Clinical Note

Ketorolac Continuous Infusion: A Case Report and Review of the Literature

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Abstract

We report a case of intractable pain due to metastatic carcinoma that was effectively managed with a continuous intravenous (IV) infusion of ketorolac. Unlike previous reports of short-term continuous IV ketorolac for postoperative analgesia, this case is unique because of the etiology of the pain and the duration of treatment. The published literature on continuous administration of ketorolac by the intravenous, intramuscular, and subcutaneous routes is also reviewed. J Pain Symptom Manage 1996;12:190–194.

Key Words
Tolmetin, analogues and derivatives; pain; prevention and control; case report; review; infusion, intravenous; injection, subcutaneous; injection, intramuscular

Introduction

Pain is ubiquitous in medical practice and the control of pain is a major issue in caring for patients. This is especially true in cancer patients, for whom pain is the most frequent and disturbing symptom of the disease. Pain affects one-third to one-half of all patients with cancer and 75%–85% of those with advanced disease. The treatment of cancer pain can be difficult and frustrating because there is no specific formula for success. However, achieving effective analgesia is possible in up to 90% of patients with the optimal use of opioids and adjuvant medications.1

Ketorolac tromethamine (Toradol®) is a parenteral nonsteroidal anti-inflammatory drug (NSAID) that was approved in 1989 for the short-term management of pain. Although initially approved only for intramuscular (IM) administration, several reports have described the safety and efficacy of ketorolac when given as intermittent intravenous (IV) injections, a route that has recently been approved.2–4 We present a case in which ketorolac was administered as a continuous IV infusion in the management of cancer pain.

Case Report

A 46-year-old man with metastatic adenocarcinoma of the esophagus, first diagnosed in July, 1993, was treated with three courses of cisplatin, doxorubicin, and 5-fluorouracil. This was poorly tolerated and proved to be ineffec-
tive, resulting in only slight reduction in the size of the distal esophageal tumor while metastases to his liver and bone increased in size and number. Despite radiation therapy to his esophagus and left jaw, he continued to have progressive local and metastatic disease associated with increasing pain. The pain was largely across the back of his shoulders, radiating to both arms; he also complained of pain in the left jaw and a generalized cramping in his pelvis and lower extremities. His pain was initially managed with oral acetaminophen and acetaminophen with hydrocodone bitartrate (12-14 tablets per day). However, worsening pain led to a change in his regimen to oral hydromorphone and oral methadone in various combinations. In spite of escalating dosages (up to 12 mg/day of hydromorphone and 60 mg/day or methadone), his pain was only relieved after 30 mg IV boluses of ketorolac. He was referred to the Pain Management Service in early January, 1994, when he was hospitalized with intractable pain. During this hospitalization, his pain control improved after his medications were changed to morphine, 10 mg/hr with 5 mg boluses every 15 min as needed via a patient-controlled analgesia (PCA) device. In addition, he received methylphenidate, 10 mg twice daily as needed, amitriptyline, 50 mg at bedtime, and IV ketorolac 60 mg every 6 hours. He was discharged on this regimen. At his next clinic visit approximately 1 month later, he stated that his pain was controlled after each ketorolac injection, but worsened 5-6 hr after administration. Because of reluctance to increase the daily ketorolac dose beyond 240 mg, his morphine infusion was increased as needed up to 17.5 mg/hr. Subsequent chemotherapy was poorly tolerated, and further treatment focused on symptom management only. During the following month, numerous attempts were made to reduce his ketorolac regimen while continuing to increase his morphine and methylphenidate doses. He was convinced, however, that the ketorolac was contributing most to his pain relief and it was continued at 60 mg IV every 6 hr. It was then decided to change his ketorolac therapy to a continuous infusion at 5 mg/hr with 30 mg IV boluses every 6 hr as needed in an attempt to lower his total daily ketorolac requirement and simplify administration. He described his pain as 3-4 (on a scale of 1-10) with this new regimen, compared to 1-2 using 60 mg boluses of ketorolac alone. The morphine infusion continued to be escalated to a maximum of 22.5 mg/hour. With improved pain control; ketorolac 30 mg IV boluses were used intermittently. By the end of the month, the ketorolac infusion was increased to 6 mg/hr. His serum creatinine remained stable at 0.5-0.7 mg/dL over this 3-month period from January through March. Shortly thereafter, he was admitted for protracted emesis and new onset of left lower quadrant pain. At that point, he had widespread disease involving his esophagus, subcutaneous tissues, bone, and liver. A diagnostic workup revealed a distal esophageal perforation in a previously irradiated area of disease. The role of ketorolac as a contributing factor was also considered. A percutaneous endoscopic gastrostomy tube was placed to decompress his stomach and total parenteral nutrition was begun because of his inability to maintain nutrition. His analgesic regimen consisted of a morphine infusion at 30 mg/hr, with 5 mg PCA boluses every 15 min as needed. Keturolac was discontinued because of its possible contribution to the gastrointestinal (GI) perforation. Five days later, difficulty balancing acceptable pain control with excessive somnolence from the morphine infusion led to another trial of ketorolac, which was restarted with a 60 mg loading dose followed by a continuous infusion at 5 mg/hr. This allowed the morphine dose to be decreased to a final dose of 18 mg/hr, with satisfactory pain control and improvement in somnolence. Additionally, intermittent bolus doses of 30 mg ketorolac were prescribed every 4-6 hr as needed for breakthrough pain, but this was used sparingly. His serum creatinine was stable for the first week of his admission at around 1 mg/dL. On hospital day 9, however, the serum creatinine increased to 1.9 mg/dL as his status began to deteriorate. Keturolac was stopped and the morphine infusion alone was used for pain management. On hospital day 12, his serum creatinine peaked at 2.5 mg/dL with a blood urea nitrogen of 94 mg/dL. He was discharged from the hospital 3 days later and expired at home shortly thereafter. The total duration of ketorolac therapy was approxi-
mately 90 days, of which the last 30 days were by continuous infusion.

