COX-2 INHIBITOR INHIBITS ONLY EARLY PHASE OF FRACTURE HEALING

Introduction:
Recently, cyclooxgenase-2 (cox-2) specific inhibitors have been reported to inhibit fracture healing. One possible hypothesis proposed for the delayed healing is that cox-2 inhibitors may inhibit growth factors such as FGFs and BMPs, which are required for fracture healing. The process of fracture healing is divided into three phases: the inflammatory, reparative, and remodeling phases. If the delayed healing is mostly caused by the inhibition of the cytokines by cox-2 inhibitors during the inflammatory phase, the effect of the cox-2 inhibitors would show time dependency for their administration. The purpose of this study was to elucidate whether cox-2 inhibitors affect the fracture healing process.

Methods:
Twelve week-old female Wister rats, weighing 250-300 (g), were used in this study. The rats were randomly assigned to four groups according to the period of administration of the cox-2 inhibitors (Figure 1). All rats were examined three weeks after fracture. The rats in group I received intraperitoneal administration of etodolac (a cox-2 specific inhibitor; Nippon Shinyaku Co. Ltd, Tokyo Japan) at a dose of 20 mg/kg body weight a day for three weeks. The rats in group II had the same dose for only one week after operation, and were termed the early administration group. The rats in group III had the same dose for only the final week of the experiment, and were termed the late administration group. The rats in group IV were the vehicle controls. According to the three point bending method proposed by Bonnarens and Einhorn (2), closed non-displaced mid shaft femoral fractures were created under general anesthesia with sodium pentobarbital (50 mg/kg body weight).

Biomechanical Measurements
Three weeks after surgery femurs were harvested, and a three point bending test was conducted for the mechanical evaluation using the MTS system (Test star-II, MTS Inc., Minneapolis, MN, USA). A load displacement curve was obtained from each specimen and the ultimate strength at failure and stiffness were calculated from the curve.

Weekly radiographic evaluation:
Immediately after surgery, and at one, two and three weeks following surgery, postero-anterior radiographs were taken to evaluate callus formation and bone healing. A radiographic scoring system for fracture healing was used for the evaluations (1).

Results:
The radiographic scores in groups I and II were significantly lower than those in group III and IV (p<0.05). The data obtained from the biomechanical testing is shown in Figure 2 and 3. The ultimate strength was 42.7 and 42.8 (N) for groups I and II, respectively. On the other hand, the ultimate strength was 78.6 and 94.8 (N) for groups III and IV, respectively. The strength in groups I and II was significantly lower than those in groups III and IV (p<0.05). The stiffness values were 53.6, 31.5, 101.7 and 118.2 (N/mm) for groups I, II, III and IV, respectively. The stiffness values in groups I and II were significantly lower than that in group IV (p<0.05).

Discussion and Conclusions:
The radiographic and biomechanical studies revealed that the fracture healing processes in rats receiving cox-2 inhibitor administration for the whole of the experimental period and rats receiving the cox-2 inhibitor for only the initial period were similar. On the other hand, the rats with administration only during the late phase of the experiment showed similar results to those in the vehicle control group. Thus, we have shown that there is time dependency of the effect of cox-2 specific inhibitors on fracture healing, since administration during the early phase after fracture could delay the healing process, whereas late administration could not.

It has been proposed that the delay in fracture healing after administration of cox-2 inhibitors is caused by the inhibition of growth factors such as FGFs or BMPs during the inflammatory phase. It has been reported that such cytokines are only expressed during the early phase after fracture in rats. Thus, the early administration of the cox-2 inhibitor in group II could delay the fracture healing. On the other hand, since such cytokines are no longer present during the late phase after fracture, the late administration of the cox-2 inhibitor could not delay fracture healing. Furthermore, the expression of cox-2 was reported to be elevated following fracture and to return to the normal level 2 weeks after the fracture. Thus, the late administration could not affect the fracture healing.

In conclusion, a cox-2 specific inhibitor delayed fracture healing, and its effects were time dependent. From this experimental study, it is suggested that this kind of analgesics should be used carefully during the initial phase of the healing process following fracture.

References: