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Off-Label Drug Uses

The Role of Subcutaneous Ketorolac for Pain Management

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This *Hospital Pharmacy* feature is extracted from *Off-Label Drug Facts,* a publication available from Wolters Kluwer Health. *Off-Label Drug Facts* is a practitioner-oriented resource for information about specific drug uses that are unapproved by the US Food and Drug Administration. This new guide to the literature enables the health care professional or clinician to quickly identify published studies on off-label uses and determine if a specific use is rational in a patient care scenario. References direct the reader to the full literature for more comprehensive information before patient care decisions are made. Direct questions or comments regarding *Off-Label Drug Uses* to jgeneral@ku.edu.

BACKGROUND

Ketorolac tromethamine (*Toradol*), a nonsteroidal anti-inflammatory drug (NSAID), is commonly used alone or in combination with other analgesics for pain management in both hospital inpatients and outpatients. Unlike the majority of other NSAIDs, it is available in an injectable formulation approved for intramuscular (IM) and intravenous (IV) routes of administration in addition to oral and intranasal administration. Its proposed mechanism of action is predominantly peripheral inhibition of prostaglandin synthesis through cyclooxygenase-1 and -2 inhibition and is thought to have more analgesic than anti-inflammatory effects.[1] It has been evaluated following surgical procedures and demonstrated decreased opioid consumption and opioid-induced adverse events.[1] Its use in the emergency department has demonstrated adequate pain management for renal colic, migraine headache, musculoskeletal pain, and sickle cell crisis.[1] The decrease in abuse and addiction potential compared to opioids may make ketorolac a preferable option in this setting. Moreover, the World Health Organization includes recommendations for NSAIDs prescribed alone or in association with opioids for subsequent ladder steps for cancer-related pain.[2] Pain due to bone metastases has been shown to benefit from NSAID use.

The safety profile of ketorolac is similar to that of other NSAIDs, with the most important adverse events affecting the gastrointestinal (GI) tract, hematological function, and renal function. Initial findings of increased risk of GI bleeding in a large US postmarketing surveillance study comparing parenteral ketorolac to opioids led to concerns regarding its use.[3] An increase in duration of parenteral ketorolac therapy greater than 5 days was associated with an increased risk of GI bleeding (odds ratio [OR], 2.20; $P = .04$). High doses (>105 mg/day) of ketorolac were also associated with increased risk, which was further increased in people older than 65 years of age.[3] Renal toxicity has been mainly demonstrated through case report data, even in patients who only received a single dose.[1] In light of these findings, dosing guidelines have been modified to recommend no more than 5 days of therapy with adjustments for age, renal function, and/or body weight less than 50 kg.[4]

Subcutaneous administration is currently not approved for use. A question that has arisen in the emergency department is whether the use of subcutaneous ketorolac is appropriate when patients present in pain with no IV access and low muscle mass. It is also thought that intermittent injections via the subcutaneous route may provide more efficacious pain control due to the slower rate of absorption by this route.[5] However, the pharmacokinetic and pharmacodynamic properties of the subcutaneous route of administration of ketorolac are not fully

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understood, the optimal and appropriate dose of this route remains undefined, and the efficacy and safety of its use has not been fully elucidated. Therefore, the purpose of this review is to evaluate the clinical data regarding the safety and efficacy of subcutaneous administration of ketorolac for pain management.

PATIENT POPULATION

Adult patients with no IV access and low muscle mass who are experiencing pain.

DOSAGE AND DURATION

Dosage range for ketorolac continuous subcutaneous infusion (CSI) is 30 to 120 mg over a 24-hour period. Bolus doses of subcutaneous ketorolac 30 mg have also been used. Duration in case reports and studies varied from 1 day to 185 days, but current recommendations limit therapy with ketorolac to less than 5 days.[4]

RESULTS

Current literature supporting the use of subcutaneous ketorolac is limited to case report and observational study data in cancer-related pain (see **Table 1**). Combined patient population of case reports (5) and observational studies (2) was small (91 patients) and included diverse pain syndromes related to cancer, including bone and neuropathic pain.[6-12] The dose and delivery method and outcome measurements were different among the studies, making data synthesis somewhat challenging. Length of therapy was extended (>5 days) in a majority of the patients and was associated with 6 GI bleeding events, but no renal adverse events were reported. As with all case report data, caution must be used in interpretation due to possible publication bias and lack of uniformity of patient population.

