Use of ketorolac by continuous subcutaneous infusion for the control of cancer-related pain

Kathryn G. Myers and Ivan F. Trotman

Department of Palliative Medicine, Michael Sobell House, Mount Vernon Hospital, Rickmansworth Road, Northwood, Middlesex HA6 2RN, UK

Summary: Ketorolac tromethamine is a newly available non-steroidal anti-inflammatory drug which is suitable for parenteral administration. We have given it by continuous subcutaneous infusion to 36 patients with pain due to advanced cancer. Improvement in pain control occurred in 29 (80%). A reduction in the dose of concomitant opioid analgesia was possible in 22 (76%) and a reduction in opioid-related adverse effects occurred in 16 (73%) of these. Ketorolac was most effective in patients who had bone or visceral pain. It was mixed safely with diamorphine in a syringe driver at concentrations up to 4 g diamorphine/10 ml and 120 mg ketorolac/10 ml. Infusion was well tolerated for periods of up to 115 days (mean 21 days; median 15 days; range 3–115 days). Four patients experienced gastrointestinal bleeding and one colonic perforation to which treatment with ketorolac may have been a contributory factor. No other clinically significant adverse effects were observed.

Introduction

Ketorolac tromethamine (Toradol, Syntex) is a non-steroidal anti-inflammatory drug (NSAID) which displays proportionately greater analgesic than anti-inflammatory action.¹ Unlike most other NSAIDs it can be used parenterally and it has been used successfully by intramuscular injection for the control of postoperative pain in a variety of clinical situations.^{2–5} Intramuscular ketorolac has been used in the management of cancer pain⁶ and we have previously reported the successful use of ketorolac by continuous subcutaneous infusion as a co-analgesic in seven patients with cancer pain.⁷ We have now treated 36 patients with ketorolac by continuous subcutaneous infusion and report our observations.

Patients

Thirty-six patients (19 female, 17 male; median age 58 years, range 19–79 years) with advanced malignant disease were treated with ketorolac by continuous subcutaneous infusion. All were in-patients at Mount Vernon Hospital within the Department of Palliative Medicine or on the oncology wards under the care of the palliative medicine team. All were receiving opioid analgesics: oral morphine, 15 (42%); diamorphine by continuous subcutaneous infusion, 20 (55%); and

dextromoramide by continuous subcutaneous infusion, one (3%). Twenty-two patients (61%) were experiencing one or more serious adverse effects attributable to opioid analgesia: drowsiness, nine (25%); confusion 12 (33%); hallucinations, ten (28%); nausea and vomiting, ten (28%). Twenty-seven patients (75%) were receiving other oral NSAIDs at the maximum recommended dosage prior to treatment with ketorolac. All had pain which was inadequately controlled by their existing medication. All described their pain as 'severe' on a four-point verbal rating scale. Each patient's pain was assessed according to its principal sites and characteristics, the patient's diagnosis and any available radiological evidence in order to classify it as predominantly bone, visceral or neuropathic in origin. Twenty-three patients had bone pain, seven had visceral pain, one had neuropathic pain, three had both bone and visceral pain, and two had complex pain with bone, visceral and neuropathic features.

Protocol

Before starting treatment with ketorolac, each patient was interviewed by one of us (KM) and was asked to give a verbal rating of their pain on a four-point scale of 'no pain, mild pain, moderate pain, severe pain'. The characteristics of the pain were elicited so that it could be classified as predominantly bone, visceral or neuropathic in origin. Ketorolac was administered at an initial

Correspondence: I.F. Trotman, M.D., M.R.C.P.
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dose of 60 mg mixed in 0.9% sodium chloride solution by continuous subcutaneous infusion over 24 hours using a Graseby MS168 syringe driver. In patients receiving diamorphine by subcutaneous infusion, the two drugs were mixed together in 0.9% sodium chloride solution in the same syringe. Other NSAIDs were discontinued. All patients were prescribed oral misoprostol (Cytotec, Searle) 200 µg three times a day. The subsequent response to ketorolac was assessed by the doctor every 12 hours by asking patients to rate their pain on the same verbal four-point scale. Patients who had no pain had their dose of opioid reduced by 20–30% every 24 hours until they developed breakthrough pain or until the dose of opioid had been reduced to zero. If breakthrough pain occurred, the dose of ketorolac was increased to 90 mg and 120 mg/24 hours with supplementary doses of opioid analgesia as required. Patients were deemed not to have responded to ketorolac if their pain was still severe or moderate after 48 hours.

