Study Title: Dosing of ketorolac

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Dosing of ketorolac

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1. Objective and Specific Aims

The non-steroidal anti-inflammatory drugs (NSAID's) are very commonly used to treat pain in Emergency Departments. In January of 2018 more than 1100 doses of the injectable NSAID ketorolac were given in the University of Missouri Emergency Department. The correct dosing of ketorolac is unclear.

Our study is designed to clarify the optimal dose of ketorolac.

2. Background and Significance

Background

Optimal pain management in the Emergency Department remains problematic[1]. NSAID are a particularly useful class of drugs in Emergency Departments because of their effectiveness and safety[2]. The parenteral form of ketorolac has become particularly popular for treatment of acute pain in Emergency Departments, demonstrated by the total of more than 1100 doses given in the University of Missouri Emergency Department in January of 2018 (internal audit).

Recently the optimal dosing of ketorolac has been questioned[3]. This study showed equal efficacy among three doses of intravenous ketorolac: the standard 30mg dose, 15mg, and 10mg. These investigators recommended a change in practice to adopt the 10mg dose as standard.

Significance

The correct dosing of analgesics and ketorolac is actually a complicated and poorly understood issue. Ketorolac, as with other NSAID's, has multiple properties that may influence its analgesic properties; it has anti-inflammatory properties similar to other NSAID, is an analgesic, and is an inhibitor of prostaglandin synthesis[2]. Also it has significant placebo effect in some circumstances. In a study of acute headaches in an Emergency Department three intramuscular injections were compared: meperidine 50mg with 25mg promethazine, ketorolac 60mg, and saline[4]. The three treatments were found to be effective and equivalent. The authors conclude that the placebo effect was so profound that analgesic effects could not be evaluated. There is also evidence that ketorolac and other NSAID's have different efficacy as a function of

the type of pain[2]; that is, that pain which is inflammation medicated may be more very responsive.

3. Objectives and Purpose

This study is designed to determine the optimal dose of ketorolac in four groups of patients that would be expected to have different mechanisms of response to NSAID's.

4. Research Design and Methods

Methods

Patients presenting to the Emergency Department with pain will be screened for inclusion into one of four groups:

1. Headache: Non-traumatic headache of less than four days duration.
2. Trauma: Patients with acute mild to moderate musculo-skeletal injury (no trauma activation) or pain of less than four days duration.
3. Colic/Abdominal pain: Patients with mild to moderate abdominal or flank pain of less than four days duration.
4. Viral syndrome: Patients with less than four days of generalized systemic complaints suggestive of an acute viral syndrome.

A pregnancy test will be administered to females of childbearing potential before administration of the study drug. Patients will be randomized to receive either 30mg of ketorolac, 10mg of ketorolac, or saline as a slow intravenous infusion over 10 minutes via a pump. Thirty minutes or later their pain score will be re-evaluated, they will be assessed for any negative effects of the treatment, additional pain medications will be offered if indicated, and the patient's involvement in the study will be concluded.

Data collected:

1. Patient demographics
    a. Age
    b. Sex
    c. Complaint
2. Pain scores
3. Side effects noted by patient or staff

5. Subjects

Subjects will be eligible for recruitment when they present to the Emergency Department with a chief complaint consistent with the four study groups. Inclusion criteria will be:

1. Age≥18y/o
2. Not pregnant or lactating (negative urinary pregnancy test)
3. No contraindication to ketorolac

Exclusion criteria

1. Age<18y/o
2. Pregnancy or lactation
3. Contraindication to ketorolac

If the subjects are eligible for inclusion they will be offered inclusion in the study by one of the Emergency Department faculty. If they refuse participation they will be treated in a standard fashion.

6. Treatment of subjects

There will be no long term follow up of patients for data. Subjects who have incomplete data will have their data discarded and removed from enrollment.

7. Statistics

End point: the primary hypothesis is that ketorolac has different effects depending on the dose and the condition. We will compare pain scores at 30 minutes or after for each of the doses and the groups.

Sample size: We plan to enroll 170 patients in each group. This is based on a change in pain scale of 2.5 with a standard deviation of 2.5, and αof 0.05 and power of 0.80[5].

An interim analysis will be performed when half of the patients are enrolled in each group. The study will be terminated if there is significant difference in the groups at this point. Dr. Chelsea B. Deroche is providing statistical support for the project.

8. Direct access to source data/documents

Access to source data and documents will be provided by the investigators for any auditing or monitoring or reviews by the IRB/IEC, or regulatory inspections.

9. Ethics

This trial proposes to the study the proper dosing of ketorolac in several different conditions and attempts to clarify the placebo effect in this setting. Standard care will not be withheld at any time during this protocol. The intervention may offer significant benefit for the patients being studied. An interim analysis is planned with termination of the study if this is the case.

10. Data handling and recordkeeping

Initial data collection will include identification of the patient by name and medical recorded number. This data will be kept in a locked cabinet in the Emergency Medicine Department. Data will be extracted from these records and recorded in a computer data base and identified only by subject number. No patient identifies will be entered in to the computer database.

11. Investigators

Starr-Mar'ee Bedy: Dr. Bedy in Pharm.D. with extensive training in the clinical use of the medications involved in this study and a history of working in the emergency department.

Kara Goddard: Dr. Goddard in Pharm.D. with extensive training in the clinical use of the medications involved in this study whose clinical duties are in the Emergency Department.

Matthew Robinson: Dr. Robinson is an Associate Professor of Emergency Medicine. He is attending physician in the Emergency Department and routinely manages patients with headache.

Julie Stilley: Dr. Stilley is Research Assistant Professor in the Department of Emergency medicine and has extensive training in research.

12. Financing and insurance

Patients will have regular charges for Emergency Department visit but will not be charged for ketorolac/placebo or its administration. Charges for any treatment will be per usual. There will be no payments to the subjects.

13. References

1. Patrick, P.A., et al., *Timely pain management in the emergency department.* Journal of Emergency Medicine, 2015. **48**(3): p. 267-73.
2. Catapano, M.S., *The analgesic efficacy of ketorolac for acute pain.* Journal of Emergency Medicine, 1996. **14**(1): p. 67-75.
3. Motov, S., et al., *Comparison of Intravenous Ketorolac at Three Single-Dose Regimens for Treating Acute Pain in the Emergency Department: A Randomized Controlled Trial.* Annals of Emergency Medicine, 2017. **70**(2): p. 177-184.
4. Harden, R.N., et al., *The placebo effect in acute headache management: ketorolac, meperidine, and saline in the emergency department.* Headache, 1996. **36**(6): p. 352-6.
5. Glantz, S.A., *Primer of biostatistics*. 7 ed. 2012: McGraw-Hill.

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Signature Date

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