

# Epidural Nonsteroidal Antiinflammatory Drugs for Cancer Pain

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**A**lthough pain relief with multimodal therapy is excellent in 45%–90% of cancer patients (1), dose escalation eventually occurs. The concurrent use of nonsteroidal antiinflammatory drugs (NSAIDs) to enhance opioid effects while decreasing the dose is recommended. Should NSAIDs and opioids fail, the spinal administration of opioids often results in improved analgesia with reduced opioid side effects (1,2).

Several reports have suggested a spinal site of action for NSAIDs (3–7) and synergy with spinal morphine (5). However, appropriate preclinical toxicity testing has not been performed for any commercially available NSAID, and intraspinal application is premature (8). We describe two cases in which epidural NSAIDs were administered by our ambulatory cancer patients without our initial knowledge or approval.

## Case Reports

### Case 1

A 17-yr-old, 74-kg male patient was evaluated for complaints of excruciating pain of the face, neck, and right shoulder due to rhinopharyngeal cancer and right knee pain secondary to metastases. On initial evaluation, the patient could barely talk because of severe pain (visual analog scale [VAS] score of 10 on a 0–10 scale). At the time, he was using intramuscular (IM) diclofenac 75 mg twice daily, IM tenoxicam 20 mg three times daily, oral tramadol 50 mg three times daily, and oral amitriptyline 50 mg at bed time without effect. The patient was hospitalized and received intravenous (IV) meperidine 60 mg every 4 h plus IV dipirona (NSAID) 500 mg every 6 h until discharge 2 days later. The patient still complained of knee pain (VAS score 5).

The patient was transferred to the pain clinic, and an epidural catheter was inserted at the L3–4 interspace without difficulty. Correct location was confirmed by appropriate sensory blockade after the injection of 10 mL 1% lidocaine.

After recovery, 2 mg of epidural morphine was injected, and the patient was managed as an outpatient with 2 mg epidural morphine administered twice daily.

One week later, the patient's mother reported that 2 mg epidural morphine provided the boy 18 h of complete pain relief but that he had experienced nausea and vomiting. Because of side effects, she decided to stop the epidural morphine and gave diclofenac 75 mg epidurally instead. The mother felt that epidural administration of the diclofenac would be less painful than the IM injection.

After the epidural diclofenac, the patient reported 48 h of complete pain relief (VAS score 0) and had no complaints of nausea or vomiting. He could move his knee without pain and had no neurologic deficits. The pain increased to a VAS score of 6, and because there was no diclofenac available at home, the mother administered epidural tenoxicam 20 mg, which gave 22.5 h of improvement in pain relief; however, the patient still complained of burning pain in the right knee (VAS score 2).

We instructed the mother to stop the epidural NSAID administration, and the dangers of its inadvertent use were discussed. The dose of morphine was titrated to 1 mg epidurally every 12 h, which resulted in anorexia and residual knee pain (VAS score 2), and at the 2-wk appointment, epidural neostigmine 100  $\mu$ g once daily was added. A month later, the patient continued to complain of mild knee pain (VAS score 2) with epidural morphine (3 mg three times daily) plus neostigmine (100  $\mu$ g twice daily).

### Case 2

A 52-yr-old, 65-kg female patient with uterine carcinoma complained of pain despite oral morphine 120 mg combined with oral amitriptyline 50 mg daily. An epidural catheter was inserted at L3–4, and correct location confirmed by appropriate sensory blockade after the injection of 8 mL 1% lidocaine. After recovery, epidural morphine was titrated to pain relief. After 1 wk, the patient was using epidural morphine 5 mg three times daily. The generalized abdominal pain had improved, but she was unable to walk because of pain in the right groin (VAS score 6) secondary to a metastatic process.

Two weeks later, the pain intensity had increased (VAS score 10) despite the use of epidural morphine, midazolam (500  $\mu$ g), and ketamine (0.2 mg/kg).

Without our knowledge, the daughter of Patient 2 met the mother of Patient 1 in the pain clinic waiting room, and they

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discussed the use of epidural diclofenac. The daughter of Patient 2 added epidural diclofenac 75 mg daily to epidural morphine 5 mg every 6 h, and the patient became pain free (VAS score 0) -and ambulatory, and had an improved appetite. After 8 days, generalized abdominal pain recurred (VAS score 6), and oral morphine 20 mg twice daily was begun. The epidural diclofenac was discontinued. The pain decreased somewhat (VAS score 3). The following week, the patient died of apparent respiratory insufficiency. The family did not allow postmortem investigation.

## Discussion

We describe two patients with cancer pain whose families decided to introduce an epidural NSAID without consulting their physicians. Patient 1 had metastatic knee pain unresponsive to intramuscular diclofenac 75 mg but responsive to epidural morphine 2 mg or epidural diclofenac 75 mg, the latter providing 48 h of analgesia devoid of adverse effects. This is in agreement with animal studies, in which IV doses of NSAID that were ineffective systemically were effective spinally (6). In these studies, neither motor dysfunction nor evidence of systemic toxicity or neurotoxicity was observed (6). In our patient, epidural diclofenac 75 mg was more effective than epidural tenoxican 20 mg.

Patient 2 suffered from intractable metastatic cancer pain in the groin, which did not improve with epidural morphine combined with both midazolam and ketamine. Pain management significantly improved when epidural diclofenac was added. Synergy between spinal ketorolac and morphine, probably through action both pre- and postsynaptically on the primary afferent, has been demonstrated in rats (5).

Inhibitors of cyclooxygenase, such as the NSAID, are effective in treating pain. After C-fiber stimulation, there is evidence of prostanoid release in the spinal cord, and cyclooxygenase inhibition blocks the hyperalgesia induced by both substance P and *N*-methyl-D-aspartate (9). Repetitive C-fiber stimulation evokes a state of spinal facilitation referred to as wind up (10) and an increase in the size of their respective fields (11). The dissociation of the C-fiber activity from the intensity of behavior reflects hyperalgesia. Several intracellular processes are involved in the spinal sensitization. Prostaglandin E<sub>1</sub> triggers a hypersensitive state at the spinal level (12), and the intrathecal administration of prostaglandins F<sub>2 $\alpha$</sub> , D<sub>2</sub>, and E<sub>2</sub> results in allodynia. Prostaglandin E<sub>2</sub>-induced allodynia is dose-dependently relieved by the glycine receptor agonist taurine, the *N*-methyl-D-aspartate antagonist ketamine, and large-dose clonidine, an  $\alpha_2$ -adrenoreceptor agonist. Prostaglandin F<sub>2 $\alpha$</sub> -induced allodynia is inhibited by clonidine and baclofen, a  $\gamma$ -aminobutyric

acid-B agonist (13). In addition, prostaglandins increase the depolarization mediated by substance P release in the dorsal horn cells (14), and the analgesic effect of spinal acetaminophen seems to be related to nitric oxide inhibition (15).

These case reports support the results of animal studies, which suggest that spinal NSAIDs may be effective. They also alert us to a potential danger of ambulatory management of epidural catheters and show the contrast between physician and family attitudes toward managing cancer pain. Finally, provided that toxicity is not observed in preclinical testing, spinal NSAIDs could advance therapy for cancer pain.

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