Clinical Note

Tolerability of Ketorolac Administered Via Continuous Subcutaneous Infusion for Cancer Pain: A Preliminary Report

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Abstract
We evaluated the local and systemic tolerability of ketorolac administered through continuous subcutaneous infusion in ten cancer patients. The patients were monitored daily for the severity and duration of pain, and the development of other symptoms. The duration of injection site varied from 1 to more than 7 days. No patients complained of local discomfort or pain. Mild local bleeding at the site of drug injection was observed in seven cases. No increase in the intensity of symptoms was observed during the infusion of ketorolac. J Pain Symptom Manage *1994;9:119–121.*

Key Words
Ketorolac, subcutaneous, cancer pain

Introduction

Continuous subcutaneous delivery with a syringe driver or pump is a useful and valid alternative to other forms of parenteral drug administration for the control of symptoms in patients with advanced malignancy.[1,2] Few studies, however, have been published concerning the tolerability of nonsteroidal antiinflammatory drugs (NSAIDs) administered via the subcutaneous route.[3]

NSAIDs represent the first pharmacologic approach to the management of cancer pain as well as a means for continuing therapy at all stages of malignancy. Among new molecules in this category, tromethamine ketorolac displays a good, nonopioid analgesic activity free of effects on the central nervous system.[4]

This preliminary study was conducted to assess the tolerability of tromethamine ketorolac administered continuously by the subcutaneous route in patients with cancer pain.

Method

Ten patients (five men and five women) participated in the study. The mean age was 56 years (SD = 10.6 years; range, 40–73 years). All patients had somatic and visceral pain due to advanced malignancy and were attending the Palliative Care Division of the National Cancer Institute. Clinical characteristics are summarized in Table 1.

Patients with pain of neuropathic origin and those with known allergies to salicylates or ketorolac were not included in the trial. All

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Table 1
Patient Characteristics

Case no.	Gender	Age	Primary tumor site	Type of pain suffered	Previous drug therapy
1	M	55	Prostate	Somatic	Piroxicam
2	M	53	Kidney	Somatic	Nimesulide
3	F	48	Breast	Somatic	Ketorolac
4	F	61	Colon	Visceral	Ketorolac
5	F	64	Breast	Somatic	Diclofenac
6	F	73	Breast	Somatic	Diclofenac
7	F	40	Breast	Somatic	Diclofenac
8	M	62	Colon	Visceral	Diclofenac
9	M	63	Thyroid	Somatic	Ketorolac
10	M	41	Lung	Somatic	Diclofenac

patients were already being treated with other NSAIDs, alone or in association with opioids.

Five patients had bone pain. One had visceral pain, one had pain due to soft tissue invasion, and three had pain of a mixed type. In all cases, pain was effectively controlled by previous therapeutic measures before starting the trial.

Ketorolac was administered by continuous infusion through a 10-mL syringe driver at a rate of 0.4 mL/hr. The syringe was attached to a polyvinyl extension tube and 25-gauge "butterfly" needle, which was inserted in the subcutaneous tissue of the thoracic subclavicular area. Thirty mg ketorolac ampules were diluted with physiologic salt solution.

The starting dose was 90 mg/day, which was increased to 120 mg/day if needed. Treatment duration was 1 week. The following parameters were assessed:

1. Presence or absence of pain at the site of injection was evaluated daily.

2. Pain was self-assessed with the help of a special checklist on which the patient noted the number of sleep hours and the severity and duration of pain on an ordinal verbal scale of five words. Each word was assigned an arbitrary value: mild = 1, moderate = 2.5, exhausting = 5, terrible = 7.5, and killing = 10. The average daily pain score is obtained by computing the hours of pain, multiplying them by the assigned severity value, and adding the products (Integrated Pain Score). The potential range of scores was 0 to 240.[5]

3. The following symptoms were assessed with a four-level verbal ordinal scale (no, a little, much, and very much) at baseline and at 1 week of ongoing treatment: lack of appetite, nausea, vomiting, dyspepsia, constipation, pyrosis, xerostomia, diarrhea, and sweating.

4. The frequency of needle changes was noted.

Results

Throughout the subcutaneous infusion of ketorolac, none of the patients experienced inflammatory reactions or burning at the site of butterfly insertion. Seven of ten patients showed mild local bleeding, which necessitated repositioning of the needle. In three patients, the injection site remained unchanged for the study period (1 week). In five cases, the injection site was changed once; in one patient it was changed twice; and only one (female) patient, with a low platelet count, required butterfly replacement almost every day. Other coagulation data were normal in all patients.

Pain control was acceptable in all patients. A change in the pain score was recorded only in cases 5, 6, and 9 (Table 2). There was no

Table 2
Integrated Score at Intake and on Day 7 of Treatment

Case no.	Day 0	Day 7	Ketorolac dose (final)
1	48	38	120
2	52.5	48	120[a]
3	32	30	90
4	46	42	120[a]
5	35	18	90[a]
6	28	47	120[a]
7	14	12	90
8	20	20	90
9	49	22	120
10	35	35	90[a]

[a]Patient treated concurrently with strong opioids.

worsening of symptoms during ketorolac infusion except for xerostomia and sweating, which increased in three out of ten patients. All patients expressed a favorable judgment of the test treatment in terms of subjective acceptability of the infusion modality, side effects, and degree of analgesia.

Discussion

NSAIDs are not commonly administered by subcutaneous infusion. Our experience raises several interesting points:

1. Ketorolac was tolerated via continuous subcutaneous pump infusion, which is the first choice alternative to oral administration in the treatment of cancer pain with drugs for which this form of delivery is suitable.

2. Data on the bioavailability of ketorolac after subcutaneous administration are not known and should be sought in order to support this form of treatment.

3. The clinical usefulness of this treatment needs to be confirmed by large studies designed to assess the end point of pain control; this cannot be addressed by our limited case series.

4. It is evident that the regular occurrence of bleeding at the injection site can constitute an obstacle to the treatment; further studies are needed to evaluate this finding, although a role of platelet dysfunction can be hypothesized on the basis of our clinical observation.

References

1. Ventafridda V, Spoldi E, Caraceni A, Tamburini M, De Conno F. The importance of continuous subcutaneous morphine administration for cancer pain control. The Pain Clinic 1986;1:47–55.

2. Bruera E. Subcutaneous administration of opioids in the management of cancer pain. In: Foley KM, Bonica JJ, Ventafridda V, eds. Advances in pain research and therapy, vol 16. New York: Raven, 1990:303–316.

3. Toscani F, Barosi K, Camerini S, Gallucci M. Sodium naproxen: continuous subcutaneous infusion in neoplastic pain control. Palliat Med 1989;3:207–211.

4. Buckley MMT, Brodgen RN. Ketorolac. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential. Drugs 1990;39:86.

5. Ventafridda V, De Conno F, Di Trapani P, et al. A new method of pain quantification based on weekly self-descriptive record of the intensity and duration of pain. In: Bonica JJ, Lindblom U, Iggo E, eds. Advances in pain research and therapy, vol 5. New York: Raven, 1983:891–895.