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Epidural Sufentanil for Acute Pain Control in a Patient with Extreme Opioid Dependency

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Chronic use of a high dose of opioids may predispose patients undergoing surgery to develop withdrawal postoperatively.[1] This syndrome may occur if their daily drug requirement is abruptly decreased either because their usage pattern is not reported to the treating physicians or because epidural or intrathecal opioids are used for postoperative pain control.[1,2] In both cases, the amount of drug reaching the central nervous system may not be sufficient to prevent the clinical appearance of the syndrome.

Traditionally, opioid agonists such as morphine, methadone, fentanyl, and sufentanil were believed to have equal maximum analgesic effect when equivalent doses were used.[3] However, maximum drug effect may be achieved by these opioids while they occupy different proportions of the available receptor subtypes.[4] This difference is a reflection of the agonist's efficacy: agents requiring low receptor occupancy are defined as having high efficacy. Studies using noncompetitive antagonists have demonstrated that sufentanil is superior to morphine in terms of relative efficacy.[5] An indication of a drug's efficacy is seen when down-regulation or inactivation of a receptor produces less of a right shift in the dose–response curve for an agent with high efficacy as compared to one with lower efficacy. This observation implies that two agents that act at the same receptor may show an asymmetric cross tolerance.[6]

This phenomenon was recently demonstrated in rats by Sosnowski and Yaksh,[7] and we observed it clinically in the following reported case.

CASE REPORT

A 43-yr-old, 160-cm, 64-kg woman was admitted in February, 1991 with a diagnosis of adenocarcinoma arising in an enterovaginal fistula with no other primary or distant sites identified. She also had a history of Crohn's disease diagnosed in 1964 that resulted in multiple hospitalizations for small bowel obstructions. She underwent a proctocolectomy and Brook ileostomy in 1970.

On admission she was receiving oral metronidazole and methadone, allegedly 10 mg twice per day. She received general anesthesia for an exploratory laparotomy and *en bloc* small bowel resection including the posterior wall of the vagina, perineal fistulous tract, and portion of the sacrum. Twenty-four hours postoperatively, she developed agitation, tachycardia, hypertension, fine finger tremor, salivation, rhinorrhea, and lacrimation. The diagnosis of acute opioid withdrawal syndrome was confirmed after her fiancé revealed that she had been taking up to 100 10-mg tablets (1,000 mg) of methadone per day. She was treated with morphine 300 mg intravenously over 70 min until the agitation stopped, and a continuous intravenous morphine infusion at 110 $mg \cdot h^{-1}$ was then started. The morphine infusion was then decreased at a rate of 5–10 $mg \cdot day^{-1}$. Ten days later, methadone 25 mg orally was given every 6 h along with intravenous morphine maintained at 30 $mg \cdot h^{-1}$ (at doses of 25 $mg \cdot h^{-1}$ she developed overt signs of withdrawal).

Thirteen days after the withdrawal episode she was returned to the operating room for sacral resection and wide excision of the fistula. A combined thoracic (T8–T9) epidural-general anesthetic was administered using thiopental 250 mg, sufentanil 30 μg, vecuronium 8 mg, and midazolam 2 mg for induction. Anesthesia was maintained with 40% O_2 and N_2O, isoflurane 0.8–1%, and a continuous intravenous infusion of morphine at 30 $mg \cdot h^{-1}$. Bupivacaine (0.5%) was continuously infused through the epidural catheter at 6–8 $ml \cdot h^{-1}$ after a bolus dose of 5 ml. The patient remained hemodynamically stable, and upon skin closure preservative-free morphine 10 mg and fentanyl 100 μg in a total volume of 12 ml were administered in the epidural space.

Upon arrival into the postanesthesia care unit (PACU), a continuous epidural infusion of 0.1% bupivacaine and 0.03% preservative-free morphine was started at 5 $ml \cdot h^{-1}$. The trachea was extubated within 15 min of her arrival to PACU, and she reported a visual analog pain score (VAPS) of 4/10. The intravenous morphine infusion was maintained at 30 $mg \cdot h^{-1}$. Thirty minutes later the patient became agitated and complained of excruciating pain in the operative site (VAPS = 10/10) with no other signs of withdrawal. A total of 50 μg sufentanil was administered epidurally, and the infusion rate of morphine–bupivacaine was increased to 10 $ml \cdot h^{-1}$. Within 10 min she reported a VAPS of 3/10 and was cooperative and calm. Two hours after her arrival to the PACU, she was discharged to the general wards in stable condition, pain-free, and cooperative. The intravenous morphine infusion was discontinued in favor of intravenous patient-controlled analgesia (PCA) with morphine at 2 mg every 6 min, with a maximum hourly dose of 20 mg. A pulse oximeter was provided to detect oxyhemoglobin saturation less than 90%.

