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Morphine and Hydromorphone Epidural Analgesia

A Prospective, Randomized Comparison

Sandra R. Chaplan, M.D., Steven R. Duncan, M.D.,† Jay B. Brodsky, M.D.,‡ William G. Brose, M.D.§*

Because evidence from uncontrolled, unblinded studies suggested fewer side effects from epidural hydromorphone than from epidural morphine, we employed a randomized, blinded study design to compare the side effects of lumbar epidural morphine and hydromorphone in 55 adult, non-obstetric patients undergoing major surgical procedures. A bolus dose of epidural study drug was given at least 1 h prior to the conclusion of surgery, followed by a continuous infusion of the same drug for two postoperative days. Infusions were titrated to patient comfort. Visual analog scale (VAS) pain scores, VAS sedation scores, and subjective ratings of nausea and pruritus were assessed twice daily. The two treatments provided equivalent analgesia. Sedation scores and prevalence of nausea did not differ significantly between groups. Prevalence of pruritus, however, differed significantly on postoperative day 1, with moderate to severe pruritus reported by 44.4% of patients in the morphine group *versus* 11.5% in the hydromorphone group ($P < .01$). On postoperative day 2, reports of pruritus by patients receiving morphine remained higher than those among the hydromorphone-treated subjects, although this difference was no longer statistically significant (32% *vs.* 16.7%, $P = .18$). We conclude that lumbar epidural morphine and hydromorphone afford comparable analgesia, but the occurrence of moderate to severe pruritus on the first postoperative day is reduced by the use of hydromorphone. (Key words: Analgesics, opioid: hydromorphone; morphine. Anesthetic technique: epidural. Complications: pruritus. Pain: postoperative.)

SIDE EFFECTS ARE common and troublesome accompaniments to epidural opioid analgesia that may limit both patient and physician acceptance of this otherwise useful technique. As many as 90–100% of subjects receiving epidural morphine or fentanyl report itching.[1,2] Other side effects include nausea in approximately 50%, and urinary retention in up to 40% of patients.[1,3] While a subject of great concern, ventilatory depression is a rare event with an occurrence in large series of 0.09–0.9%.[4,5]

Although several opioids are in widespread clinical or investigational use as agents for epidural analgesia, morphine remains the standard of comparison. We have previously reported our favorable (albeit anecdotal) experience with lumbar epidural hydromorphone for postthoracotomy analgesia.[6] Recent literature generally emphasizes the similarity of the two compounds; hydromorphone differs chemically from morphine only by two double bonds and shares the same octanol-pH 7.4 buffer distribution coefficient and kinetics of rostral migration in human CSF as the parent molecule.[7,8] Nonetheless, most reports note that, in comparison to morphine, hydromorphone appears to have both a faster onset and shorter duration of action when used as an epidural analgesic.[9] Our clinical experience suggested that epidural hydromorphone may be associated with fewer bothersome side effects than morphine. Accordingly, we undertook a randomized, double-blinded comparison of hydromorphone *versus* morphine epidural analgesia. This study was designed to examine the incidence of nausea, itching, and sedation associated with the equianalgesic epidural administration of hydromorphone and morphine in the postoperative setting.

Methods

Informed consent was obtained at a preoperative interview from 55 adults scheduled to undergo major thoracic, abdominal, or pelvic surgery, following the guidelines of the Medical Committee for the Use of Human Subjects in Research at Stanford University Medical Center. Exclusion criteria were: pregnancy, routine use of opioids, bleeding dyscrasias, neurologic disorders, age greater than 80, weight in excess of 100 kg or less than 40 kg, evidence of systemic infection, or superficial infection of the lumbar area. Patients requiring postoperative ventilatory support were excluded only if restrictions regarding perioperative opioid were exceeded (below), or if the administration of sedatives to improve patient acceptance of mechanical ventilation was considered necessary.

Catheters were inserted in a lumbar interspace prior to surgery, and epidural placement was confirmed with local anesthetic. Patients underwent general, regional, or combined anesthesia at the discretion of the operating room anesthesia team. The intraoperative administration of prophylactic antiemetics or antipruritics was prohibited. Systemic opioid use was restricted to fentanyl, in a dose not to exceed 3 μg/kg. Drug group assignments were

* Clinical Fellow, Department of Anesthesia, Stanford University School of Medicine, Stanford, California.

† Assistant Professor, Pulmonary and Critical Care Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania.

‡ Professor, Department of Anesthesia, Stanford University School of Medicine, Stanford, California.

§ Assistant Professor, Department of Anesthesia, Stanford University School of Medicine, Stanford, California.

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Address reprint requests to Dr. Chaplan: Department of Anesthesiology, 0818, University of California, San Diego, 9500 Gilman Avenue, La Jolla, California 92093-0818.

made by the hospital pharmacist using a computer-generated random number series. Following assignment, patients received a double-blinded bolus of either morphine sulfate or hydromorphone *via* the epidural catheter, diluted in preservative-free normal saline to a volume of 10 ml, at least 1 h before the conclusion of surgery. Upon arrival in the PACU, a double-blinded epidural infusion of the same opioid was initiated. A ratio of 5:1 (morphine: hydromorphone) was used for the bolus doses, based on previous clinical observations that determined approximate equianalgesic ratios for single epidural doses of the agents (unpublished). A slightly more dilute ratio, 3:1, was chosen for continuous administration by infusion (morphine, 0.15 mg/ml or hydromorphone, 0.05 mg/ml in normal saline) since the duration of clinical effects for morphine exceeds that of hydromorphone.[9] Study solutions were prepared by the hospital pharmacy. The protocol for bolus doses and initial infusion rates is outlined in table 1.

Breakthrough pain was treated by increasing the infusion rate as needed to provide comfort, or, when patients requested immediate relief, with epidural boluses of 50–100 μg fentanyl. Nausea was treated initially with 2.5–5 mg iv nalbuphine. Patients with refractory nausea received 10 mg iv metoclopramide. Pruritus was treated with 2.5–5 mg nalbuphine iv as needed. Bladder catheters were introduced in the operating room and maintained during the study period for most patients. Patients were monitored in ward environments using impedance apnea monitors for the first 24 h (set to alarm at respiratory rates less than 8 breaths/min or apneic pauses ≥ 20 s) pulse oximetry, and nurse observations of respiratory rate at 2-h intervals. Excessive sedation, or respiratory depression (defined as respiratory rate ≤ 8 breaths/min), was treated by decreasing or withholding the infusion, and with intermittent doses of naloxone if necessary.

Epidural catheters were determined to be non-functional if displaced on inspection, or, in cases of unsuccessful pain relief, when segmental bands of hypesthesia did not result from test doses of local anesthetic. Alternative pain medication was then prescribed, and all subsequent data for that patient were discarded.

Data on analgesia and side effects were collected for 2 postoperative days. No data were used from the day of operation so as to allow the effects of the anesthetic to dissipate. Twice daily on service rounds, beginning the morning of postoperative day 1, patients were asked to rate their incisional pain using a 10-cm pen-and-paper visual analog scale (VAS), in which 0 = no pain and 10 = worst pain imaginable. One score was obtained for pain at rest and a second score for pain with activity such as deep breathing or coughing. A self-rating was also solicited for level of sedation using a 10-cm VAS, in which 0 = fast asleep and 10 = wide awake. Patients were asked to rate itching and nausea at each visit and to grade their symptoms as 0 = none, 1 = mild, 2 = moderate, and 3 = severe. Moderate or severe itching was scored as a positive response. Mild or no itching was considered a negative response, since virtually all patients reported minor skin irritation from dressings, nasal oxygen cannulae, pneumatic leggings, and shaving of the incisional area. Medications for side effects, recorded by the nursing staff, were compared. Doses of fentanyl administered for episodes of breakthrough pain were similarly recorded and compared.

Statistical Analysis

Data were analyzed using unpaired two-tailed *t* tests for intergroup comparisons of continuous variables. Chi-square analysis or Fisher exact tests were used for dichotomous variables. Stratified inter- and intragroup comparisons were made using one-way ANOVA tests for continuous variables. Chi-square or Mantel-Haenszel tests for trends were used to evaluate dose responses for ordinal variables. Absolute doses of nalbuphine and fentanyl were compared using the Mann-Whitney ranked sum test.[10] Unless otherwise indicated, results are reported throughout as mean ± SD. Significance was defined as $P < .05$.

Results

The study groups were similar with respect to age, sex, and type of surgical procedure (table 2). Two patients in the morphine group asked to be withdrawn from the study, one on day 1 because of intermittent abdominal wall muscle spasms with poor pain control (prior to data

TABLE 1. Dosage Protocol for Double-blinded Administration of Epidural Morphine or Hydromorphone (Intraoperative Bolus Followed by Postoperative Continuous Infusion)

	Morphine			Hydromorphone		
	Thoracic	Abdominal	Pelvic	Thoracic	Abdominal	Pelvic
Bolus (mg)	7.5	5	4	1.5	1	0.8
Bolus (vol; ml)	10	10	10	10	10	10
Infusion concentration (mg/ml)	0.15	0.15	0.15	0.05	0.05	0.05
Initial rate (ml/h)	6	4	3	6	4	3
Initial rate (mg/h)	0.9	0.6	0.45	0.3	0.2	0.15

TABLE 2. Patient Characteristics

	Morphine	Hydromorphone
N	27	27
Female	6	6
Male	21	21
Age (mean ± SD; yr)	62 ± 14	59 ± 13
Thoracic procedures	5	6
Abdominal procedures	12	13
Pelvic procedures	10	8

collection), and one on day 2 because of severe pruritus (partial data included). One patient in the hydromorphone group was treated with a continuous naloxone infusion throughout the study period, in violation of the protocol. The infusion was initiated in the PACU approximately 3 h 45 min after administration of the study drug bolus, when brief apneic episodes were noted. This patient was withdrawn from analysis for all purposes save respiratory depression, since the continuous administration of an opioid antagonist was considered likely to have biased data regarding analgesia and side effects. Partial data were analyzed for four morphine group and five hydromorphone group patients whose catheters were withdrawn prematurely in response to the development of fever or otherwise became non-functional during the study period. Data were analyzed for a total of 54 of the original 55 patients, 27 of whom received morphine and 27, hydromorphone.

Neither scores for pain at rest nor scores for pain with movement differed statistically between the two groups at any time (figs. 1 and 2). Intragroup pain scores stratified for level of surgical procedure were no different in either drug group. Stratified comparison of the morphine and hydromorphone groups showed no differences among patients undergoing similarly categorized surgical procedures, except on the morning of the first postoperative day, when thoracotomy patients receiving morphine reported significantly more pain with cough or movement (mean 6.0 ± 1.7) than patients receiving hydromorphone (mean 2.6 ± 1.9; $P < .02$).

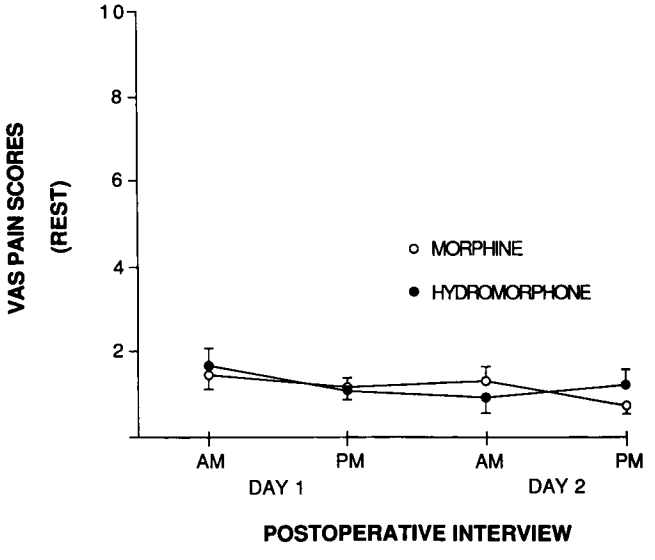

FIG. 1. Visual analog pain scores (mean ± SE) for morphine and hydromorphone groups at rest: 0 = no pain; 10 = worst pain imaginable.

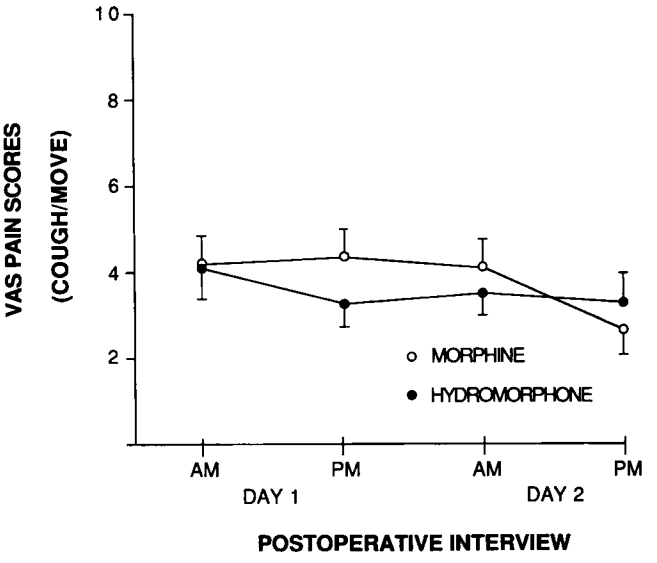

FIG. 2. Visual analog pain scores (mean ± SE) for morphine and hydromorphone groups with coughing or movement: 0 = no pain; 10 = worst pain imaginable.

