Original Article

Patterns of Ketorolac dosing by emergency physicians

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BACKGROUND: Ketorolac tromethamine is a non-steroidal anti-inflammatory drug (NSAIDs) that is widely used in the emergency department (ED) for the treatment of moderate-to-severe pain. Ketorolac, like other NSAIDs, exhibits an analgesic ceiling effect and previous research suggests that 10 mg is possibly the ceiling dose. Do the patterns of ketorolac dosing by emergency physicians follow its analgesic ceiling dose?

METHODS: This was a single center retrospective, descriptive study to characterize patterns of ketorolac administration in ED patients. Data for all patients who received ketorolac during the ten year study period from January 1, 2003 to January 1, 2013 were collected from the electronic medical record of an urban community ED with an annual volume of 116 935 patients.

RESULTS: There were 49 605 ketorolac administrations during the study period; 38 687 (78%) were given intravenously, 9 916 (20%) intramuscularly, and 1 002 (2%) orally. Through the intravenous route, 5 288 (13.7%) were 15 mg, 32 715 (84.6%) were 30 mg, 15 (0.03%) were 60 mg, and 669 (1.7%) were other varying doses. Through the intramuscular route, 102 (1.0%) were 15 mg, 4 916 (49.6%) were 30 mg, 4 553 (45.9%) were 60 mg, and 345 (3.5%) were other varying doses. The most common diagnoses at discharge were renal colic (21%), low back pain (17%) and abdominal pain (11%).

CONCLUSION: The data show that ketorolac was prescribed above its ceiling dose of 10 mg in 97% of patients who received intravenous doses and in 96% of patients receiving intramuscular doses.

KEY WORDS: Ketorolac; NSAID; Analgesic ceiling; Acute pain; Prescription pattern

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INTRODUCTION

Ketorolac tromethamine is a non-steroidal anti-inflammatory drug (NSAID) that is widely used in the emergency department (ED) for the treatment of moderate-to-severe pain. Ketorolac is available in oral, parenteral, intranasal and ophthalmic solution forms and possess significant analgesic potency. Ketorolac provides several advantages over other currently available analgesics as it is not associated with tolerance, euphoria, withdrawal effects, respiratory depression, nausea and vomiting, urinary retention or sedation while conferring an opioid sparing effect. Nonetheless, its use is limited by a range of severe side effects including interstitial nephritis, renal failure, hypersensitivity reactions,

with gastrointestinal (GI) hemorrhage being the most concerning.^[1,2]

The concept of "analgesic ceiling" postulates that the dose above the one that results in analgesic effect will not provide additional pain relief and might contribute to side effects.^[1] Despite the absence of randomized controlled trials in emergency medicine literature comparing analgesic efficacy of different doses of parenteral ketorolac, the available data strongly supports the analgesic ceiling dose of ketorolac at 10 mg.^[1,2] In spite of this, the majority of research conducted on ketorolac in the ED and recommendations in emergency medicine textbooks advocate three-to-six fold higher dosages.^[3–6] In our study, we sought to determine whether

prescription practices of ED physicians followed the analgesic ceiling dose of ketorolac during parenteral administration.

METHODS

We conducted a single center retrospective, descriptive study to characterize patterns of ketorolac administration in ED patients. No patient or provider-level identifying information were included and all data gathered was aggregated. Therefore the study was exempt from informed consent requirements by the Maimonides Medical Center institutional review board and was given the approval number of 2013-10-07.

Study setting and population

The study was performed at an urban New York City community teaching hospital with a total ED patient annual census >120 000.

Study protocol and data collection

Data for all patients who received ketorolac during the ten year study period from January 1, 2003 to January 1, 2013 was gathered from the emergency department information system (Healthmatics ED, Allscripts, Chicago, IL).

The following data elements were extracted from the electronic medical record for each patient and administration through the use of a custom Perl script accessing the Allscripts backend database: route, dosing, date of administration, diagnosis and ICD9 codes (primary, secondary, tertiary, and quaternary), patient age, and patient sex.

Aggregate numbers were then generated by using simple arithmetic within the Perl script to determine total administrations, administrations per route, median age per gender with percentages generated through spreadsheets.

