

Epidural Bupivacaine/Sufentanil Therapy for Postoperative Pain Control in Patients Tolerant to Opioid and Unresponsive to Epidural Bupivacaine/Morphine

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Background: Opioids are thought to have equal analgesic effects when equivalent doses are used. However, sufentanil may achieve maximum effect while occupying fewer spinal opioid receptors (higher intrinsic efficacy). Therefore, sufentanil may be more effective than morphine when administered intraspinally in opioid-tolerant patients.

Methods: This study evaluated 20 chronic cancer pain patients who underwent abdominal surgery for tumor resection. All patients used large doses of morphine ($> 250 \text{ mg/day}^{-1}$) preoperatively for 3 months or longer. Intraoperatively, patients received combined general-epidural anesthesia with 0.5% bupivacaine and 0.02% morphine at 8 ml/h^{-1} . Postoperative continuous epidural analgesia with 0.1% bupivacaine and 0.02% morphine at 5 ml/h^{-1} plus intravenous patient-controlled analgesia morphine (3 mg every 6 min) was given. Epidural infusions were increased every 30 min by 1 ml/h^{-1} to achieve a dynamic (during coughing) visual analog pain score (VAPS) of less than 5/10. If the desired VAPS was not achieved after 6 h or the epidural morphine infusion was increased to 2 mg/h^{-1} , 50 μg of sufentanil in 10 ml of normal saline was given as an epidural bolus dose. The epidural infusion then was switched to 0.0002% sufentanil ($2 \mu\text{g/ml}^{-1}$) and 0.1% bupivacaine (1 mg/ml^{-1}) at 7 ml/h^{-1} . Further titration to maintain a dynamic VAPS of less than 5/10 occurred every 4 h.

Results: Mean preoperative daily oral morphine use was $380 \pm 97 \text{ mg}$ (range 290–490) for 4 ± 1 months. Before the switch to sufentanil, patients had received a mean maximum morphine dose of $8.8 \pm 0.2 \text{ mg}$ intraoperatively plus $9.0 \pm 1.2 \text{ mg}$ during $4.2 \pm 0.3 \text{ h}$ postoperatively ($1.8 \pm 0.4 \text{ mg/h}^{-1}$), at which

point VAPS ranged between 7–10/10. All patients experienced adequate analgesia within 1 h of starting sufentanil therapy. The mean sufentanil dose during the first 4 h of treatment was $17 \pm 0.2 \mu\text{g/h}^{-1}$. At this time, VAPS ranged from 0–3/10. Satisfactory analgesia was achieved with sufentanil at a lower than a calculated equally potent dose of morphine ($23 \mu\text{g/h}^{-1}$ vs. $17 \mu\text{g/h}^{-1}$, $P < 0.01$). Intravenous patient-controlled analgesia morphine requirements were also lower (7.8 mg/h^{-1} vs. 2.0 mg/h^{-1} , $P < 0.01$). Length of morphine and sufentanil therapies were $5 \pm 3 \text{ h}$ and 10 ± 2 days, respectively. No patient experienced signs or symptoms of opioid withdrawal.

Conclusions: These results suggest that sufentanil can be used successfully in opioid-tolerant patients who do not experience adequate pain control in the early postoperative period despite a large dose of epidural morphine. Moreover, sufentanil should be considered an effective alternative therapy for postoperative pain control in chronic opioid users using high doses of oral opioids before surgical intervention. (Key words: Analgesics, epidural: morphine; sufentanil. Analgesics, opioid: withdrawal. Anesthetic techniques: epidural. Pain: postoperative.)

CANCER patients with chronic pain usually require large doses of opioids due to disease progression, tolerance, or a combination of both. Tolerance usually develops within 1 to 2 weeks after therapy has been started.^{1,2} Patients using high doses of opioids may require surgery. Therefore, postoperative pain control and physiologic withdrawal may be a problem. We have suggested that chronic pain patients treated for postoperative pain exhibit cross-tolerance between systemic and epidural morphine.³ This cross-tolerance results in higher morphine–bupivacaine requirements than those of opioid-naïve patients to obtain the same degree of pain control.³ However, some chronic opioid users who receive large doses of opioids preoperatively will not experience adequate postoperative pain control despite large doses of epidural bupivacaine–morphine.