Twenty-one of 27 (77.8%) patients in the morphine-treated group on day 1 and 20 of 26 (76.9%) on day 2 received no fentanyl for breakthrough pain. Similarly, 17 of 26 (65.4%) hydromorphone-treated patients on day 1 and 18 of 24 (75%) on day 2 did not require supplemental fentanyl. Mean fentanyl doses on day 1 were 14 ± 31 μg (morphine group) and 54 ± 108 μg (hydromorphone group; NS), and on day 2, 23 ± 55 μg and 53 ± 112 μg, respectively (NS). The occurrence of breakthrough pain requiring medication was not associated with anatomic region of operation (data not shown).

No difference in mean VAS sedation scores between the two groups was observed at any determination (fig. 3). Likewise, intragroup comparisons revealed no significant variations (data not shown).

During the two days of observation, nausea was reported by 12 of 27 (44.4%) patients receiving morphine, and 13 of 26 (50%) receiving hydromorphone (NS). Small absolute differences between the groups in reports of moderate to severe nausea likewise did not reach statistical significance (morphine 6 of 27 or 22.2%, hydromorphone 10 of 26 or 38.5%, $P = .32$). Similarly, no relationship between operative region and occurrence of nausea was evident (data not shown).

On postoperative day 1, 12 of 27 (44.4%) of the morphine group reported moderate or severe itching, compared to 3 of 26 (11.5%) of the hydromorphone group ($P < .01$; fig. 4). The disparity between groups continued the second postoperative day, with 8 of 25 (32%) of the morphine group reporting moderate to severe itching *versus* 4 of 24 (16.7%) of the hydromorphone group, although this difference was no longer statistically significant. The mean nalbuphine dose in the morphine group was 3.2 ± 5.4 mg on day 1 (10 of 27 patients treated or 37%) and 1.6 ± 3.8 mg on day 2 (6 of 26 or 23%) *versus* 2.1 ± 5.1 mg on day 1 (7 of 26 or 26.9%) and 1.1 ± 2.7 mg on day 2 (6 of 24 or 25%) in the hydromorphone group (NS). When the two treatment arms were internally stratified, no relationship to the three anatomic operative regions was discernible for either itching or dosage of nalbuphine.

Four patients in the morphine group were treated with naloxone (1–3 intermittent doses) for respiratory rates less than 8 breaths/min. Times elapsed between administration of the study bolus and detection of slowed respiratory rates meeting treatment criteria were: 14 hr 15 min, 10 hr 45 min, 6 hr 40 min, and 4 hr 30 min. As mentioned earlier, one patient in the hydromorphone group was treated for brief apneic pauses 3 hr 45 min after receiving the study bolus. Differences in rates of these respiratory events (4 of 27 [14.8%] *vs.* 1 of 27 [3.7%], morphine and hydromorphone groups, respectively) did not achieve significance.

Discussion

These data show that moderate to severe pruritus associated with epidural opioid analgesia is significantly less

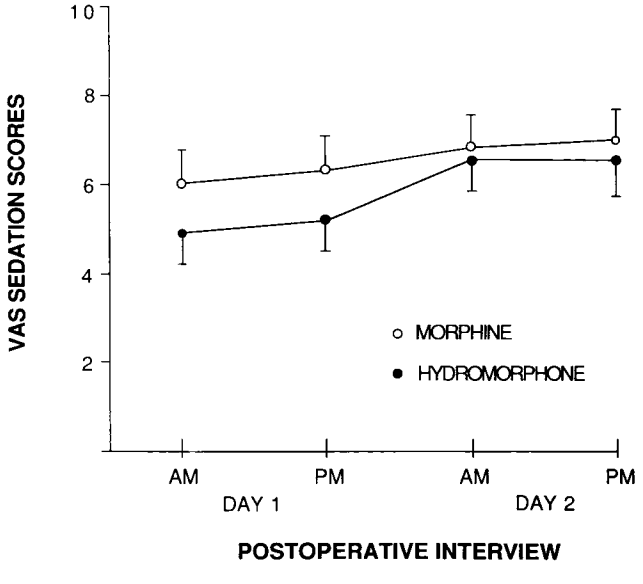

FIG. 3. Visual analog sedation scores (mean ± SE) for morphine and hydromorphone groups: 0 = fast asleep; 10 = wide awake.