RESULTS

There were 49 606 ketorolac administrations given to 34 026 patients over the ten year period, of which 38 688 (77.99%) given intravenously, 9 916 (19.99%) were given intramuscularly, and 1 002 (2.02%) were given orally. Of those that received intravenous administration, 5 288 (13.67%) were given 15 mg, 32 715 (84.56%) were given 30 mg, 15 (0.03%) were given 60 mg, and 669 (1.7%) were given other varying doses (Table 1). Of those that received intramuscular administration,

Table 1. The percentage of different doses of ketorolac administered via intravenous and intramuscular routes

Route	Doses	Frequency	Percent
IV	10 mg	203	0.5
	15 mg	5 288	13.8
	30 mg	32 714	85.6
	60 mg	15	<0.1
IM	10 mg	361	3.7
	15 mg	57	0.6
	30 mg	4 896	49.6
	60 mg	4 553	46.1

Table 2. The 10 most common diagnoses during the study period

Most common diagnoses	Percent
Calculus of kidney (592.0), calculus of ureter (592.1), urinary calculus (592.9)	10.92
Lower back pain (724.2), backache unspecified (724.5), sciatica (724.3), other symptoms referable to back (724.8)	8.98
Abdominal pain specified and unspecified (789)	7.06
Chest pain unspecified (786.5), other chest pain (786.59), painful respiration (786.52), cough (786.2), shortness of breath (786.05), precordial pain (786.51)	5.48
Headache (784.0), other headache syndromes (339.89), tension headache (307.81)	4.86
Urinary tract infection (599.0), acute pyelonephritis (590.1), pyelonephritis unspecified (590.8)	4.36
Renal colic (788.0), dysuria (788.1)	3.74
Pain in joint (719)	2.6
Other and unspecified ovarian cyst (620.2), torsion of ovary (620.5)	1.05
Unspecified viral infection (79.99)	1.02

102 (1.02%) were given 15 mg, 4 916 (49.57%) were given 30 mg, 4 553 (45.92%) were given 60 mg, and 345 (3.48%) were given other varying doses.

The median age of male patients administered ketorolac was 42 years of age with the first and third quartile being 30 and 53, respectively. The youngest patient was 2.5 months of age and the oldest at 106 years. The median age of female patients administered ketorolac was 42.5 years of age with the first and third quartile being 28 and 54, respectively. The youngest patient was 1.4 years of age and the oldest at 102 years. Of the 34 026 patients who received ketorolac, 5 243 were at least 65 years old.

The most common diagnoses at discharge were calculus of the ureter and kidney (10.92%), lower back pain (8.98%), and abdominal pain (7.06%) (Table 2).

DISCUSSION

The results of the study demonstrate that ketorolac was prescribed above ceiling dose in 97% of patients who received intravenous doses and in 96% of patients who received intramuscular doses. To the author's knowledge,

this is a first descriptive study in the EM literature that evaluated prescription practices of ketorolac for acute pain management in the ED in correlation with analgesic ceiling dose of ketorolac. The study clearly demonstrates that the analgesic dose of ketorolac was not followed in most if not all patients and that only 0.5% of patients in intravenous group and 3.7% in intramuscular group were given ketorolac in accordance with the 10 mg analgesic ceiling dose.

