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Long-term ketorolac use: an evidence-based summary of safety and efficacy

Chronic pain is a complex condition encountered commonly in clinical practice. Nonsteroidal anti-inflammatory drugs (NSAIDs) may be useful for a variety of chronic pain syndromes, either used alone, or in conjunction with other medications. While many NSAIDs are indicated for chronic conditions, such as osteoarthritis or rheumatoid arthritis, ketorolac (Toradol®) is indicated only for short-term use (i.e., maximum of seven days oral therapy or two days intramuscular therapy).[1] This summary provides a brief review of the literature regarding long-term use of ketorolac.

Clinical Trials

Only one clinical trial examining long-term use of ketorolac was identified. A randomized, double-blind trial of one year duration compared the safety and efficacy of oral ketorolac 10 mg (n=553) and ASA 650 mg (n=270), each taken up to four times daily as needed, in patients with various chronic pain states.[2] Osteoarthritis was the primary source of pain in 74% and 71% of patients on ketorolac and ASA, respectively.[2] Average daily doses reported were approximately 30 mg for ketorolac and 1850 mg for ASA.[2] The dropout rate due to upper gastrointestinal (GI) complaints in the first week was 2.4% in the ketorolac group versus 0.4% in the ASA group; however, dropout rates for GI-related pain or discomfort were similar for both agents after the first two weeks.[3] Of note, a higher proportion of patients in the ketorolac group completed the 52 weeks of treatment, as more patients in the ASA group withdrew for reasons related to lack of efficacy.[2] Crude rates (defined as the number of participants reporting an event at least once during the study) of peptic ulceration (PU) or upper GI bleeding likely related to study drugs were 1.6% (n=9) for ketorolac and 1.1% (n=3) for ASA.[2] Higher crude rates of renal dysfunction (defined as serum creatinine values > 177 µmol/L) were also reported in ketorolac-treated patients (1.8%) compared with ASA-treated patients (1.2%).[3] It should be noted, however, that crude rates are biased in favour of ASA, since patients remained on ketorolac significantly longer than ASA.[2,3] Nonetheless, after adjustment for time, ketorolac-treated patients still had a higher cumulative occurrence of ulcers or upper GI bleeding than ASA-treated patients over a six month period.[3] Investigator-rated overall therapeutic effect scores (a measure of efficacy) favoured ketorolac over ASA, with 48% of patients on ketorolac receiving a rating of good or very good, versus 29% of patients on ASA.[2]

Case Reports

A few case reports[4-7] and case series[4,8] have documented long-term ketorolac use. Parenteral ketorolac, administered

intramuscularly, intravenously by bolus injection or continuous infusion, or by continuous subcutaneous infusion, has been reported to provide good pain control in patients with cancer-related pain inadequately controlled by conventional therapies.[4-6,8] Doses ranged from 60 to 240 mg/day for periods ranging from three days to nine months. Most patients received concomitant cytoprotective therapy with misoprostol or famotidine. Reductions in opioid requirements and opioid-related adverse effects were documented for some patients.[4,8] In general, therapy was reported to be well tolerated based on results of GI, renal, and hematological parameters, where available; however, one patient developed a perforated esophagus and elevated serum creatinine, possibly related to ketorolac use.[5] Of note, this patient did not receive cytoprotective therapy. Oral administration of ketorolac 10 mg four times daily for chronic, refractory low back pain was reported to cause weight gain of 20 kg and 29.5 kg in two obese patients receiving the drug for 12 months and 10 months, respectively.[7]

Summary and Evaluation

Few reports of long-term use of ketorolac were found. Case reports suggest that extended use of parenteral ketorolac may be beneficial for managing chronic pain in cancer patients. Oral ketorolac appears to be helpful for other nonmalignant chronic pain states, primarily osteoarthritis. However, limitations of the current literature preclude the applicability of these results to general practice. Firstly, the above-mentioned randomized, controlled trial did not report on comparability of baseline patient demographics, such as age, medical history, medication use (e.g., anticoagulants, corticosteroids, diuretics), smoking status, and alcohol intake, all of which may have influenced study outcomes. In addition, the authors did not include measures of statistical significance with respect to adverse events, making it difficult to interpret the impact of apparent differences. Furthermore, it is not possible to draw firm conclusions regarding the efficacy of ketorolac for specific types of pain, as patients with various types of pain were included in the study. Nor can case reports provide reliable information regarding efficacy.

Randomized, controlled trials comparing ketorolac with nonaspirin NSAIDs, including the COX-2 inhibitors, in the treatment of chronic pain are lacking. However, results of a case control study comparing the GI toxicity of different NSAIDs suggest that ketorolac was approximately five times more likely to cause upper GI bleeding than other NSAIDs.[9] The excess risk of this complication was apparent within the first week of therapy, and was higher with longer durations.[9] A postmarketing surveillance study also reported an increased risk of GI bleeding with parenteral ketorolac when given for more than five days, as compared with therapy for five days or less.[10] These findings indicate that the incidence of serious GI events appears to increase with duration of treatment. Therefore, when chronic use is required, it would be prudent to select other NSAIDs for which long-term safety and efficacy data are available.

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