PHARMACY PRACTICE

Cost Implications of Ketorolac Therapy

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Ketorolac is a nonsteroidal anti-inflammatory drug (NSAID) which is currently being marketed as an analgesic for postoperative pain.[1] Because of the high cost of the drug relative to conventional therapy, it has attracted much discussion about the issue of cost effectiveness.[2] The manufacturer and some authors have suggested that total cost and not just direct drug cost should be considered.[3,4] One aspect that influences total cost is the morbidity associated with drug toxicity.[4] We present three cases of adverse effects secondary to ketorolac which emphasize the need for careful assessment of any new therapy.

Case 1

A 32 year-old non-smoking female was seen in the emergency department after feeling unwell for two days and after a syncopal episode the previous day. She also reported black stools for three to four days. Ten days prior to admission she had reconstructive surgery of her mandible and maxilla. She was subsequently prescribed penicillin V 300 mg and ketoralac 10 mg, both to be taken orally four times daily, with which she had complied. In the emergency room, she experienced hematemesis and complained of lightheadness.

Social and family history were unremarkable. She consumed no alcohol. The patient had a previous history of non-ulcer dyspepsia several years prior, which had responsed to six months of cimetidine without recurrence. Past medical history was otherwise negative.

On examination, the patient appeared pale. There was no stigmata of liver disease. Her supine blood pressure was 112/70 mmHg with a heart rate of 108 beats per minute. Upon standing, her blood pressure fell to 98/60 mmHg and her heart rate increased to 132 beats per minute. Physical examination was remarkable for a hematoma in her mouth and her jaw was wired. Her abdomen was soft, non-tender without masses. Bowel sounds were present and rectal examination revealed dark stool positive for occult blood. Serum biochemistries were normal except for the following: a WBC of 10.7 x 10^9/L (N 4-9), a BUN of 8.9 mmol/L (N 2.5-7) and a chloride of 109 mmol/L (N 95-105). Hemoglobin was markedly depressed at 60 g/L (N 115-160) with a hematocrit of 0.18 (N 0.35-0.47). Plasma thromboplastin time was slightly low at 25 seconds (N 26-37). Electrocardiograph showed sinus tachycardia.

Oral medications were discontinued and the patient was transfused with three units of red blood cells, given crystalloid and commenced on intravenous ranitidine. She underwent endoscopy the following morning, which revealed bright red blood and "coffee grounds" across the greater curvature of the stomach. No lesions were seen in the esophagus, fundus, antrum or duodenum. A small umbilicated mound in the upper body of the posterior wall was seen but was not actively bleeding. This potential Dieulafoy's lesion was injected with 0.5 ml of absolute alcohol.

The patient's hospital stay thereafter was unremarkable and she was discharged home with a prescription for ranitidine and ferrous sulfate.

Case 2

An 82 year-old male was admitted to hospital because of an upper gastrointestinal hemorrhage. The patient had a dark stool one day prior to admission and vomited one to two spoonfuls of blood on the day of admission before coming to hospital. The patient experienced no loss of consciousness, no lightheadedness, minimal nausea and transient abdominal pain that resolved spontaneously. In the emergency room, the patient vomited approximately 600 mL of bright red blood. The patient had been prescribed ketorolac 10 mg po tid four days earlier for arthritic complaints.

The patient's past medical history involved remote cholecystectomy and prostatic surgery. He also had a history of hypertension for which he had been taking an undisclosed med-

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ication for several years. He had a remote past history of smoking. There was no history of significant ethanol intake. Review of systems was remarkable only for vague right leg pain which the patient considered to be arthritis.

On physical examination, the patient was in no acute distress. There was no pallor or stigmata of liver disease. His supine blood pressure was 145/80 mmHg which fell to 120/60 mmHg upon standing. His heart rate increased from 100 beats per minute lying to 120 beats per minute standing. The rest of the examination was normal except for the presence of an S_4 heart sound. On examination of the abdomen, there were no ascites, tenderness, masses, organomegaly, or bruits; bowel sounds were normal. Rectal exam was normal.

The hemoglobin and hematocrit were 112 g/L and 0.34 respectively on admission which fell to 84 g/L and 0.24 upon rehydration. BUN was slightly elevated at 11.4 mmol/L.

The patient underwent endoscopy. The esophagus had changes consistent with Barrett's esophagus at 23 - 34 cm from incisors. There were no varices. A hiatus hernia of 4 cm was noted. In the antrum, an ulcer of 0.5 cm without recent hemorrhage was seen. The duodenum was free of ulcers but duodenitis was present. On retroflection of the endoscope into the hernia, two large acute gastric ulcers were seen immediately beneath the gastroesophageal junction. One was 1-1.5 cm and had numerous tiny red dots; the other was 0.5-1 cm and had adherent clot. Both were injected with 0.5 ml of absolute alcohol. Following hydration, two units of packed red blood cells were administered. The patient was treated with intravenous ranitidine and subsequently, omeprazole when the intravenous was discontinued. He improved and was discharged home after five days.