Two randomized clinical trials of ketorolac CSI in the postoperative setting demonstrated decreased opioid consumption after laparoscopic day surgery (n = 33) and postcaeserean delivery (n = 20).[13,14] Differences in ketorolac doses used in the studies and in outcome measurements preclude generalizing these data to other areas of postoperative care. This collection of literature gives insight that the analgesic effect of ketorolac is still present when given subcutaneously and that doses at slow infusion rates appear to be tolerated with minimal severe adverse effects.

Case Reports/Series

Blackwell et al[6] published the first case series regarding the use of subcutaneous ketorolac for pain control in the setting of advanced malignant disease. The use of ketorolac CSI was initiated in

Table 1. Case reports and observational studies of subcutaneous ketorolac in cancer-related pain

Reference	No. of patients	Age, years	Ketorolac CSI dose, mg per 24 hours	Duration of therapy, days	Change in opioid dose, %	Adverse effects (n)
Blackwell[6]	7	52-81	30-60	8-31	29↓ – 100↓	None observed
Blackwell[8]	2	58-78	30-60	5-NR	NR[a]	NR
De Conno[11]	10	40-73	90-120	1-7	Not assessed[b]	Mild local bleeding (7), xerostomia (3), sweating (3)
Duncan[7]	10	29-36	<60-150	3-22	300↑ – 100↓	NR
Hughes[10]	25 (30 episodes)	43-83	60-90	3-185	≥25↓ in 3 episodes[c]	Melena (1), local rectal bleeding (1)
Myers[12]	36	19-79	30-120[d]	3-115	0–100↓[e]	GI bleeding (4), colonic perforation (1)
Ripamonti[9]	1	48	120	75	100↓	None observed

Note: CSI = continuous subcutaneous infusion; GI = gastrointestinal; NR = not reported

[a]Patients were reported to be pain-free upon initiation.

[b]Pain effectively controlled by other therapeutic measures prior to the study.

[c]Pain improved in 27 episodes.

[d]Twenty-two of 36 patients received a bolus dose of 30 mg ketorolac subcutaneously prior to start of infusion.

[e]Opioid dose reduced in 22 patients, with 9 becoming opioid-free.

a 79-year-old female whose pain had been uncontrolled by opioids and oral NSAIDs. The ketorolac CSI was started at a dose of 90 mg over 24 hours, and pain relief was observed within 2 hours of initiation. She remained on treatment for 14 days with no adverse events reported. Use of ketorolac CSI in 6 more patients was also reported. Reasons for use included inadequate analgesia with opioids plus oral NSAIDs and/or disabling side effects from opioids. Bony metastases were present in 5 of the 6 patients. All patients became symptom-free upon initiation of ketorolac, and opioid requirements were reduced in all patients, with 4 of 7 becoming opioid free. Misoprostol 200 mcg daily was prophylactically started in all patients, and no adverse events were reported.

In response to Blackwell and colleagues, Duncan and Hardy[7] reported on their clinical use of ketorolac CSI in 10 cancer patients. These patients did not show consistent opioid dose reductions as with Blackwell and colleagues. Five demonstrated opioid dose reductions, but 4 required increased opioid doses. The authors were unable to identify the reason for increased opioid need. Duncan and Hardy encouraged further evaluation of this route of administration to fully elucidate its importance.

Blackwell et al[8] followed up their previous case series with 2 case reports of ketorolac CSI for successful treatment of resistant pain in hypertrophic pulmonary arthropathy. Ripamonti et al[9] reported its use for neuropathic pain in a 48-year-old male who had initially received ketorolac IM and was then transitioned to ketorolac CSI 120 mg over 24 hours for continuous pain control. He received misoprostol and remained on therapy for 75 days with no apparent side effects.

The last case series data were reported in a letter to the editor by Hughes et al.[10] They reported use of ketorolac CSI for severe cancer-related pain that was uncontrolled despite opioids and oral NSAIDs in 25 patients on 30 separate episodes over a 15-month period. The most common starting dose was 60 mg over 24 hours, which was increased to 90 mg as needed. Prophylactic misoprostol or omeprazole was initiated in all patients. Pain improved in 27 of 30 episodes, with an opioid dose reduction of more than 25% in 3 episodes. Bleeding events (melena and local rectal bleeding) occurred in 2 patients who were on ketorolac for more than 20 days. No other major adverse events were reported. These case reports demonstrate pain settings where subcutaneous ketorolac provided analgesia without significant adverse events when other standard options had failed or were intolerable.