Sufentanil appears to have a greater antinociceptive effect than does morphine in both opioid-tolerant

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animals⁴ and humans.⁵ Therefore, we conducted a study to evaluate the efficacy of epidural sufentanil–bupivacaine infusions in chronic cancer patients taking large doses of oral opioids who did not experience adequate postoperative pain control despite receiving large doses of epidural morphine–bupivacaine both intraoperatively and during the early postoperative period. The hypothesis is that patients with opioid tolerance obtain adequate pain control with epidural sufentanil when an equivalent dose of epidural morphine fails to provide adequate analgesia.

Methods

After gaining the approval by our Committee on Human Research and obtaining patient consent, we studied 20 cancer patients requiring postoperative pain control.

To be included in the study, the patients had to: (1) be a cancer patient scheduled for abdominal surgery and using a large dose of oral morphine sulfate (> 250 mg/day⁻¹), (2) have satisfactory control of chronic pain (visual analog pain score (VAPS) $< 4/10$, where 0 = no pain and 10 = excruciating pain), (3) have had no changes in opioid intake during the 2 weeks before surgery, and (4) have a VAPS $> 5/10$ despite epidural morphine infusions of ≥ 1.5 mg/h⁻¹ for at least 4 h.

Exclusion criteria were: (1) refusal to permit epidural catheter insertion, (2) coagulopathy, (3) existing neurologic deficit, (4) preoperative therapy with < 250 mg oral morphine per day or the use of opioid treatment for less than 3 months regardless of the dose, (5) changes in the dose of opioids in the 2 weeks before surgery, (6) pain intensity $> 4/10$ in the VAPS, and (7) antihypertensive therapy with clonidine or captopril.

After routine monitors were placed in the operating room, the patient was placed in the right lateral decubitus position and given an epidural catheter through which midazolam (1–2 mg) and sufentanil (5–10 μ g) were administered intravenously (IV) for sedation. For upper abdominal procedures, catheters were introduced in the T7–T8 or T8–T9 interspace via a paramedian approach. For lower abdominal procedures, catheters were inserted in the T9–T10 or T10–T11 interspace. All catheters were tested for intravascular or subarachnoid placement with 3 ml 1.5% lidocaine plus epinephrine (5 μ g/ml⁻¹). General anesthesia was induced with thiopental (2–3 mg/kg⁻¹), and sufentanil (0.5–1 μ g/kg⁻¹ IV). After the administration of a prim-

ing dose of 0.001 mg/kg⁻¹, vecuronium (0.1 mg/kg⁻¹ IV) was used to facilitate tracheal intubation. Bupivacaine 0.5% was then injected through the epidural catheter in 5 ml increments to a maximum of 10–15 ml, depending on the number of dermatomes that needed to be anesthetized. Immediately after the administration of the first bolus dose of bupivacaine, a continuous infusion of 0.5% bupivacaine and 0.026% morphine (8 mg in 30 ml) was started at 8 ml/h⁻¹ and titrated according to hemodynamic stability.

