THE EFFECT OF COX-2 SPECIFIC INHIBITORS ON FRACTURE HEALING IN THE ADULT RAT FEMUR

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Introduction: Numerous studies have demonstrated that administration of non-steroidal anti-inflammatory medications (NSAIDs) results in delayed healing and decreased strength of post-fracture bone (1-3). Many orthopaedists hesitate to prescribe or continue anti-inflammatory medications for fracture or postoperative pain control due to this putative inhibitory effect. Recently, COX-2 specific inhibitors have shown equivalent analgesic efficacy vs. conventional NSAIDs with fewer unwanted side effects (4, 5). COX-2 specific inhibitors primarily inhibit production of PGE2, a prostaglandin believed to play a primary role in the inflammatory cascade. The goal of this study was to determine whether COX-2 specific inhibitors affected fracture healing to the same degree as conventional NSAIDs. To assess changes in fracture healing and strength as a function of COX-2 inhibitor administration, we determined biomechanical and radiographic properties at 4,8, and 12 weeks after nondisplaced femur fracture in the adult rat.

Methods: All procedures conformed to the guidelines of the Penn State IACUC(#2001-110). 57 adult male Wistar rats weighing 300 g were randomly placed into three groups of 19 rats. All three groups underwent nondisplaced right femur fractures according to the method of Bonnarens and Einhorn (6). Left femurs were pinned and remained intact to serve as controls. Group I received no drug, Group II received indomethacin at 1 mg/kg/day and Group III received celecoxib at 3 mg/kg/day p.o. starting postoperative day (POD) 1. These doses are in the range of average recommended therapeutic doses (3, 7). The administered dose of drug was mixed with chocolate and fed to each rat daily to assure consistent and accurate dosing. Fractures from each subgroup were analyzed at the 4th, 8th, and 12th week. Radiographic analysis was performed to assess callus maturity and bridging bone formation. Callus strength was assessed by 3-point bending and compared to contralateral control, and stage of fracture union was determined by stiffness and failure location according to the classification by White et al. (8). Data were grouped and analyzed using standard GLM ANOVAs with SNK post-hoc comparisons for all groups and unpaired t-tests between groups with an a priori significance level of 0.05.

Results: At 4 weeks, the indomethacin group had significantly less stiffness (Figure 1) and strength (Figure 2) relative to vector-treated controls. Strength was expressed as bending moment (M) to failure. The indomethacin group also demonstrated morphological evidence of delayed healing relative to the celecoxib and vector-treated groups (not shown). Radiographically, the indomethacin group had both decreased callus formation and decreased bridging bone formation, though this result was not significant with the numbers available (Figure 3). There were no significant differences between the celecoxib group and vector-treated controls at 4, 8, and 12 weeks. Though the celecoxib femurs appeared to have more fibrous tissue than controls at 4 and 8 weeks, radiographic callus formation, mechanical strength and stiffness were not signifcantly different. By 12 weeks, there were no significant radiographic, morphological or biomechanical differences between any of the groups.

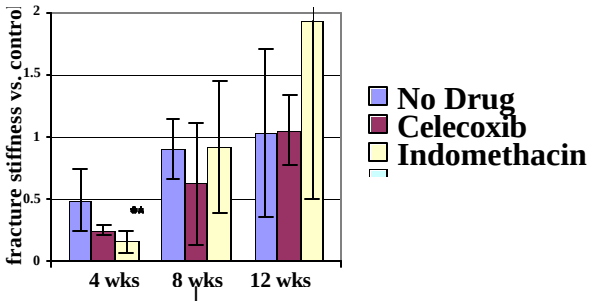

Figure 1. Average percentage of fracture stiffness (N/mm) vs. intact control (p<0.05)**

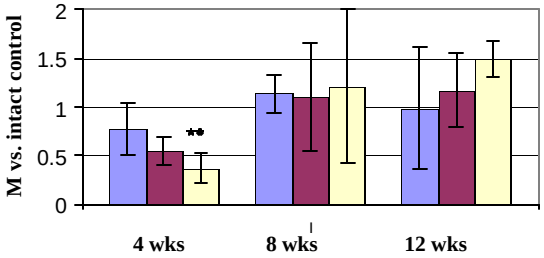

Figure 2. Average strength (bending moment [M]) vs. intact control (p<0.05)**

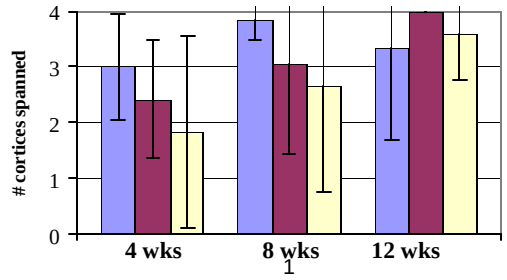

Figure 3. Radiographic Evidence of Healing

Discussion/Conclusions: Indomethacin administration inhibits callus strength and stiffness at 4 weeks after femoral fracture in the adult rat. Celecoxib, a COX-2 specific inhibitor, does not delay fracture healing after 4, 8, or 12 weeks. At 4 and 8 weeks, fibrous healing predominates in the celecoxib group vs. controls; however, mechanical strength and radiographic healing are not significantly different.

Many orthopaedists rely upon narcotic analgesia for postfracture and postoperative pain, with associated significant morbidity. Studies regarding the effects of COX-2-specific inhibitors on fracture healing have yielded varying and often conflicting results, and much remains to be elucidated. The results of this study will help practicing orthopaedic surgeons make treatment choices for postfracture and postoperative pain management with COX-2 specific inhibitors based upon concrete experimental data. Future studies will focus on a histological and torsional analysis of fracture callus as well an elucidation of the pathways and factors involved in fracture healing.

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