MEDICAL MYTHOLOGY

Myth: Parenteral ketorolac provides more effective analgesia than oral ibuprofen

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Introduction

Acute pain is an extremely common presenting symptom to the emergency department (ED), making it imperative that emergency physicians provide adequate, safe and cost-effective analgesia. Nonsteroidal anti-inflammatory drugs (NSAIDs) are often first-line treatments for moderate to severe pain. Physicians can choose between intramuscular (IM) or intravenous (IV) ketorolac and an oral NSAID. The mechanism of action (reversible inhibition of prostaglandin synthesis at the level of cyclooxygenase) is identical irrespective of the route the medication is given.[1] Despite the similar pharmacodynamics, many physicians believe that parenteral ketorolac is more efficacious, despite a greater cost and a more invasive route of administration. To investigate this myth (i.e., that parenteral ketorolac provides greater analgesic effect than an oral NSAID), we conducted a review of the literature, with specific focus on ibuprofen as the prototypical — and least expensive — oral NSAID.

Methods

The terms "ketorolac" and "ibuprofen" were searched in MEDLINE and PubMed, revealing 17 and 67 articles, respectively. Articles were limited to English language and those involving human subjects. All abstracts were reviewed. Articles directly comparing oral ibuprofen with IM or IV ketorolac were included. To ensure no important papers were missed, an ancestral search of identified articles was also performed.

Results

In 1994, Wright and associates evaluated the effectiveness of a single dose of 800 mg of oral ibuprofen (n = 95) versus 60 mg of IM ketorolac (n = 70). This was a retrospective analysis of data collected during a prior prospective survey of pain management efficacy, in patients presenting to the ED with acute pain due to a large variety of causes.[2] Using the 100-mm visual analog pain scale (VAS) they found a mean score reduction of 34 in the ibuprofen group and 35 in the ketorolac group. They concluded that the 2 have almost identical efficacy in those presenting with acute pain of varied sources, and that unless oral administration is contraindicated, ibuprofen is superior given its ease of administration, its significantly lower cost, and the lack of pain associated with administration.[2]

In 1995, Turturro and colleagues compared 800 mg of oral ibuprofen with 60 mg of IM ketorolac in a prospective, double-blind, randomized trial of 82 patients presenting to the ED with acute traumatic musculoskeletal pain.[3] They used the 100-mm VAS to quantify pain at baseline, 15, 30, 45, 60, 75, 90 and 120 minutes post dosing. They found no significant differences in mean pain scores at baseline or at any time point throughout the 2-hour period. They noted that the ibuprofen group exhibited lower mean pain scores in the later intervals of the study; however, it was not statistically different. They concluded that oral ibuprofen and IM ketorolac provide similar analgesia with similar onset of action in minor-to-moderate acute musculoskeletal pain and reasoned that IM ketorolac should be reserved for those

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patients with contraindications to oral intake due to its painful administration and its higher cost (170 times that of ibuprofen at their institution at the time of the study).[3]

In yet another prospective, randomized, double-blind study in the ED, Neighbour and Puntillo investigated the analgesic efficacy of 60 mg of IM ketorolac versus 800 mg of oral ibuprofen in patients with self-assessed pain scores of 5, 6, 7 or 8 on a numerical rating scale of 0–10 (0 corresponding to "no pain" and 10 corresponding to "worst possible pain") for a variety of pain etiologies.[4] Patients' pain levels were assessed at 0, 15, 30, 45, 60, 90 and 120 minutes after administration of analgesic. They found no statistical differences in pain levels between study groups at any time point in the study, further emphasizing conclusions reached in the 2 prior ED studies.

In a 1998 prospective, randomized, double-blind study conducted in surgical patients, Mixter and coworkers investigated the use of 60 mg of IV ketorolac at the time of trocar insertion versus 800 mg of oral ibuprofen 1 hour before surgery in laparoscopic hernia repairs.[5] All patients were discharged within 5 hours of completion of surgery, and patients were instructed to take ibuprofen 400 mg orally every 4 hours for 24 hours regardless of pain level. They measured pain using the 100-mm VAS at time of discharge and found no significant difference between the ketorolac group (VAS = 35) and the ibuprofen group (VAS = 30). They also measured pain 18 hours after discharge, and found an identical score in the 2 groups (VAS = 20). Like the previous ED studies comparing the 2 drugs, the authors concluded that oral ibuprofen offers equal pain control at lower cost and reduced potential for adverse drug events for post-surgical patients.[5]

