**COX-2 SELECTIVE NSAID DECREASES BONE INGROWTH IN VIVO**

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**Introduction:**
Oral non-steroidal anti-inflammatory drugs (NSAIDs) have been previously shown to interfere with fracture healing and bone ingrowth. Whether this effect is due to cyclo-oxygenase-1 inhibition (COX-1), COX-2 inhibition, or through a yet unidentified pathway is unknown. In this study, we examine the effects of a COX-1 and COX-2 inhibitor, versus a COX-2 inhibitor alone on bone ingrowth into a titanium chamber implanted in the rabbit tibia.

**Materials and Methods:**
Institutional guidelines for the care and use of laboratory animals were strictly followed. The Drug Test Chamber (DTC) was implanted in the proximal tibia of 8 mature NZW rabbits (Figure 1). The chamber provides a continuous 1x1x5 mm canal for tissue ingrowth. After a six-week period for osseointegration of the outer cylinder of the chamber, the contents of the inner core can be harvested repeatedly by disassembling the parts without disturbing the osseointegrated outer cylinder. The contents of the initial 6 week harvest were discarded. Thereafter, the following oral treatments were given for 4 weeks each, followed by a harvest in each case: drinking water alone, the percentage of bone ingrowth averaged 24.8±2.9% and 29.9±4.5% respectively. Naproxen sodium in the drinking water decreased bone ingrowth significantly (15.9±3.3%), compared to drinking water treatment (p=.031). Bone ingrowth averaged 18.5±2.4% when Rofecoxib was inserted directly in the rabbit’s mouth (p=.035 compared to drinking water). There was no statistical difference in bone ingrowth when Naproxen sodium or Rofecoxib treatments were compared (p=.706). Both Naproxen sodium (p=.026) and Rofecoxib (p=.02) decreased the number of CD51 positive cells per section compared with drinking water alone.

**Results:**
After each treatment, the chamber was filled with longitudinally oriented woven bone in a fibrovascular stroma. With drinking water alone, the percentage of bone ingrowth averaged 24.8±2.9% and 29.9±4.5% respectively. Naproxen sodium in the drinking water decreased bone ingrowth significantly (15.9±3.3%), compared to drinking water treatment (p=.031). Bone ingrowth averaged 18.5±2.4% when Rofecoxib was inserted directly in the rabbit’s mouth (p=.035 compared to drinking water). There was no statistical difference in bone ingrowth when Naproxen sodium or Rofecoxib treatments were compared (p=.706). Both Naproxen sodium (p=.026) and Rofecoxib (p=.02) decreased the number of CD51 positive cells per section compared with drinking water alone.

**Discussion:**
This study suggests that bone formation is suppressed by oral administration of an NSAID which contains a COX-2 inhibitor. This may be due to suppression of the initial inflammatory stages associated with fracture healing and bone ingrowth, or direct effects of COX-2 inhibition on mesenchymal cell/osteoblast proliferation, differentiation or maturation. Further studies are indicated to assess these biological mechanisms, as the effects of COX-2 inhibitors currently taken for arthritis and other conditions may delay fracture healing and bone ingrowth.

The tissue in the chamber was harvested after each 4 week treatment and snap frozen. Serial 6 µm longitudinal sections were cut from frozen specimens using a cryostat. Sections were stained with hematoxylin and eosin for general morphological and morphometric analysis. Osteoclast-like cells were identified by immunohistochemical staining using a monoclonal antibody directed against the alpha chain of the vitronectin receptor, CD51. The data were analyzed using an analysis of variance and post hoc paired t tests.

**Figure 2**
Percent Bone Ingrowth

**Figure 3**
Total Number of Osteoclasts

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