

Letters

More on the Use of Nonsteroidal Anti-Inflammatories in the Management of Cancer Pain

To the Editor:

The debate on the role of nonsteroidal anti-inflammatory drugs (NSAIDs) in the management of cancer pain has been highlighted by Jenkins and Bruera in a recent review article.¹ These authors point out the lack of evidence that NSAIDs play a specific role as analgesics or adjuvants in the strategy for cancer pain relief. We report a case that demonstrates the efficacy of an NSAID as an adjuvant to opioid analgesia in the setting of insufficient efficacy from morphine alone.

The patient was a 63-year-old man who was seen in our outpatient clinic for severe epigastric pain due to an advanced angioinvasive gastric adenocarcinoma. Liver and lymph node metastases were already present at surgery. CT scan had shown progression of the liver metastases, retroperitoneal metastatic nodes, local relapse at the gastric anastomosis, and findings suggestive of peritoneal carcinomatosis.

Worsening pain, vomiting, and constipation suggested admission to the hospital for symptom control. At admission, the patient's pain syndrome was characterized by continuous epigastric pain referred posteriorly, which did not change with position or food ingestion. A second pain occurred in sudden episodes, referred to the right lower abdominal quadrant with radiation to the upper abdomen. This pain was described as superficial to the abdominal wall, lancinating, arising from a circumscribed abdominal area where nodules could be palpated. These breakthrough pains (BKP) had a frequency of at least 2–3 times a day and an intensity of 8 on a 0–10 numerical pain scale. After one episode of coffee ground vomitus, an esophagogastrroduodenoscopy (EGDS)

with biopsy showed chronic gastritis, no obstruction, and no bleeding.

The outpatient clinic analgesic regimen included morphine slow-release oral tablets at doses up to 240 mg/day, which was then changed to oral methadone (39 mg/day) and supplemental doses of ketorolac (30 mg injections twice daily). The ketorolac was then changed to ketoprofen (up to 100 mg injections three times daily) for BKP episodes that were not controlled by the opioid alone. At admission, considering the documented gastritis and the need to provide treatment for the BKP episodes, an intravenous (IV) morphine infusion was started using a patient-controlled analgesia (PCA) programmable pump (SEVIT CADD PCA 5800 R®) and the NSAID was discontinued. Table 1 shows the PCA regimen together with the daily pain scores assessed using a 0–10 numerical scale.

While continuous epigastric pain was completely controlled, BKP was not relieved despite the use of PCA. After a few days, an NSAID was reintroduced on an as needed basis. In fact, when measuring BKP intensity, the administration of a 25 mg morphine IV bolus reduced the score from 8/10 to 6/10 for two hours, while indomethacin (50 mg IV) reduced pain intensity to 3/10 for about 10–12 hours. Morphine bolus dose titration was limited by the onset of severe nausea, requiring haloperidol 1 mg IV/day, and significant bolus-related sedation. The patient judged the effect of the morphine bolus completely unsatisfactory and associated with significant side effects. In contrast, he considered indomethacin as providing 100% pain relief.

Renal function was normal and gastrointestinal bleeding was not evident at EGDS. Therefore, indomethacin 50 mg IV twice daily was added to the analgesic regimen. The option of a celiac plexus block and of switching the route

Table 1
Morphine and Indomethacin Dosages Used During the Admission

Day	Morphine IV mg/day	P.R.N. Morphine bolus q1h mg/bolus	Number of Daily P.R.N. Doses	Daily Total Dose of Morphine	NSAID Number of Daily Doses	Daily Pain Score (0–10)
1	170	10	1	180	0	8
2	192	10	7	282	0	7
3	240	15	11	405	0	6
4	288	15	12	468	0	5
5	360	15	3	405	1	5
6	360	15	4	440	1	3
7	360	20	3	420	2	3
8	360	20	2	400	2	3
9	360	20	1	380	2	2
10	360	20	0	360	2	2
11	360	20	1	380	2	2
12	360	20	2	400	2	3
13	360	20	4	440	2	4
14	480	25	2	530	2	4
15	480	25	2	530	2	5

of administration to an epidural catheter were excluded due to the characteristics of the pain (which suggested a non-visceral pathogenesis), the patient's poor general conditions, and the insufficient response to opioids.