Discussion

Ketorolac is a relatively new nonsteroidal anti-inflammatory drug and the only one marketed in a parenteral form in the United States with an indication for the treatment of pain. It differs from other NSAIDs by exhibiting potent analgesic effects, with only moderate anti-inflammatory activity. Although initially approved only for intramuscular administration, its safety and efficacy when given as intermittent IV injections is well documented, and this method of administration has been approved as well. More recently, short-term continuous IV administration has been studied to control postoperative pain. We have described what we feel is the first report of ketorolac given as a long-term continuous IV infusion for the management of cancer pain.

In a recent double-blind, multicenter trial, for example, Ready and colleagues compared continuous infusion ketorolac, ketorolac by intermittent IV bolus, and placebo in the management of postoperative pain. Two-hundred seven patients who had undergone general, gynecologic, or orthopedic surgery and reported at least moderate pain postoperatively were randomized to receive PCA morphine sulfate plus one of three treatments: a 30 mg IV bolus of ketorolac followed by a 5 mg/hr continuous infusion and IV placebo (0.9% NaCl) injections q5h (infusion group); a 30 mg IV bolus of ketorolac followed by 15 mg IV q3h and a placebo infusion (bolus group); or an initial IV placebo bolus followed by IV placebo q3h and a placebo infusion (placebo group). One-hundred forty-two patients completed the 24 hr study. Both ketorolac groups required less morphine than did placebo recipients and had significantly lower pain scores 4–6 hr after starting the study. Differences between the high- and low-dose ketorolac groups appeared slight, but were not evaluated statistically. The same group of investigators also compared continuous intramuscular (IM) ketorolac and intermittent IM injections to placebo in a 48-hr postoperative study. Patients received either a 6.25 mg IM bolus of ketorolac, followed by 2.5 mg/hr IM, 10 mg of IM ketorolac q4h, or placebo; all patients received supplemental morphine as needed. PCA morphine requirements in the ketorolac groups were 25%–50% less than those in the placebo group after the first 24 hr, an effect that persisted for the continuous IM group through the second 24 hr as well. Pain scores in patients receiving ketorolac by either technique were lower than for Continuous infusions of ketorolac have also been given by PCA. For example, Rodriguez et al. compared ketorolac to metamizole (a NSAID), lysine clonixinate (a NSAID), and tramadol (an opioid agonist) in the control of postoperative pain in women undergoing abdominal hysterectomy. All analgesics were given intravenously by PCA beginning with a bolus dose 15 min after surgery, followed by continuous infusion with additional bolus doses every 30 min on demand. Patients in the ketorolac group received an initial 10 mg dose postoperatively, followed by a 5 mg/hr infusion; demand doses were also 5 mg. All agents provided effective analgesia during the study, as assessed by VAS at 4, 6, 12, and 24 hr after surgery. Except for superior analgesia in the tramadol group compared to the lysine clonixinate group at 12 and 24 hr, there were no significant differences among the analgesics. Other authors have also described successful treatment of postoperative pain using continuous IV ketorolac with intermittent boluses via PCA.