Case 3

A 32 year-old female with a long history of endometriosis was transferred to our facility because of long standing right lower quadrant pain for approximately three months and recent onset of epigastric pain associated with nausea and vomiting. She had recently been seen at another facility where she had undergone a number of procedures including an abdominal scan and abdominal and pelvic ultrasound, none of which helped identify a cause for the pain. She received ketorolac 30 mg intramuscularly q4 - 6h as needed for pain control for several doses prior to being transferred to our facility for further investigation of her pain. In addition to the ketorolac, she was receiving ranitidine 150 mg po bid and bisacodyl suppositories prn. Her past medical history was remarkable for a hysterectomy with a left salpingo-opherectomy and a hiatus hernia. She reportedly had multiple allergies to medications including meperidine, codeine, morphine, erythromycin, tetracycline and diphenhydramine.

On admission the patient was relatively comfortable, vital signs were stable and she was afebrile. Her abdomen was tender to palpation in the right upper quadrant. Her abdomen was soft and bowel sounds were present. Her hemoglobin at the time of admission was 123 g/L. Serum amylase was normal. The patient refused oral diet and indicated she had not eaten for several days prior to admission to our facility, claiming that it made her abdominal pain worse.

Ketorolac parenteral therapy was continued q4 - 6h as needed, usually every six hours but for several days she did receive the drug up to five times daily. Because of ongoing complaints of abdominal pain unameliorated by ketorolac, the patient underwent endoscopy on day four, which revealed inflammation at the lower esophageal sphincter consistent with gastroesophageal reflux. Old blood was noted in the stomach and on the inferior posterior surface of the duodenum was a large necrotic duodenal ulcer which may have been perforating into the pancreas. The ulcer was treated with omeprazole and ketorolac was discontinued.

DISCUSSION

As an inhibitor of prostaglandin synthesis, ketorolac possesses greater systemic analgesic activity relative to anti-inflammatory potency than do NSAIDs such as indomethacin and naproxen.[5] Like other NSAIDs gastrointestinal complaints have been reported. One trial of 553 patients receiving ketorolac for chronic pain had a reported incidence of gastrointestinal pain, dyspepsia and nausea of 12%, 11% and 7%, respectively.[6] In that study, 1.6% of patients developed peptic ulcer disease or upper gastrointestinal bleeding vs. 1.1% of ASA users. Thus, the drug is indicated only for short term management of pain.[1] Bleeding complications have been reported in post marketing surveillances of ketorolac and as of April 1992 the Health Protection Branch Adverse Drug Reaction Reporting program had received 11 reports of gastrointestinal hemorrhage, two of which were fatal.[7]

In this series, several issues regarding risk of toxicity merit mentioning. Only one of the three cases involved an older patient, although advanced age is described as a risk factor.[8] In the first case, the patient reported minimal oral intake for a short period after her surgery and that she was confined to bed. Traditionally, patients have been advised to take their NSAID medications with food and remain upright for approximately 30 minutes after ingestion.[9] It would seem prudent to attempt to follow this guideline until evidence to the contrary is available. Further, as in case number three it would be ad-

visable not to prescribe any NSAID, including ketorolac, for patients with undiagnosed abdominal pain.

The role of NSAIDs has been the topic of some discussion as the use of these agents particularly those with long half-lives may increase the risk of postoperative complications.[10] As well, ketorolac like other NSAIDs has been shown to prolong bleeding time and inhibit platelet aggregation.[11] The role of NSAIDs in these complications when given postoperatively is unknown but may have been a factor in our cases.

To calculate the costs of morbidity associated with ketorolac toxicity, five days of hospitalization at $700/day was chosen since it approximated the stay of two patients. The costs of either ranitidine 150 mg po bid or omeprazole 20 mg po daily were used to calculate the cost of outpatient therapy for six weeks. Therefore, in our limited exposure to this drug, the total cost avoidance had a non-NSAID been used, was more than $10,000 (about $3,500 per patient).

While ketorolac has been proven a useful analgesic, the risks require careful assessment in light of these toxicities. Prior to inclusion of a drug such as ketorolac onto formulary, the impact of associated costs needs to be addressed.

REFERENCES

1. Product Monograph Toradol, 1992.
2. Kostrzewa DM. Is ketorolac more cost effective? (Letter) *Am J Hosp Pharm* 1991; 48:2128.
3. Mayo M, Bynum L. Is ketorolac more cost effective? (Letter) *Am J Hosp Pharm* 1991; 48:2128.
4. Dukes MNG. Economic costs of adverse drug reactions. *Pharmacoeconomics* 1992; 1:153-4.
5. Buckley MM-T, Brogden RN. Ketorolac. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential. *Drugs* 1990; 39:86-109.
6. Rubin P, Yee JP, Ruoff G. Comparison of long-term safety of ketorolac tromethamine and aspirin in the treatment of chronic pain. *Pharmacotherapy* 1990; 10:105-6 S.
7. Anon. GI bleeding with Toradol®. Canadian Adverse Drug Reation Newsletter. 1992; 2:3-4.
8. Fries JF, Williams CA, Block DA, et al. Nonsteroidal anti-inflammatory drug associated gastropathy: incidence and risk factor models. *Am J Med* 1991; 91:213-22.
9. Anon. Advice for the patient. Drug information in lay language. Vol II 9th edition 1989. USP DI pg 146.
10. Connell CS, Panush RS. Should nonsteroidal anti-inflammatory drugs be stopped before elective surgery: *Arch Intern Med* 1991; 151:1963-6.
11. Greer IA. Effects of ketorolac tromethamine on hemostasis. *Pharmacotherapy* 1990; 10:71-6 S.