



Ceiling dose of Ketorolac in Treatment of Moderate to Severe Acute Pain in an Emergency Department Setting

Nicole Babiak, PharmD Candidate 2020¹

¹*University of Findlay College of Pharmacy*

Abstract

Ketorolac is a nonsteroidal anti-inflammatory medication that is commonly used in emergency department settings for patients with moderate to severe acute pain. Because ketorolac use is not recommended to exceed 5 days due to adverse effects, its use is most commonly seen for acute pain than chronic pain. Some cautions with this medication include increased risk for cardiovascular events, gastrointestinal complications, renal complications, and increased risk for bleeding. These adverse effects typically cause providers to refrain from use in an outpatient setting. Various studies look at ketorolac's ceiling dose in order to limit unnecessary amounts of drug administered to a patient. With this, various studies were taken into consideration to see what the ceiling dose for ketorolac is, and if providers follow the results of these studies. Results are conclusive that a ceiling dose of ketorolac is 10mg, as opposed to the typical dose of 30 to 60 mg; yet prescribers continue to administer greater than the ceiling dose for ketorolac.



Ketorolac (Toradol®) is a nonsteroidal anti-inflammatory drug that reversibly inhibits COX-1 and COX-2.¹ With this inhibition, there is prevention of the precursors of prostaglandins, with demonstrated efficacy to treat moderate to severe pain.² In 1990, ketorolac was first used to treat acute pain, more specifically postoperative pain. Today, ketorolac use is common in an emergency department setting for acute moderately severe pain management. Ketorolac is void of euphoria, dependence, and respiratory depression, as opposed to alternative agents used in acute pain including opioids. There are a wide variety of routes of administration which include intramuscular, intranasal, ophthalmic, intravenous, and oral providing greater convenience for providers.³ Doses for pain management intramuscularly is 60 mg as a single dose or 30 mg every 6 hours; alternatively can be given as 10 to 30 mg as a single dose according to Canada product labeling.² Intravenously, doses include 30 mg as a single dose or 30 mg every 6 hours.² Each have a max of 120 mg per day, with a max use of 5 days.²

Although there are many benefits associated with the use of ketorolac, this drug is not void of side effects. Some common adverse effects include headache, gastrointestinal pain, dyspepsia, and nausea.¹ More specifically, 1.2% of patients greater than 65 years old experienced a peptic ulcer with ketorolac doses less than or equal to 60 mg for a total daily dose and

with doses of 90-120 mg daily, the rate was 2.2%.¹ To this day, there are multiple black box warnings, cautions, interactions, and contraindications that requires weighing the risk versus benefits for each patient case. Ketorolac has many disease and drug-drug related concerns and other considerations prior to the administration to a specific patient. This includes the various black box warnings of bleeding and hemorrhagic effects, increased cardiovascular events, gastrointestinal events, and hypersensitivity reactions. Other considerations include central nervous system effects, hepatic effects, hyperkalemia, renal effects, and skin reactions. The considerations for special populations include patients greater than 65 years old, patients during labor and delivery, pediatric patients, and patients weighing less than 50 kg. Pharmacokinetics also plays a role in specific patients; as half-life is greater in elderly patients, and clearance is decreased in renal impairment. With these various concerns, it is important to administer the lowest effective dose to limit these adverse effects. Like with most drugs, the greater the dose and extended duration of therapy; the increased risk for complications. In order to limit the number of adverse reactions, while still allowing for a max benefit of pain relief, various studies looked at ketorolac effectiveness at various doses; since being released in the early 1990's.^{4,5,6} There have been multiple studies demonstrating a ceiling dose associated with ketorolac; yet one piece of literature demonstrates practitioners in an emergency





department setting are prescribing greater than the ceiling dose, with about 97% of prescribers prescribing doses greater than the doses seen in literature.⁷ There is a lull in literature looking at the implementation of the ceiling dose of ketorolac, with many studies demonstrating ceiling doses in various hospital settings. The purpose of this review is to increase awareness of this practice that can potentially increase patient outcomes.

CEILING DOSE OF KETOROLAC

A ceiling dose is the most effective dose to treat a certain disease state, with limiting the number of adverse effects. With ketorolac, a ceiling dose has been established in various studies.^{4,5,6} For example, in Motov 2017, a randomized control trial was conducted in an emergency department setting investigating three doses of ketorolac; 10, 15, and 30mg. Patients part of this trial required to have moderate to severe pain, a pain score of 5 or greater on a numeric pain scale ranging from 0-10.⁶ Patients were excluded if there was chronic pain lasting greater than 30 days, any contraindications, or use of other additional analgesia. This blinded trial had one arm for each dose of ketorolac, with follow-up at baseline, 15, 30, 60, 90, and 120 minutes.⁶ The primary outcome looked at the delta between pain rating score at baseline and at 30 minutes; with a significant value being considered 1.3.⁶ There was no significant difference in efficacy between the three arms. For instance, the baseline for 10, 15,