After surgery, patients were transferred to the post-anesthesia care unit or the surgical intensive care unit where an epidural infusion of 0.1% bupivacaine and 0.02% morphine was started at 5 ml/h⁻¹, and IV patient-controlled analgesia (PCA) morphine (3 mg every 6 min) was provided within 20 min of arrival. If patients complained of pain within the first 4 h of therapy, a test dose of 0.25% bupivacaine (10 ml in 5 ml aliquots) was administered to determine proper position of the catheter. If testing by the pin-prick technique indicated that no sensory block had developed, the catheter was removed and the patient was withdrawn from the study. Conversely, if pain relief was achieved, the infusion rate was increased by 1 ml/h⁻¹ every 30 min until the pain intensity in the VAPS was $\leq 4/10$. If a VAPS of $\leq 4/10$ was not achieved after 6 h or the epidural morphine infusion was ≥ 2 mg/h⁻¹, sufentanil (50 μ g in 10 ml of normal saline solution) was administered as an epidural bolus, and the epidural infusion was switched to 0.0002% sufentanil (2 μ g/ml⁻¹) and 0.1% bupivacaine was infused at 7 ml/h⁻¹. Further titrations to maintain a VAPS of $\leq 4/10$ were performed every 30 min during the first 6 h of treatment and every 2 h thereafter by increasing the infusion rate by 1 ml/h⁻¹. No further epidural bolus of sufentanil was administered.

All patients were evaluated with the VAPS scale by the Acute Pain Service every 6 h for pain. Signs of withdrawal (opioid craving, anxiety, yawning, perspiration, lacrimation, rhinorrhea, insomnia, mydriasis, piloerection, tremors, hot and cold flashes, hypertension, tachycardia, hyperpyrexia, tachypnea, vomiting and diarrhea),⁶ signs of subcutaneous catheter migration (increased use of IV PCA morphine associated with no sensory block after a test dose of 0.25% bupivacaine with 5 μ g/ml⁻¹ epinephrine), subdural or subarachnoid catheter migration (sudden and rapid progression of the sensory block with increasing somnolence), and overdosing were assessed. The catheter insertion site was evaluated every 24 h for signs of infection. In ad-

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dition, ward nurses evaluated patients every 2 h for quality of pain control and side effects, so that infusion rates could be adjusted.

Dynamic pain scores (intensity of pain when patient moved) were kept below 4/10 by titrating infusions of 1 ml/h⁻¹. If no pain control was achieved (VAPS > 4/10) after 2 consecutive hours and the use of IV PCA morphine was 18 mg or more during that period, the position of the catheter was reassessed as described above. If no sensory block developed, patients were given IV PCA dihydromorphine therapy and withdrawn from the study. Conversely, if sensory block developed, the infusion rate was increased by 1 ml/h⁻¹. When dynamic pain scores remained less than 4/10 and IV PCA morphine use was less than 12 mg during a 6 h period (while awake), the infusion rate was decreased by 1 ml/h⁻¹. Epidural catheters were removed when the infusion rate was 2 ml/h⁻¹ and the dynamic VAPS was < 4/10 during a 6 h period.

Data recorded for analysis included the amount of epidural morphine that patients received both intraoperatively and postoperatively before the switch to sufentanil was made (T₁), the total time of postoperative epidural morphine infusion, and the mean infusion dose of sufentanil 4 h after the switch (T₂). A two-sided *t* test was used to compare the mean effective dose of sufentanil (T₂) with the dose of morphine that patients were receiving before the change (T₁). For this comparison, the dose of morphine was converted to sufentanil equivalents based on a 80:1 ratio.^{4,7,8} Therefore, the null hypothesis was that T₂ ≥ T₁ for a patient, *i.e.*, if a given amount of epidural morphine did not achieve pain control, then, based on the assumption that morphine and sufentanil are equally analgesic, the equivalent amount of sufentanil also should be insufficient for pain control. The null hypothesis therefore was rejected at the *P* < 0.05 level.

Results

Twenty patients, aged 31 ± 6 yr, undergoing major abdominal procedures for cancer were enrolled in the study during an 18-month period. Twelve patients were male and eight were female. Preoperative mean oral morphine usage was 380 ± 97 mg/day⁻¹ (range 290–490) for 4 ± 1 months.

