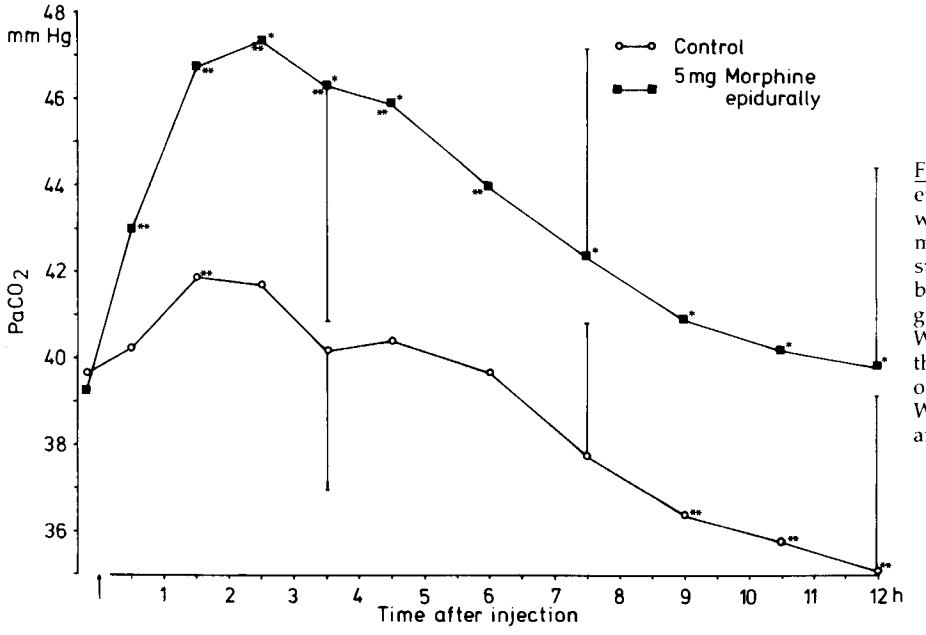

Figure 2. Mean ± SD $PaCO_2$ for 12 hr after epidural anesthesia with bupivacaine, 0.75%, with 0 mg (n = 14) and with 5 mg epidural morphine (n = 13). For clarity only a few standard deviations are presented. Symbols: $^{**}P < 0.05$ comparing the values of a group with its starting values (Mann–Whitney–Wilcoxon test); $^{*}P < 0.05$ comparing the values of the morphine group with those of the control group (Mann–Whitney–Wilcoxon test); ↑, start of epidural anesthesia.

sufficient analgesia; increasing the dose intensifies analgesia slightly and prolongs duration of analgesia but also increases the dose-dependent side effects such as urinary retention, pruritus, and respiratory depression.

References

1. Crawford RD, Batra MS, Fox F. Epidural morphine dose response for postoperative analgesia. Anesthesiology 1981;55:A 150.
2. Gerig HJ, Kern F. Postoperative Analgesie mit Morphium epidural nach Hüftoperationen. Anaesthesist 1982;31:87–9.
3. Martin R, Salbaing J, Blaise G, Tétreault J-P, Tetréault L. Epidural morphine for postoperative pain relief: a dose-response curve. Anesthesiology 1982;56:423–6.
4. Mihic DN, Binkert E, Hess FA, Orucevic J, Turner J. Die peridurale Morphingabe zur Behandlung postoperativer Schmerzen. Regional Anaesthesie 1982;5:42–6.
5. Rosen MA, Hughes SC, Shnider SM, Abboud TK, Norton N, Dailey PA, Curtis JT. Epidural morphine for the relief of postoperative pain after delivery. Anesth Analg 1983;62:666–72.
6. Bromage PR, Camporesi EM, Durant PAC, Nielsen CH. Nonrespiratory side effects of epidural morphine. Anesth Analg 1982;61:490–5.
7. Camporesi EM, Nielsen CH, Bromage PR, Durant PAC. Ventilatory CO_2–sensitivity after intravenous and epidural morphine in volunteers. Anesth Analg 1983;62:633–40.
8. Chambers WA, Sinclair CJ, Scott DB. Extradural morphine for pain after surgery. Br J Anaesth 1981;53:921–5.
9. Jörgensen H. Lumbar epidural anesthesia with bupivacaine 0.75%. A clinical evaluation of 371 cases. Regional-Anaesthesie 1982;5:30–3.
10. Bläss J, Gerber H, Spelina K. Untersuchung über epidurales Morphin. Wirksamkeit—Lösungsmittel—analgetische Supplementation. Anaesthesist 1982;31:340–4.
11. Rifat K. Pentazocine in sequential analgesic anaesthesia. Br J Anaesth 1972;44:175–81.
12. Jones RDM, Jones JG. Intrathecal morphine: naloxone reverses respiratory depression but not analgesia. Br Med J 1980;281:645–6.
13. Huskisson EC. Measurement of pain. Lancet 1974;2:1127–31.
14. Scott J, Huskisson EC. Graphic representation of pain. Pain 1976;2:175–84.
15. Gothe B, Altose MD, Goldman MD, Cherniack NS. Effect of quiet sleep on resting and CO_2-stimulated breathing in humans. J Appl Physiol 1981;50:724–30.
16. Gustafsson LL, Schildt B, Jacobson K. Adverse effects of extradural and intrathecal opiates: report of a nationwide survey in Sweden. Br J Anaesth 1982;54:479–86.
17. Rawal N, Wattwil M. Respiratory depression after epidural morphine—an experimental and clinical study. Anesth Analg 1984;63:8–14.