ΔThe Dose-Response Effect of the Mast Cell Stabilizer, Ketotifen Fumarate, on Post-Traumatic Joint Contractures

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Purpose: Posttraumatic joint contracture (PTJC) is a debilitating complication following an acute fracture or intra-articular injury, which can lead to loss of motion at the affected joint. Prior research has shown that, in a rabbit model, treatment with ketotifen can significantly reduce the severity of joint contracture; however, the doses used previously were 0.5 mg/kg or 1.0 mg/kg twice daily, and there was no dose-response relationship shown over this narrow range. Prior to clinical testing in humans, knowledge of the dose-response relationship is required and an optimal dose range needs to be identified where contracture reduction is maximized while side effects are avoided. We hypothesize that there will be a linear dose-response effect of ketotifen on posttraumatic contractures and joint capsule properties, using an in vivo rabbit model.

Methods: After obtaining IRB approval, an in vivo model of PTJC of the knee was created, using a combination of intra-articular injury and internal immobilization in skeletally mature New Zealand White rabbits. Five groups of animals were studied (n = 10 per group): a nonoperative control group, a group with the operatively created PTJC and no pharmacological treatment (operative contracture group), and three groups with the operatively created PTJC treated with a mast cell stabilizer, ketotifen fumarate, at doses of 0.01 mg/kg, 0.1 mg/kg, and 5.0 mg/kg ketotifen twice daily (the 0.01-mg/kg, 0.1-mg/kg, and 5.0-mg/kg ketotifen groups). After 8 weeks of immobilization, flexion contractures were measured using a custom rabbit-knee-gripping device, attached to a hydraulic materials testing machine (MTS, Eden Prairie, MN) and the posterior aspect of the joint capsule was harvested for immunohistochemical quantification of myofibroblast and mast cell numbers.

Results: Flexion contractures developed in the operative contracture group and the severity of the contractures exhibited a dose-response reduction in all three of the groups treated with 0.01 mg/kg, 0.1 mg/kg, and 5.0 mg/kg of ketotifen, respectively; however this effect was greatest between the 0.01-mg/kg and 0.1-mg/kg doses. The joint capsule myofibroblast and mast cell numbers in the operative contracture group were significantly increased compared with the values in the control group ($P < 0.001$), and the myofibroblast and mast cell numbers in the 0.1-mg/kg and 5.0-mg/kg ketotifen groups were significantly reduced compared with the values in the operative contracture group ($P < 0.001$). There were 2 implant failures, 1 deep infection resulting in death, and 2 pre-experimental deaths during the acclimatization period.

Conclusion: The use of a mast cell stabilizer, ketotifen fumerate, reduces the biomechanical and cellular manifestations of joint capsule fibrosis in a rabbit model of posttraumatic joint contracture and a dose-response relationship was identified. Reduction in biomechanical and cellular contracture properties began at the 0.1-mg/kg dose, which is lower than previously studied doses. This study suggests that an inflammatory pathway, mediated by mast cell

Δ OTA Grant

• The FDA has not cleared this drug and/or medical device for the use described in this presentation (i.e., the drug or medical device is being discussed for an "off label" use). For full information, refer to page 600.

activation, is involved in the induction of joint capsule fibrosis after traumatic injury. The range of doses used in this study includes both human-equivalent dosing and the currently used therapeutic dose for the treatment of asthma in humans.

See pages 99 - 147 for financial disclosure information.