It is notable that prior to the recent reports of continuous intravenous administration of ketorolac, various authors described success with continuous ketorolac administration by the intramuscular (IM) and subcutaneous (SC) routes. Gillies et al., for example, compared 1.5 and 3 mg/hr of ketorolac by IM infusion to placebo for 24 hr postoperatively.

Patients in both ketorolac groups required approximately 30% less PCA morphine than did placebo recipients and had significantly lower pain scores 4–6 hr after starting the study. Differences between the high- and low-dose ketorolac groups appeared slight, but were not evaluated statistically. The same group of investigators also compared continuous intramuscular (IM) ketorolac and intermittent IM injections to placebo in a 48-hr postoperative study. Patients received either a 6.25 mg IM bolus of ketorolac, followed by 2.5 mg/hr IM, 10 mg of IM ketorolac q4h, or placebo; all patients received supplemental morphine as needed. PCA morphine requirements in the ketorolac groups were 25%–50% less than those in the placebo group after the first 24 hr, an effect that persisted for the continuous IM group through the second 24 hr as well. Pain scores in patients receiving ketorolac by either technique were lower than for
those treated with placebo, but not significantly so. Interestingly, with the exception of the last measurement at 48 hr, pain scores in the intermittent group were lower than pain scores in the continuous IM group.

Blackwell and colleagues described two patients with uncontrolled pain from hypertrophic pulmonary osteoarthropathy, a syndrome associated with bronchogenic carcinoma. Each patient had failed multiple oral NSAIDs, corticosteroids, and oral morphine, as well as palliative radiotherapy. Both patients, however, became pain free after starting a continuous subcutaneous (SC) infusion of ketorolac at 1.25-2.5 mg/hr. The same authors have also described continuous SC infusion of ketorolac in the management of cancer pain in seven adults with advanced disease. Patients received ketorolac because of inadequate analgesia with opioids or opioid-related side effects. All patients became symptom-free after starting ketorolac (1.25-3.75 mg/hr) and opioid doses were reduced by 50-100% within 24 hr. Although side effects from ketorolac were not described, all patients were prescribed misoprostol 200 μg once daily.

Two potentially severe side effects of NSAIDs are gastric irritation and renal dysfunction. Despite 30 days of nearly continuous IV therapy (90 days of total IV therapy), our patient experienced minimal toxicity. Although ketorolac may have contributed to his distal esophageal perforation, this area was susceptible because of prior irradiation and tumor invasion. Furthermore, his serum creatinine remained stable throughout his therapy until his condition declined, at which time his serum creatinine peaked at 2.5 mg/dL. No other side effects from ketorolac were noted. Although not used in our patient, the addition of a gastroprotectant should be considered if continuous infusion ketorolac is used, given that many cancer patients may be predisposed to gastritis secondary to chemotherapy or pre-existing ulcer disease. Blackwell and colleagues successfully prescribed low dose misoprostol (200 μg/day) in their patients, which may provide adequate gastric protection with minimal side effects.

Although the morphine-sparing effect of parenteral ketorolac has been well documented in the management of postoperative pain, this property was not clearly seen in our patient initially. In fact, he required increasing doses of morphine to control his pain, despite receiving 240 mg/day of ketorolac. It was not until later in his course, when he was receiving morphine alone, that the reintroduction of ketorolac allowed the morphine infusion to be lowered without loss of pain control.

Continuous IV ketorolac provided effective analgesia in our patient at a lower total daily dose than was required with intermittent IV administration. The drug's efficacy is highlighted by our patient's perception that, despite concomitant morphine, ketorolac contributed most to his pain relief. We find it interesting, however, that at least initially, our patient rated pain relief from intermittent IV boluses better than that afforded by continuous infusion, a finding that parallels that of Ready et al. and Gillies et al. Whether this is due to higher peak levels attained with bolus dosing is unknown. Studies comparing the pharmacokinetics, as well as the analgesic effects and toxicity of continuous IV administration and intermittent IV dosing of ketorolac may help answer this question.

In conclusion, although certainly not the first step in the management of cancer pain, we feel that continuous infusion ketorolac represents a potentially valuable method of analgesia. However, given the potential toxicities of a continuous infusion of ketorolac, especially in patients already at risk for side effects from chemotherapy and/or their disease, its use in this manner must be approached with caution. Controlled trials are clearly needed to identify those patients who will benefit most from this method of delivery and to confirm the favorable risk-benefit ratio that we saw in our patients.

References

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