The earliest research on analgesic efficacy of ketorolac clearly demonstrated no added benefit in doses greater than 10 mg with respect to pain control. Staquet and colleagues^[7] in a placebo-controlled, double-blinded trial that evaluated intramuscular (IM) injections of ketorolac in doses of 10, 30, and 90 mg and a placebo in cancer-related pain demonstrated no difference in the degree of pain relief among any of the three doses. Minotti and colleagues^[8] designed a double-blind study comparing two single-dose regimens of IM ketorolac of 10 mg and 30 mg with 75 mg diclofenac for patients due to cancer-related pain and demonstrated no difference in pain relief for all three groups. Peirce and colleagues^[3] compared intravenous ketorolac with morphine for the relief of moderate-to-severe postoperative pain and for side effects in 125 women undergoing major abdominal gynecologic surgery. Patients were randomly assigned to receive an initial intravenous dose of ketorolac 10 mg, ketorolac 30 mg, morphine 2 mg, or morphine 4 mg, administered in a double-blind fashion. The results showed no significant differences among the treatment groups in terms of area under the time-effect curves for pain intensity differences or pain relief. Similarly, Brown and colleagues^[4] compared intravenous ketorolac and intravenous morphine for relief of postoperative pain in 122 patients who were randomly assigned to receive single intravenous injections of ketorolac 10 mg, ketorolac 30 mg, morphine 2 mg, or morphine 4 mg. The study demonstrated a lack of statistically significant differences among the two ketorolac doses of 30 mg and 10 mg and the high dose (4 mg) of morphine in terms of controlling acute post-operative pain. In addition, there is data demonstrating increased risk of hematoma formation, prolonged bleeding time and worsening post-operative bleeding after administration of a single dose of 15 or 30 mg of intravenous ketorolac. Cawthorn and colleagues^[5] in a retrospective analysis of perioperative ketorolac administration (15 mg or 30 mg single intravenous pushes) and rates of postoperative bleeding in patients who underwent reduction mammoplasty demonstrated that patients who received ketorolac were

at an increased risk of requiring surgical re-exploration for hematoma evacuation ($RR=3.6$; 95% confidence interval [CI] 1.4–9.6) and hematoma formation not requiring re-exploration ($RR=2.2$; 95%CI 1.3–3.6). Authors concluded that a single perioperative intravenous dose of ketorolac was associated with a greater than three-fold increase in the likelihood of requirement for surgical hematoma evacuation.

Bean-Lijewski and colleagues^[6] conducted a double-blind, placebo-controlled trial evaluating the effect of ketorolac as a single intramuscular dose of 0.75 mg/kg on bleeding time and postoperative pain in children and demonstrated prolongation of bleeding time by 53 ± 75 seconds ($P=0.006$). Singer et al^[9] conducted a similar trial for evaluating the effect of a single 60 mg intramuscular dose of ketorolac on 4-hour bleeding time in healthy volunteers. The results showed that bleeding time was increased from a mean baseline time of 3 minutes 34 seconds (± 1 minute 20 seconds) to a mean 4-hour post-injection time of 5 minutes 20 seconds (± 3 minutes 8 seconds). The mean prolongation of bleeding time was 1 minute 46 seconds (50% increase with 95%CI, 25%–75%).

Gallagher and colleagues^[10] conducted a chart review of 169 patients undergoing tonsillectomy who were given intravenous ketorolac and demonstrated a postoperative hemorrhage rate of 10.1% in comparison to a rate of 2.2% in those given opioid medication.

The study has several limitations. First, a retrospective study design provides no information about analgesic efficacy and side effects of ketorolac given intravenously or intramuscularly. Second, our electronic medical records allow clinicians to choose quickly between 15, 30, and 60 mg for IV doses and 30, 60 mg for IM doses in addition to manual input. Thus, order sets and pathways could influence clinician's prescriptive practices as physicians will take the most efficient and expedient path in medication ordering. Third, the establishment of the ketorolac ceiling dose in previous studies were done in very specific patient populations (spine stabilization surgery, cancer pain, gynecologic surgery) as such the external validity of the ceiling dose may not apply to the ED patient population. Fourth, ketorolac dosage formulations may vary by institution and provider patterns given that ketorolac is supplied in 15 mg and 30 mg vials. Lastly, based on percentage of patients receiving doses of ketorolac three-to-six times higher than suggested by an analgesic ceiling dose, it could be assumed that ED providers have been trained to use higher doses as recommended by manufacturers and emergency medicine Textbooks.

CONCLUSION

Ketorolac was prescribed above its analgesic ceiling dose of 10 mg in 99.5% of patients who received intravenous doses and 96.3% of those who received intramuscular doses. Based on these results, randomized trials in the ED comparing administration of the analgesic ceiling dose of parenteral ketorolac to traditionally utilized dosing regimens are needed to further evaluate the concept of achieving analgesic efficacy with smaller doses.

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Ethical approval: The study was approved by the Maimonides Medical Center institutional review board.

Conflicts of interest: The authors declare there is no competing interest related to the study, authors, other individuals or organizations.

Contributors: Soleyman-Zomalan E proposed the study and wrote the first draft. All authors read and approved the final version of the paper.

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