In 22 of the patients (61%) a bolus of 30 mg ketorolac was administered subcutaneously to assess the likely response before starting continuous subcutaneous infusion. Patients whose pain improved by two or three points on the verbal rating scale within 4 hours of the bolus dose being administered had their dose of concomitant opioid analgesic reduced immediately by 25–30% before starting ketorolac by infusion in order to prevent the emergence of opioid-related adverse effects due to removal of the opioid antagonist effect of the pain.

Results

Complete pain control was achieved in 29 patients (80%) within 48 hours of starting ketorolac infusion and response was maintained for at least 72 hours. Five patients (14%) made no response to both a test dose of ketorolac and subcutaneous infusion over 48 hours, and ketorolac was therefore withdrawn. Two others (6%) made a transient response to ketorolac infusion which lasted for less than 48 hours.

Of the 29 patients who responded, pain control was achieved with ketorolac at dose rates of 60 mg/24 hours in 20 patients (69% of responders), 90 mg/24 hours in six patients (21%) and 120 mg/24 hours in two patients (7%). In one patient the dose rate was successfully reduced to 30 mg/24 hours once the pain was fully controlled. A reduction in the dose of opioid analgesia within 48 hours of starting ketorolac infusion was possible in 22 (76%) and in nine of these patients opioid analgesics were eventually withdrawn completely (Figure 1). Sixteen of these 22 also experienced a

Figure 1 Maximum reduction in dose of opioid possible after starting ketorolac infusion (% initial dose) versus initial opioid dose (oral morphine equivalent in mg) in 29 patients with complete pain relief. ● = patient with predominantly bony pain; ○ = patient with predominantly visceral pain.

reduction in the severity of opioid-related adverse effects. Seven patients (24%) became pain free but no reduction in their opioid dose was possible.

Twenty-five (86%) of the 29 patients who responded to ketorolac had bone pain or bone and visceral pain combined, and four (14%) had visceral pain alone. Of the seven patients who failed to respond to ketorolac, one had bone and visceral pain combined, three had visceral pain alone, one had neuropathic pain, and two had complex pain with bone, visceral and neuropathic components.

Patients received continuous infusions of ketorolac for an average of 21 days (range 3–115, median 15 days). Twenty-one (72%) of the 29 responders remained on subcutaneous ketorolac until they died of their cancers. Attempts to convert three of these to oral ketorolac were unsuccessful. Two patients (7%) were successfully converted to oral ketorolac and four (14%) were converted to other oral NSAIDs. Ketorolac infusion was discontinued in two patients because of adverse events.

Four patients experienced gastrointestinal bleeding whilst receiving ketorolac. In one of these ketorolac was discontinued permanently. In another, ketorolac infusion was cautiously continued and the two others were converted to other oral NSAIDs once recovered from the acute episode. A fifth patient had a colonic perforation and ketorolac was discontinued.

Ketorolac and diamorphine were mixed in 0.9% sodium chloride solution in the same syringe driver in 20 patients with concentrations of diamorphine of 40–4,000 mg/10 ml and ketorolac 60–120 mg/10 ml. There was no macroscopic precipitation in

the syringe driver at these concentrations and pain control in all remained unchanged or improved. No clinically significant changes in renal function, water or electrolyte balance were observed in any patient during ketorolac infusion.