Two hours after sufentanil had been administered in PACU, she reported pain (8/10) and became restless. She attempted to self-med-

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icate *via* PCA 43 times and received 3 injections during that period. A second bolus of 50 μg sufentanil was administered epidurally, and the solution was changed to 0.0002% (2 $\mu g \cdot ml^{-1}$) sufentanil and 0.1% bupivacaine infused at 7 $ml \cdot h^{-1}$. One hour later she reported to be very comfortable (VAPS 2/10), and PCA use was one attempt and one injection in that hour. Her epidural infusion was maintained at this rate over the next three postoperative days with excellent rest and dynamic pain control (VAPS 2/10–4/10). Her hourly PCA usage was 6–8 mg morphine. No episodes of oxyhemoglobin saturation < 90% occurred during this period. In addition, she remained hemodynamically stable and no signs of withdrawal developed.

On the fourth postoperative day (84–88 h) after the epidural sufentanil infusion had been started, the patient consented to having samples of cerebrospinal fluid (CSF) drawn from the cisterna magna and the L4–L5 interspace as well as blood for the determination of sufentanil concentration. Sufentanil concentrations in the lumbar and the cisterna magna CSF and in plasma were 0.34 and 0.19 $ng \cdot ml^{-1}$ and 0.28 $ng \cdot ml^{-1}$, respectively. On day 19 after starting the epidural sufentanil infusion we began to decrease the rate by 2 $\mu g \cdot h^{-1} \cdot day^{-1}$ until it was discontinued uneventfully 5 days later, 7 h after restarting methadone 25 mg orally every 6 h. No signs of opioid withdrawal were seen postoperatively following this second surgery. After consultation with the chronic pain service, the patient was discharged, 30 days after the surgery.

Discussion

Pain from tumor invasion can require large doses of opioids to provide effective analgesia.[8] Ingestion of large amounts of opioids creates problems for the postoperative management of these patients, because they can develop opioid withdrawal syndrome or experience inadequate pain control. Moreover, opioid-dependent patients also may be unable to obtain pain relief with intraspinal opioid administration because of their drug tolerance.[9,10] Drug tolerance at the spinal level is characterized as being time-dependent[11] and dose-dependent,[12] reversed once the agonist is withdrawn,[13] and specific to the receptor–agonist complex.[12,14] The physiology of tolerance/cross-tolerance at the spinal level is not known, but data suggest that it may be related to either desensitization or uncoupling of the receptor from the guanosine triphosphate binding subunit. Reduce affinity for the agonist or down-regulation due to loss in binding sites can result from these processes.[15–19]

Cancer patients taking doses of morphine greater than 30 mg per day have both an increase in postoperative epidural opioid requirements and a need for a longer duration of therapy than do patients not receiving such large doses.[20] In these patients, epidural morphine was given in two to four times the normal dose (0.5–0.7 $mg \cdot h^{-1}$) both to achieve adequate pain control and to prevent opioid withdrawal.[20] However, evidence exists that at high doses morphine can produce localized spinal convulsions, hyperalgesia,[21,22] and allodynia[23]—phenomena that are unresponsive to naloxone reversal. Because our patient was receiving 3 $mg \cdot h^{-1}$ of morphine epidurally with unsatisfactory pain control, we decided to change the infusion to sufentanil despite the commonly accepted theory that intraspinal opioids acting on the same receptor may exhibit cross tolerance. Moreover, reports of myoclonic movements and the risk of neurotoxicity associated with high doses of intrathecal sufentanil raise concerns about its administration.[24] However, the patient had good epidural analgesia with the bolus sufentanil injections for the breakthrough pain experienced in the PACU and in the surgical ward, and there were no signs of neurotoxicity during the treatment period.