As seen in table 1, the mean intraoperative use of morphine was 8.8 ± 0.2 mg during 4.2 ± 0.3 h. Before the switch to sufentanil (T₁), patients were receiving 1.8 ± 0.4 mg/h⁻¹ (1800 ± 432 μg/h⁻¹) of epidural

morphine (23 ± 5 equianalgesic μg/h⁻¹ of sufentanil), at which point pain intensity, as judged by VAPS, ranged between 7/10 and 10/10. The length of epidural morphine–bupivacaine therapy was 5 ± 2 h. Therefore, patients received a total of approximately 17 mg of epidural morphine during 9 h of intra- and postoperative therapy before the switch to sufentanil–bupivacaine therapy was made. Moreover, during this period of time, patients self-administered 39 ± 9 mg of morphine via IV PCA.

During the first 4 h of therapy with sufentanil (T₂), patients received 17.0 ± 0.2 μg/h⁻¹ (*P* < 0.01, T₂ vs. T₁) and used only 8 ± 3 mg of morphine via PCA, while recorded VAPS ranged from 0/10 to 3/10. Thus, all patients experienced adequate pain control within first 4 h of sufentanil–bupivacaine therapy. The length of epidural bupivacaine–sufentanil therapy was 10 ± 2 days. The daily doses of sufentanil and IV PCA morphine during the first 6 postoperative days decreased from 268 ± 34 μg/day⁻¹ to 187 ± 48 μg/day⁻¹ and 92 ± 7 mg/day⁻¹ to 5 ± 3 mg/day⁻¹, respectively (table 2).

No patient experienced signs or symptoms of opioid withdrawal.

Discussion

Cross-tolerance after opioid administration by different routes may limit the effectiveness of postoperative epidural morphine unless three to four times the usual doses are used.^{3,4,9,10} Current evidence suggests that tolerance occurs as a result of progressive loss of receptor site action due to prolonged agonist exposure. Desensitization or uncoupling of the receptor from the guanosine triphosphate-binding subunit decreases agonist binding affinity.^{11–15} Loss of receptors from the cell surface also may result in fewer binding sites and decreased action.^{11–15} Thus, the desensitization to agonist binding and the loss in the number of opioid receptors results in higher dose requirements. Cross-tolerance at the spinal level is characterized as being both time- and dose-dependent^{16,17}, as well as specific to the receptor complex.^{17,18}

Traditionally, opioid agonists such as morphine, fentanyl, and sufentanil were believed to have equal maximum analgesic effect when equivalent doses were used.¹⁹ However, it is possible that maximum drug effect can be achieved by these opioids while they occupy different proportions of the available receptor subtypes.²⁰ This difference is a reflection of the agonist's efficacy: Agents that require low receptor occupancy

Table 1. Summary of Perioperative Data (n = 20)

	T1 (Amount of Epidural M ₅₀ , Given until Conversion)	T2 (First 4 h of Epidural Sufentanil Therapy)
Intraoperative use (mg)	8.8 ± 0.2	—
Duration of surgery (h)	4.2 ± 0.3	—
Duration of postoperative epidural morphine use (h)	5.0 ± 2.0	—
Rate of epidural opioid use (mg/h)	1.8 ± 0.6	0.017 ± 0.0002 (17 ± 0.2 µg/h)
Total intravenous morphine patient-controlled analgesia use (mg)	39 ± 9	8 ± 3
VAPS	7–10	0–3
Duration of epidural sufentanil therapy (days)	—	10 ± 2

(e.g., sufentanil) are defined as having high effectiveness. A study using noncompetitive antagonists (b-funaltrexamine) has demonstrated that sufentanil is more effective than morphine in terms of relative efficacy.²¹ At the highest concentration of b-funaltrexamine, sufficient receptors were blocked and morphine was converted into a partial agonist. Conversely, sufentanil remained a full agonist and retained full intrinsic activity.