Discussion

Non-steroidal anti-inflammatory drugs have a well-established place as co-analgesics in the treatment of cancer pain.⁸ Most can be given only by the oral route, though some can be given rectally or by intramuscular injection. The major advantage of ketorolac is that it can be given by continuous subcutaneous infusion and this makes it particularly useful in advanced cancer where other routes of administration can become unreliable or impractical. Naproxen and diclofenac have also been given subcutaneously^{9,10} but irritation at the injection site may limit their long-term use.

This report shows that introduction of ketorolac by continuous subcutaneous infusion in 36 patients with severe uncontrolled cancer-related pain resulted in symptomatic improvement in 29 (80%). We found that the best responses to ketorolac occurred in patients with predominantly bone-related pain. The seven patients who failed to respond all had neuropathic or visceral pain.

Opioid analgesics are an essential component of pain management in many patients with advanced cancer. Some cancer pain, however, is incompletely responsive or resistant to opioids, and adverse effects can compromise symptom control. All the patients in our series were taking opioid analgesics when ketorolac was introduced. Some had pain which appeared to be resistant to large increases in opioid dose. Others were unable to tolerate the dose of opioid necessary to control their pain because of distressing adverse effects. Improved pain control following the introduction of ketorolac enabled a reduction in opioid dose in 22 patients with a concomitant improvement in opioid-related adverse effects in 16. Nine patients were able to stop taking opioids altogether.

Ketorolac has proportionately greater analgesic than anti-inflammatory action¹ and may therefore be an effective analgesic where other NSAIDs have failed to produce benefit. In our series, 22 (76%) of the 29 patients whose pain improved with subcutaneous ketorolac had already taken other NSAIDs orally at maximum recommended doses without significant improvement in their pain. Whether this is due to unique properties of

ketorolac or simply a result of parenteral administration remains to be ascertained.

Like other NSAIDs, ketorolac alters platelet function, prolongs bleeding time and may predispose to gastrointestinal bleeding. Recent Committee on Safety of Medicines (CSM) guidelines¹¹ have recommended caution in the use of ketorolac in patients aged over 65 years and those with a history of peptic ulceration. In our study four patients had gastrointestinal bleeding whilst receiving ketorolac. Two of these patients had upper gastrointestinal malignancies, the third had bleeding from the distal colon related to radiation proctitis (upper gastrointestinal endoscopy was normal) and the fourth suffered upper gastrointestinal bleeding when high-dose dexamethasone was introduced. All four of these patients were over 65 years of age. A fifth patient who developed a colonic perforation after starting ketorolac had recently received chemotherapy including high-dose steroids for the treatment of non-Hodgkin's lymphoma. It may be wrong to assume that all these episodes were causally related to ketorolac as there may have been other contributing factors. Nonetheless, the apparent added risk of upper gastrointestinal bleeding in patients with upper gastrointestinal malignancies or patients who require treatment with high-dose steroids must be very carefully assessed.

The CSM guidelines suggest that parenteral treatment with ketorolac should not exceed 48 hours. In our study, however, ketorolac was well tolerated for much longer periods, 13 (36%) of the 36 receiving continuous subcutaneous infusion for 21 days or longer with no adverse effects. Where ketorolac produces a significant improvement in symptom control in patients with advanced cancer, longer periods of treatment may be justifiable as the benefits may balance or exceed possible risks. Ketorolac was mixed with diamorphine in 0.9% sodium chloride in a syringe driver in 20 patients. We have no experience of mixing ketorolac with other drugs and formal miscibility studies are required. Two patients experienced minor painless bleeding from injection sites which was managed by regular changes of dressing with no long-term adverse effects to the skin.

Our experience suggests that ketorolac has a valuable place alongside other NSAIDs as a co-analgesic in patients with advanced cancer. Its major advantage is that it can be given by continuous subcutaneous infusion using a syringe driver. Our results indicate clear benefits when ketorolac is given by this route and properly controlled trials of its use are now required.

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