Observational Studies

De Conno et al[11] evaluated the local and systemic tolerability of ketorolac CSI in cancer patients who had their pain well-controlled by other therapeutic measures prior to enrollment. Ten patients participated in this study and received ketorolac CSI 90 mg over 24 hours. If necessary, doses were increased to 120 mg. Pain at injection site, patient-assessed pain scores, patient-reported symptoms, and frequency of needle changes were all assessed. No pain at injection site was noted but 7 of 10 patients showed mild local bleeding, which required repositioning of the inserted needle. Pain control was noted to be acceptable in all patients, with slight increases in pain scores from day 0 to day 7 in 3 of the patients. Authors concluded that ketorolac CSI is tolerable, but they also noted that the bioavailability of ketorolac after subcutaneous administration remains unknown and that its clinical usefulness needs to be confirmed by larger studies.

Myers and Trotman[12] expanded the findings of Blackwell et al[6] and reported the single-center observations of 36 inpatients with advanced malignant disease–associated pain treated with ketorolac CSI. All patients were receiving oral opioids. Prior to initiation of the ketorolac CSI at a rate of 60 mg over 24 hours, a verbal 4-point rating of the patient's pain was obtained. Oral misoprostol was initiated in all patients. Subsequent response to ketorolac was assessed by the physician every 12 hours by verbal 4-point scale. Doses were adjusted accordingly up to a maximum dose of 120 mg. Of note, 22 of the 36 patients received a 30 mg ketorolac bolus subcutaneously prior to initiation of CSI to assess likely response. Complete pain control was achieved in 29 of the 36 patients at 48 hours. Five patients had no response to the bolus dose and CSI over 48 hours and ketorolac was withdrawn. Two patients had transient response that lasted less than 48 hours. Of the responders, 20 patients required a dose of 60 mg over 24 hours. Twenty-two patients had opioid dose reductions and 9 had all opioids withdrawn. Seven patients became pain-free but did not have a reduction in opioid dose. Of those who responded, 25 had bone pain or bone and visceral pain combined. Of the 7 who failed ketorolac, all had neuropathic or visceral pain involvement. Average length of treatment was 21 days. Four patients had GI bleeding and one had colonic perforation. No clinical significant changes in renal function were observed.

Randomized Clinical Trials

Despite the apparent benefit seen in the case series, no randomized controlled trials have evaluated the use of subcutaneous infusion of ketorolac in cancer-related pain. However, 2 clinical trials have been completed within the setting of surgical procedures.

Campbell et al[13] completed a randomized, double-blinded, placebo-controlled study to evaluate use of subcutaneous ketorolac infusion for 24 to 36 hours following laparoscopic surgery. Four-day postoperative follow-up assessed the impact of ketorolac CSI compared to only oral opioid analgesia on return to normal function. Patients received either ketorolac 10.5 mg bolus dose or an equivalent volume of saline administered subcutaneously, followed by either an infusion rate of ketorolac 1.75 mg/h or saline. Other analgesics were standardized between groups – intravenous fentanyl in the recovery ward and oral codeine in the day stay unit. Patient diaries assessed recovery to normal function. The primary outcome was time until patients reported the first pain score of 0. According to power calculation, a sample size of 72 patients would be needed to detect a reduction of one day in time to freedom from pain. Thirty-three patients received ketorolac and 39 received placebo. Baseline demographics were similar between groups. In the recovery ward, the ketorolac group required significantly less fentanyl compared to placebo (median 40 mcg vs 80 mcg; $P = .016$). In the day stay unit, the ketorolac group required significantly less codeine tablets compared to placebo (median 0 tablets vs 1 tablet; $P = .005$). Pain scores were similar at discharge. On postoperative day 1, the ketorolac group required fewer codeine tablets compared to placebo (median 1 tablet vs 3 tablets; $P = .028$). No adverse effects were reported in patients who received ketorolac infusion. In terms of the primary outcome, however, the ketorolac group did not demonstrate significant beneficial effect on discomfort or pain scores after laparoscopic surgery and thus did not hasten return to normal function.