In an experimental model in which animals were made tolerant to different opioid agonists with chronic opioid infusions, a marked right shift in the dose–response curve for morphine was found (greater than 100-fold). In contrast, the infusion of sufentanil resulted in a significantly smaller shift (less than tenfold).²² This observation implies that two agents that act at the same receptor may show an asymmetric cross-tolerance.²³

In humans, the tolerance and cross-tolerance phenomenon remains controversial. Patients receiving intrathecal morphine have shown less than a threefold increase in the dose required to achieve pain control during a 3-month period.^{24,25} Conversely, patients with well controlled cancer pain using oral opioid therapy who underwent surgery and complete tumor removal (source of pain) demonstrated cross-tolerance when treated with epidural morphine for postoperative pain control.^{3,5}

In this study, patients with well controlled chronic cancer pain receiving 380 ± 97 mg/day⁻¹ of oral mor-

phine before admission to the hospital experienced severe postoperative pain (VAPS 7–10/10) despite large doses of epidural morphine administered both intraoperatively (8.8 ± 0.2 mg during 4.2 ± 0.3 h) and postoperatively (9.0 ± 1.2 mg during 5 ± 2 h), along with bupivacaine (0.5% intraoperatively and 0.1% postoperatively). Therefore, in this group of patients, the administration of approximately 17 mg epidural morphine during approximately 9 h (or 1.88 mg/h⁻¹) plus the use of 39 ± 9 mg of IV morphine during a 5 ± 2 h period failed to produce even moderate analgesia. These doses of morphine are 3–4 times the perioperative doses required by opioid-naïve cancer patients to experience adequate pain control within the first 6 h of treatment.^{3,26} Moreover, in a previous study, we demonstrated that chronic opioid users receiving 180 ± 99 mg/day⁻¹ of oral morphine (less than half the dose that patients received in this study) could experience adequate pain control when epidural morphine was administered at 1 mg/h⁻¹ in combination with 0.1% bupivacaine.³

This study was designed to switch from epidural morphine–bupivacaine therapy to sufentanil–bupivacaine therapy when patients reported dynamic VAPS > 5/10 after 4–6 h of therapy, and/or epidural doses of morphine exceeded 2 mg/h⁻¹ for four reasons. First, we have demonstrated that patients who used moderate amounts of morphine preoperatively experienced adequate pain control with epidural bupivacaine–mor-

Table 2. Epidural Sufentanil and Morphine Intravenous Patient-controlled Analgesia Use

Postoperative Day	0	1	2	3	4	5
Sufentanil (µg)	268 ± 34	346 ± 24	319 ± 31	264 ± 30	240 ± 37	187 ± 48
Intravenous morphine patient-controlled analgesia	92 ± 7*	18 ± 13	10 ± 6	9 ± 5	6 ± 3	5 ± 3

Data are mean ± SD.
* Includes 39 ± 9 mg self-administered during 5 ± 2 h of morphine epidural therapy.

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phine at doses of 1 mg/h^{-1} . Second, spinal cross-tolerance is directly proportional to both the average agonist concentration at the receptor site and the time of exposure^{16,27,28}; therefore, the degree of cross-tolerance between the two routes of administration experienced by chronic opioid users depends on the previous treatment dose, the length of therapy, and the amount of agonist presented to the receptor by the new route of administration. Third, animal data show that at large doses, morphine can produce localized spinal convulsions, hyperalgesia,²⁹ and allodynia,³⁰ all of which are unresponsive to naloxone reversal. Moreover, hyperalgesia also has been described in a human being given intraspinal doses of morphine (47 mg/day^{-1}) after receiving a bolus dose of 4 mg of morphine.³¹ Fourth, we felt that it would be unethical to allow patients to experience pain for more than 4–6 h while epidural morphine–bupivacaine infusions were titrated to achieve pain control.

The use of epidural sufentanil resulted in complete pain control within 1 h of treatment despite statistically significant lower equivalent analgesic doses of morphine that were associated with poor pain control, suggesting that the phenomenon of higher intrinsic activity seen in animals also may be important in humans.