and 30 mg are as follows: 7.7, 7.5, and 7.8 with reduction to 5.1, 5.0, and 4.8 at 30 minutes respectively. Rescue analgesia used was morphine, which had similar use between the three groups. Some limitations include selection bias, as this was a single-center study with convince sampling according to variable of the research and pharmacy. Another limitation includes duration of follow up, which limits the ability to differentiate long term adverse effects between the three groups including renal and gastrointestinal. These both should be considered when determining the validity and impact of this trial. Overall, based on the results, Motov considered the ceiling dose for ketorolac to be 10 mg. Based on a recent letter to the editor in the Annals of Emergency Medicine, Heller demonstrated concern with Motov 2017 and the



Knowledge Check: True or False?
One conclusion from Motov 2017 was that there was increased efficacy seen with higher doses of ketorolac.

Answer: False

conclusion of similar analgesic efficacy between the three doses of 10, 15, and 30 mg.⁸ Heller states a lack of consideration for the area under the curve for ketorolac at lower doses, meaning that the duration of





effect for ketorolac was not addressed for the various doses. There is discussion concerning the variable half-life of ketorolac, and since the follow up time was only until 120 minutes in Motov 2017. Heller states that there is limitation as to how clinically significant the results were.

Broadening the spectrum to look at other studies that are not specific to the emergency department are also considered in order to see the trends of recommended ketorolac doses. Around the time ketorolac being used on the market; Staquet 1989 published a double-blind study looking at intramuscular administration of ketorolac in cancer pain.⁹ 126 patients were administered either 10, 30, or 90 mg and assessed level of pain via the standard verbal scale.⁹ The authors concluded that there was a statistical superiority to placebo for each dose of ketorolac, including the 10mg dose.⁹ This was determined by the pain intensity differences, with similarity between 90, 30, and 10mg at six hours 6.68, 6.85, and 7.40 respectively.⁹ It was also noted that 10 patients experienced an adverse effect post administration of ketorolac, with there being a relationship with the lower number of adverse effects with the lower dose. The mean time to remediation, because of inadequate pain relief for the three doses was 7.04 hours combined, with little difference between the three doses.⁹ Another study by Minotti 1998, compared two doses of ketorolac, 10 and 30 mg, and diclofenac 75 mg.⁵ Pain was assessed at various points

in therapy from 30 minutes to 6 hours, focusing on if there was a need for rescue analgesia. Overall, there were no statistical differences between the efficacy of the pain relief for the three arms.⁵ This study also concludes with the two other studies previously mentioned, that 10 mg of ketorolac is non-inferior to higher doses.⁵

IMPLEMENTATION OF CEILING DOSE

In order to see if the ceiling dose is implemented in an emergency room practice, Soleyman-Zomalan 2017 conducted a retrospective observational study.⁷ Data was collected over a ten-year period noting the dose of ketorolac administered; in addition to indication and various patient demographics. The three main indications for the use of ketorolac included pain associated with urinary tract, lower back, and abdomen. The main route of administration for treating these conditions with ketorolac was intravenous (77.9%) followed by intramuscular, and then oral. Of the 49,605 doses of ketorolac included in this study; 48,117 patients received supratherapeutic doses greater than or equal to 15 mg.⁷ Specific trends for each route of administration are as follows: 95.5% of all administrations for intramuscular were given at doses of 30 and 60 mg, and the intravenous trend was 84.9% for doses given at doses of 30 and 60 mg. The results showed that that in the emergency department, 97% of prescribers used above the ceiling dose for acute pain.⁷ This leads to an increased likelihood for adverse effects

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giving the patients without a benefit for their pain.

significance of implementing lower doses of ketorolac.

CONCLUSION

With this review of literature; there is seen to be a lack of implementation for the ceiling dose of ketorolac, although there are various studies to demonstrate a ceiling dose. The main question, based on this information, why are providers still using greater than the ceiling dose? Some possible reasons include lack of knowledge and awareness. Practitioners may have not reviewed the recent literature for the ceiling dose for ketorolac. A force of habit could be another reason for the continued use of the higher doses. Also, practitioners may use drug databases including Lexicomp or Micromedex in order to determine dosing, which would also explain the elevated doses; as these databases recommend elevated doses. Lastly, there could be concern based on the current literature; as to how clinically significant they are in practice. With this, there should be education for the various providers in the emergency department including practitioners and pharmacists in aims of increasing awareness and knowledge of 10 mg ceiling dose of ketorolac. By increasing the knowledge and awareness, pharmacists will be more comfortable being able to make a recommendation to use the ceiling dose of ketorolac in the emergency department setting. In addition to education, there should be further research in the ceiling dose of ketorolac, pharmacokinetics, and clinical



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