This regimen provided very good pain relief and side effects were limited to constipation. Therapy was carried on at the patient's home and remained effective until the patient's death 7 days later due to acute respiratory failure of unknown cause.

Comment

According to an operational definition of opioid responsiveness (maximal analgesia obtainable with dose titration until the onset of unacceptable side effects),² the pain syndrome of this patient was poorly responsive to systemic morphine administration, while it showed much better response to indomethacin. Explanations usually offered for this type of clinical response are based on tolerance to morphine analgesic effect or on the pathophysiology of the pain syndrome. In this case, inflammatory processes at the serosal tissue levels could have been a major contributory mechanism of BKP pathophysiology, justifying the sensitivity to NSAID effects and poor response to opioid analgesia.

Some studies show an opioid sparing effect with the combined use of an opioid and an NSAID.^{1,3} Bruera and Jenkins question the usefulness of this sparing effect. However, experts in evidence-based medicine agree that lack of

evidence does not prove lack of efficacy. Clinical experience suggests that, in some cases, NSAIDs have a unique role in producing potent analgesia. These observations deserve study and clinical trials before being translated into guidelines. The "analgesic ladder" approach of the World Health Organization suggests the use of NSAID at each step, but the benefit of this approach has not been well demonstrated¹ and the potential dangerous side effects of NSAIDs must be balanced against their usefulness. Also, the availability of COX-2 selective inhibitors (not available in Italy in parenteral preparations) requires that the efficacy and toxicity of these drugs is tested in the cancer pain model.

An excessive faith in opioid titration alone may be the cause of high-dose opioid toxicities and poor analgesic outcome.⁴ It is possible that a more careful and refined use of adjuvants for specific pain features and indications can reduce the likelihood of these toxicities and improve the control of some difficult pain conditions.^{5,6}

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Difficulties in Pain Control Among Injection Drug Users with Necrotizing Fasciitis

To the Editor:

Pain management among substance abuse patients remains a challenge for pain control specialists. Clinically, patients who are chemically dependent often require more opioid to control their postoperative pain.¹ Patients with necrotizing fasciitis require aggressive surgical debridement of necrotic skin and often limb amputation to ensure survival.² Although injection drug use (IDU) is a risk factor for necrotizing fasciitis, limited information exists as to whether pain control is adequate in this patient population during surgical management in the hospital. Patients who present with a history of IDU have been noted to report a higher level of pain than those patients that present without a history of substance abuse.^{3,4} We report here a review of the quality of

pain control for IDU patients with necrotizing fasciitis. We assessed whether or not differences exist in reported pain levels among IDU and non-IDU patients during the course of aggressive surgical management of necrotizing fasciitis.

Case Review

We reviewed the quality of pain control management among cases of necrotizing fasciitis in IDU and non-IDU patients that originated at the UC Davis Medical Center from 1984–1999. We scored the effectiveness of pain control among 107 cases of necrotizing fasciitis, 59 (55%) which were IDU and 48 (45%) which were non-IDU. IDU were defined as patients who, at the time of admission to the emergency room, indicated that they were current or previous injection drug users or had recently injected or skin-popped drugs. Pain management was scored on three qualitative levels. Effective management was defined by fewer than 6 patient complaints of 8 or greater (on a pain scale of 0–10) per 24-hour period for the duration of hospitalization. Ineffective management was defined by greater than 6 patient complaints per 24-hour period during hospitalization. When patient complaint scores were not recorded or available, pain management was scored as unknown.

Overall, pain management was effective for 50% of cases and ineffective for 21% of cases. IDU were significantly ($P < 0.05$) more likely to receive ineffective pain control (29%) compared to non-IDU (13%). All patients received some form of pain medication; 94 (88%) received morphine.

Comment

Effective pain management for a disease such as necrotizing fasciitis remains a challenge due to the aggressive surgical debridement involved in the management of such cases. In this series of patients, 13% had more than 10% of their total body surface area removed, and three-quarters had up to 5% of their skin removed. While a spectrum of pain medications were prescribed, morphine was the most common pain medication, used in nearly 90% of the cases. However, 21% of the cases of necrotizing fasciitis had ineffective pain management.

Among IDU patients, pain management was significantly more likely to be ineffective than among non-IDU. Given the extensive surgical