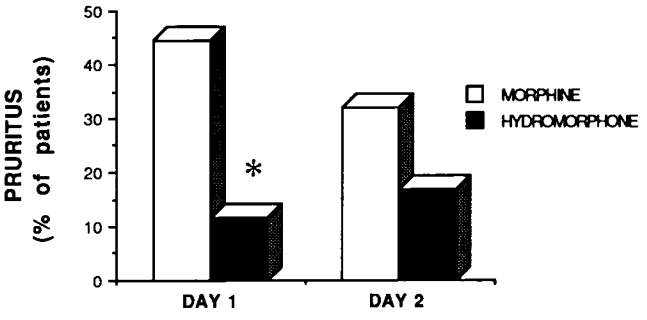

FIG. 4. Percent of patients in morphine and hydromorphone groups reporting moderate or severe pruritus on postoperative days 1 and 2. *$P < .01$.

prevalent in hydromorphone-treated patients than among those receiving morphine. Four times as many patients treated with morphine experienced itching of moderate or greater severity on postoperative day 1, compared to the hydromorphone group. At the same time, the hydromorphone and morphine treatment regimes were demonstrated to be equally analgesic. Moreover, there were no appreciable differences among the treatments of other measured side effects (*i.e.*, sedation and nausea).

The observed difference between the two structurally similar agents cannot be explained at this time, since the pathogenesis of spinal opioid-induced pruritus has not yet been elucidated.[11] Systemic administration of morphine is widely known to be accompanied by more pruritus than comparable therapy with hydromorphone, a likely result of much greater histamine release by the former. Histamine release is probably not the mechanism of spinal opioid-associated pruritus, however, since itching frequently follows spinal administration of agents that do not release histamine and, in any event, these symptoms are refractory to treatment with antihistamines.[3]

Although still largely inferential, several lines of evidence suggest that the pruritus that complicates epidural or subarachnoid analgesia may be an excitatory phenomenon mediated by central opioid receptors. In particular, the presence of epidural opioid-associated pruritus is much better correlated with CSF rather than plasma concentrations of the responsible agent, itching is usually promptly ameliorated by treatment with opioid antagonists, and this side effect tends to be associated with use of selective *mu* receptor agonists.[12–14] The ability of low doses of *mu* agonists to (paradoxically) cause CNS excitation has been demonstrated recently by measurement of naloxone-reversible prolongation of action potentials generated by dorsal root ganglion cells in culture.[15] Whether central excitation explains the development of pruritus, however, remains only speculative at this time.

Our protocol was designed to determine whether there was a marked difference in side effect profiles between morphine and hydromorphone. The study design enabled detection of a significant difference in pruritus associated

with these agents, but nonetheless, certain shortcomings of the experimental protocol are notable. In particular, the absence of stringent criteria for treatment of pruritus, although a practical necessity given the circumstances at our institution (as well as a consideration for patient care), hindered comparative assessments of the number and amount of nalbuphine dosages in the two treatment groups. For instance, the presence of mild pruritus (if verbalized) was a criterion for nursing staff to administer antipruritics using a range of doses. The interval treatment of pruritus, in turn, likely biased subsequent detection of the side effect, which may (along with the possible development of tolerance) account for the decreased prevalence of this complication on postoperative day 2. Similar limitations apply to the assessment of treatments for sedation and nausea, as well as confounding overall analyses of correlations between side effects and dosages. The relatively limited number of subjects here was also likely to hinder meaningful analyses of dose-related effects.

The proportion of patients exhibiting decreased respiratory rates was surprisingly high in our study and considerably exceeded, at least in the morphine group, the incidences described in the Scandinavian surveys[4,5] and recently by Ready *et al.*[16] In contrast to these previous reports, we used larger initial doses of epidural opioid, and our more intensive monitoring protocol could possibly have resulted in increased sensitivity. We did not design our study to rigorously analyze untoward respiratory events, since we assumed *a priori* that the available number of study subjects would be far too small to yield valid comparisons.

In summary, our study found that hydromorphone compared favorably to morphine for continuous infusion epidural analgesia. Equianalgesic effects were readily obtained among surgical patients after various major pelvic, abdominal, and thoracic procedures. No differences were apparent between treatment groups in terms of the number of patients experiencing sedation or nausea as a complication of therapy. The prevalence of pruritus among patients receiving hydromorphone, however, was less than that reported by morphine-treated subjects on the first postoperative day. While this disparity appears meaningful, the explanation for the observation awaits a better understanding of opioid actions at the receptor level. On the basis of this comparison, hydromorphone appears to present a reasonable and, in some respects, clinically advantageous alternative to morphine for epidural opioid analgesia.

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