Carvalho et al[14] conducted a randomized, double-blinded, controlled study in the setting of caesarean delivery. The study evaluated the effects of subcutaneous local bupivacaine with low-dose ketorolac or hydromorphone compared to only bupivacaine on postcaesarean pain and on the concentration of key inflammatory markers in the surgical wound exudates. Specifically, the investigators wanted to evaluate doses of ketorolac and hydromorphone that would be considered ineffective if administered systemically in order to assess their localized effect. Sixty healthy women with term pregnancy were enrolled and randomized 1:1:1 to receive a subcutaneous surgical wound infiltration for 48 hours. The 3 groups include bupivacaine 0.5% at 10 mg/h as active control, bupivacaine 0.5% at 10 mg/h with ketorolac 0.6 mg/h, and bupivacaine 0.5% at 10 mg/h with hydromorphone 0.04 mg/h. Postoperative pain management was facilitated by oral opioid analgesic and IV morphine for severe pain and cumulative amounts were documented. Pain scores at 4, 24, and 48 hours postcaesarean delivery were reported at rest and during activity using a numerical verbal pain scale from 0 to 10. Delayed wound healing was assessed during the initial 48 hours and at 6-week follow-up. Wound exudates were collected at 4, 24, and 48 hours and evaluated for presence of key inflammatory markers. The primary outcome was reduction of inflammatory markers with a secondary goal of analgesic effect among treatment groups. Baseline demographics were similar among groups. For the primary outcome, ketorolac significantly decreased interleukin-6 ($P = .012$) and interleukin-10 ($P = .005$) compared to bupivacaine alone. Analgesic use (morphine equivalents) was significantly less in the group that received ketorolac in addition to the bupivacaine compared to the group receiving bupivacaine alone ($P = .02$). The area under the concentration curve (AUC) pain scores during movement were significantly less with ketorolac compared to bupivacaine alone ($P = .018$). No significant adverse events or study-related complications were observed, and no delayed wound healing was reported.

SAFETY

The safety profile regarding subcutaneous ketorolac is limited. Refer to labeling for complete prescribing information (eg, Warnings/Precautions, Adverse Reactions, Drug Interactions).

Adverse reactions reported in the case series and studies included melena, local rectal bleeding, mild local bleeding, xerostomia, sweating, GI bleeding, and colonic perforation.[10-12] Of the 144 patients who received ketorolac CSI, GI bleeding occurred in 6 patients and no patient had renal dysfunction.

THERAPY CONSIDERATIONS

Subcutaneous administration of ketorolac appears to provide analgesic benefit in both cancer-related and postoperative pain. Ketorolac CSI has shown minimal adverse effects regarding GI or renal issues. However, only 2 studies used bolus doses of subcutaneous ketorolac; the main delivery method seen in literature is ketorolac CSI, which is not commonly

used in the hospital setting. Based on current evidence, routine use of subcutaneous ketorolac cannot be recommended for use as intermittent bolus doses but appears to be a safe option when no other route of administration is available. Ketorolac CSI may be considered when patients have been unresponsive to other pain modalities.

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ezogabine induces melanin synthesis or, alternatively, hampers the degradation of melanin. Nuclear magnetic resonance imaging and mass spectrometry results provided no evidence of drug deposition in the tissue. However the authors state that they cannot rule out the presence of drug derivatives or metabolites that could not be detected by their analysis.

The US Food and Drug Administration has since published a statement announcing that ezogabine can cause blue skin discoloration and pigment changes in the retina. In evaluating 605 patients, 6.3% were found to have skin discoloration. At this time, all the patients had not been analyzed, so the rate may be an underestimation. One-third of patients given eye examinations had retinal pigment changes. It is not known whether the pigment is deposited in other organs as well or whether the changes are reversible.

The authors state that the mainstay of treatment for drug-induced dyspigmentation is sun avoidance with application of sunscreen and, if possible, interruption of the implicated drug. In most cases, these measures lead to improvement; however, it may be slow improvement. The significant improvement in the mucocutaneous dyspigmentation following discontinuation of ezogabine, as observed in the first patient, suggests that ezogabine-induced dyspigmentation might be reversible.

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