Interestingly, in one of the first studies comparing ketorolac with ibuprofen in post-op patients, Morrison and Repka did find a significant difference in pain control.[6] In this prospective, randomized, double-blind study, they compared a single dose of 60 mg of IV ketorolac intraoperatively (n = 20) with a single dose of 600 mg of ibuprofen 30–45 minutes after completion of strabismus surgery (n = 20). Pain was assessed with the 100-mm VAS. At 2 hours post-op, the VAS for ketorolac patients was 15 and for the ibuprofen patients it was 50. At 5 hours post-op, the VAS for ketorolac patients was 20 and for the ibuprofen patients it was 44. They concluded that IV ketorolac was more effective than oral ibuprofen in controlling postoperative pain in patients undergoing strabismus surgery. However, the study design needs further scrutiny before taking this data at face value: there were multiple methodological flaws, and the results, as the authors themselves point out, should be interpreted with caution.[6] In their study, the oral ibuprofen was not distributed in its commercially available formulation; instead, it was crushed and administered in unmarked capsules, which may have altered the analgesic's pharmacodynamics. Even more importantly, in the protocol IV ketorolac was given at least 30–45 minutes before the oral ibuprofen was administered. Multiple studies have shown that as patients receive repetitive painful stimuli over time without analgesia, the overall total perception of pain significantly increases.[7,8] Those patients in this study receiving oral ibuprofen late in the course of their care had time to suffer from this so-called "wind-up" phenomenon, which is a complex neurotransmitter-based phenomenon that results in "pain begetting pain."[9] It is impossible to draw conclusions from a study comparing the efficacy of 2 drugs when the oral format was given well after the IV preparation. A balanced study would instead have allowed the oral format to be given *prior* to the IV one.

Discussion

The studies discussed in this paper dealt with patients who had a wide variety of pain syndromes, but there is some anecdotal evidence and a limited number of published studies touting the efficacy of parenteral ketorolac when used specifically for the treatment of renal colic. It has been shown in multiple studies that ketorolac is as good as, if not better than, low dose meperidine in providing effective pain relief in renal colic.[10–14] Similar results were found in studies comparing the efficacy of ketorolac with diclofenac in patients with renal colic.[15,16] Safdar and colleagues compared ketorolac to morphine for the treatment of acute renal colic using a prospective randomized, controlled, double-blinded design.[17] Patients received either 5 mg of IV morphine or 15 mg of IV ketorolac at time zero with a repeat dose of the same at 20 minutes. A third group received both agents at both time intervals. They found no significant difference in efficacy between the ketorolac and morphine groups in relief of pain, but did find a significant reduction in pain in the combination group. They therefore concluded that a combination of morphine and ketorolac provides greater analgesia than using either of the agents alone.[18] Despite the plethora of trials comparing ketorolac with narcotics and proving the utility of NSAIDs for the treatment of renal colic, there are no identifiable studies comparing parenteral ketorolac with oral ibuprofen in this setting. It is quite possible that, as in the treatment of other acute pain syndromes, ibuprofen may provide equal analgesia. Given that vomiting is frequently a part of the presentation of renal colic, a parenteral NSAID may be preferred.

Many physicians continue to administer IM or IV ketorolac regardless of the aforementioned studies, perhaps due to the belief that patients respond better to parenteral analgesia

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because the patients consider them "stronger" medicines. Schwartz and associates investigated this perceived placebo effect in a fascinating prospective, randomized, double-blind study in which patients were unknowingly given 800 mg oral ibuprofen in a flavoured drink and then given either a placebo IM injection or a placebo pill. In this interesting study design, neither group received IM medication. They found no significant difference in pain reduction via the VAS and concluded that the use of IM administration of NSAIDs for pure placebo effect appears unwarranted.[18]

In addition to a lack of improved efficacy and no benefit from a placebo injection effect, there are potentially serious downsides to this tactic. First, there is the risk of a needle-stick injury to health care personnel from unnecessarily using a parenteral medication when an oral form will work just as well. Second, even though all NSAIDs have the potential to exacerbate renal dysfunction, parenteral ketorolac seems particularly potent in this regard. In fact, in several European countries the 60-mg form of ketorolac was taken off the market due to its association with acute renal failure. It is also interesting to note that the manufacturer suggests that the oral dose of ketorolac be 10 mg but the parenteral form be 30–60 mg. Which other drug has a higher dose when given parenterally than orally? The exact implications of this dosing conundrum remain unclear, although an unacceptably high risk of gastrointestinal adverse events is felt to be the root cause of the lower oral dose.

Conclusion

The higher cost of ketorolac, the pain and difficulty associated with its administration, the risk of extravasation, and the exposure of practitioners to possible needle-stick injuries, all argue that there is no use for IM or IV ketorolac over oral ibuprofen in the ED for routine analgesia, unless oral administration of ibuprofen is unfeasible or contraindicated. Only in specific acute pain syndromes associated with nausea and vomiting, like renal colic, may its use be warranted. The belief that IM/IV medications are perceived as being stronger than oral medications and therefore result in a more powerful placebo effect has also been shown to be false. With the exception of 1 study in post-op patients with a significantly flawed study design, the evidence overwhelmingly shows that inexpensive and relatively safe oral ibuprofen has equal efficacy to the more expensive and potentially dangerous IM or IV ketorolac.[2–6]

Competing interests: None declared.

Disclosures: Dr. Herbert owns and edits EM:RAP and CMEdownload.com, a Web site that includes online EM education products.

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