There are three alternative hypotheses to explain this observation. First, drug kinetics are responsible for the difference in responses seen between morphine and sufentanil. Because patients were receiving large doses of oral morphine, one could hypothesize that changes in the blood–brain barrier, peripheral metabolism, and drug distribution could be responsible for the asymmetric response seen between the two agents. However, there is no evidence that central metabolism or changes in the blood–brain barrier play a significant role in altering morphine's efficacy.^{32,33} Likewise, a change in drug distribution does not appear to be a significant factor, as other agents, such as local anesthetics and α_2 agonists, remain effective.³³ Second, because patients received large doses of epidural morphine before the switch to sufentanil, it is possible that the long half-life of morphine contributed synergistically to the analgesic effects seen with sufentanil. However, during the course of sufentanil therapy, a steady decrease in the requirements was seen from day 0 to day 5 (table 2). This observation suggests that the delayed effects of morphine were not clinically important. Third, the magnitude of interaction between sufentanil and bupivacaine is unknown. Although morphine interacts synergistically with both bupivacaine^{34,35} and lido-

caine,^{36,37} the degree or even presence of synergy can be affected greatly by the dose ratio of each component used in the combination. Therefore, sufentanil's greater potency, when compared to morphine, may be due to more pronounced interaction with bupivacaine at the particular doses used. Because there are no data evaluating interactions between sufentanil and bupivacaine, we can only speculate on the existence of a synergistic effect based on the results observed, but comments regarding the magnitude of this possible synergism cannot be made.

Sufentanil's higher intrinsic efficacy appears to be related to its ability to exert an analgesic effect at a lower fractional receptor occupancy than morphine, as tolerance causes the population of total opioid receptors to decline. For example, rats that received either intrathecal sufentanil or morphine infusions at equianalgesic doses demonstrated that sufentanil was nine times more potent as an antinociceptive drug than morphine on the first day of infusion and 44 times more potent on the seventh day of the study.⁴ Therefore, the sufentanil–morphine potency ratio appears to widen as tolerance develops, making sufentanil a more effective opioid analgesic in the presence of tolerance.

Reports of myoclonic movements and the risk of neurotoxicity associated with large doses of intrathecal sufentanil raise concerns about its epidural administration.³⁸ However, doses as high as $600\text{--}800 \text{ }\mu\text{g/day}^{-1}$ were administered epidurally to humans for several weeks to control cancer pain. Boersma *et al.* demonstrated that despite the presence of very high concentrations of sufentanil in the white and gray matter of the spinal cord around the site of the catheter tip, no evidence of histopathologic changes was noted.³⁹ Because drug toxicity expressed as behavioral changes can occur in the absence of histopathologic changes,⁴⁰ close neurologic evaluation of patients for these changes is paramount.

Finally, a cost analysis between epidural sufentanil and epidural morphine is appropriate. The cost of 1 mg of preservative-free morphine at our hospital is \$1.05. The cost of $1 \text{ }\mu\text{g}$ of sufentanil is \$0.15. Therefore, patients who receive 2 mg/h^{-1} of morphine or $14 \text{ }\mu\text{g/h}^{-1}$ of sufentanil will incur similar expenses. However, the cost of providing adequate analgesia was less when sufentanil was used in these patients. First, patients did not experience pain control at a morphine infusion rate of 2 mg/h^{-1} ; therefore, larger doses of morphine would have been needed to provide adequate analgesia. Conversely, adequate pain control was pro-

vided with sufentanil infusion rates of $14 \mu\text{g}/\text{h}^{-1}$. Second, patients used high doses of IV PCA morphine ($39 \pm 9 \text{ mg}$) while receiving epidural morphine. This cost must be added to the cost of epidural morphine therapy. Conversely, IV PCA morphine use significantly decreased ($8 \pm 3 \text{ mg}$) during the first 4 h after epidural sufentanil therapy was instituted.

In conclusion, epidural bupivacaine-sufentanil therapy can be used successfully in the concentrations described in this study in opioid-tolerant patients who are receiving high doses of oral morphine before surgery and are unresponsive to epidural morphine. However, to demonstrate fully the greater relative potency of sufentanil compared to that morphine in chronic opioid users who have developed tolerance, a study evaluating sufentanil use in opioid-naïve *versus* tolerant patients is needed.

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