Equianalgesic doses of epidural morphine and sufentanil have been reported to have a 60–100:1 ratio (500 $\mu g \cdot h^{-1}$ *vs.* 8.3 $\mu g \cdot h^{-1}$).[25] In this patient epidural morphine at a dose of 3 $mg \cdot h^{-1}$ (six times normal) was ineffective, whereas epidural sufentanil infusion of 14 $\mu g \cdot h^{-1}$ (1.7 times normal) completely controlled the pain. Thus, the approximate therapeutic epidural morphine–sufentanil ratio in this opioid-dependent patient was 213:1. Given that morphine at the concentration used did not produce adequate pain relief at the highest dose administered, the true potency ratio must in fact exceed this value; *i.e.*, sufentanil is more active than we would have anticipated as compared to morphine.

There are several explanations for epidural sufentanil's superior analgesia when compared with morphine. First, different agonists acting at the same receptor may exert equal physiologic effects by occupying different fractions of the receptor population.[26] Indeed, sufentanil needs to occupy a smaller fraction of the available receptors (higher intrinsic efficacy) than morphine to render the same antinociceptive effect.[5] The significance of efficacy in the present context is that in the presence of a given degree of receptor inactivation, agonists with higher occupancy requirements will show the greater decrease in the apparent potency (see ref. 25). In the present circumstances, it has been shown, for example, that in rats that received either intracathecal sufentanil or morphine infusions at equianalgesic doses, sufentanil was nine times more potent as an antinociceptive drug than morphine on the 1st day of infusion and 44 times more potent on the 7th day of the study.[7] Thus, the sufentanil–morphine potency ratio appears to widen as tolerance developed. We found this phenomenon to be true in our patient, whose pain responded to the infusion of sufentanil as judged by decreasing VAPS and PCA morphine use.

The difference between concentrations in the cisterna magna and the lumbar space (0.19 *vs.* 0.34 $ng \cdot ml^{-1}$) reflect both CSF circulation and elimination kinetics. Di Chiro demonstrated that the slow passage of labeled proteins from lumbar to cervical subarachnoid spaces was faster than could be accounted for by diffusion alone.[27] Thus, admixing of the fluid coming from both the brain

and the spine occurs, and a drug that is injected in the epidural space reaches supraspinal centers mainly by rostral transport.[28-30] The lower concentration of sufentanil in the cisterna magna may be explained by absorption from the CSF into the lipid-rich areas of the spinal cord, resulting in lower concentrations in the cisterna magna. This is consistent with pharmacokinetic data for fentanyl that showed that mean maximal cervical CSF concentration after lumbar epidural administration was 90% lower than the concentration in the lumbar CSF.[31] In addition, significant vascular uptake of sufentanil as demonstrated by plasma levels of 0.28 ng · ml^{-1} decreased the availability of the drug for rostral spread, further lowering cisterna magna concentrations.

Despite vascular uptake and lipid redistribution, relatively high concentrations of sufentanil were found in the cisterna magna (56% of the lumbar levels and 68% of the plasma levels). This concentration in the cisterna magna may have contributed to halting the development of withdrawal, more than did the plasma levels, by providing higher opioid concentrations in the limbic system. Indeed, data in humans have already suggested that the transport of highly lipid-soluble opioids (fentanyl) into the cervical and lumbar CSF following intravenous administration is negligible.[31] However, supraspinal effects produced by such serum levels may have acted synergistically with the spinal effects in the pain control experienced by the patient, based on the data of Lehmann *et al.*, who studied the pharmacokinetics of sufentanil for intravenous postoperative PCA.[32] They reported serum concentrations that ranged from 0.01–0.56 ng · ml^{-1} in patients who received 8 ± 4 $\mu g \cdot h^{-1}$ sufentanil. These plasma concentrations suggest that levels in our patient were within the minimum effective sufentanil plasma concentrations, thus contributing to analgesia.

The major route of epidural opioid distribution is vascular uptake, regardless of physicochemical properties.[28] While the rate of both systemic and CSF distribution is faster for lipophilic opioids after injection into the lumbar epidural space,[28-30] the relations among opioid ionization (polarity), the rate of systemic absorption, and its influence on opioid levels in the cisterna magna needs further study.

In conclusion, epidural sufentanil successfully replaced morphine for postoperative pain control in a patient receiving large doses of opioids for cancer pain. No signs of opioid withdrawal developed during the epidural treatment despite low parenteral use. Although there is a danger in attempting to define such clinical cases in terms of a single theoretical construct, the present results are in accord with the predicted outcomes associated with changes in receptor number, or increase in pain state and the changes in the apparent potency of agonists that act at the same receptor but that differ in relative efficacy.

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