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Prediction of Bone Healing in Rats after Treatment with Parecoxib

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S u m m a r y. Parecoxib inhibits fracture healing in rats when administered postoperatively. The purpose of this study was to estimate the possibility of bone healing in rats after fracture and treatment with parecoxib for the first postoperative week. Closed mid-diaphyseal fractures of the left femoral shaft were generated, and parecoxib was administered intraperitoneally for one week, immediately after fracture. Bone healing was evaluated radiographically 2 and 6 weeks after fracture. Bone healing can be predicted by the equation f(x)=y=17.5x-25, where y is the percentage of bone healing, and x is time in weeks after fracture.

INTRODUCTION

Selective and non-selective cyclo-oxygenase (COX) inhibitors have demonstrated inhibitory effects on bone healing (1-7). In previous studies we have demonstrated that parecoxib, a new selective COX-2 inhibitor, delays early fracture healing in rats, when it is administered for one week after bone fracture (8-10) but we concluded that this effect was rather transient, as the long-term effects seemed to be non significant (11-14). We have also stressed the importance of the reversibility of this delay in fracture healing, as, from a clinical point of view, what seems to be more important with the use of COX inhibitors post-operatively, is not their transient inhibition on bone healing but the reversibility of this inhibition and their long-term effects on bone healing and rehabilitation (14).

The purpose of this study is to estimate the reversibility of the inhibitory effect of parecoxib on bone healing and to develop a model for the prediction of bone healing in *Albino Wistar* rats after a short treatment with parecoxib.

METHODS

A total of 40 adult male *Albino Wistar* rats, 12-week-old, weighing 250-350 g were used in this study. The animals were divided in two groups, before operation: group A (20 animals) and group B (20 animals). In all rats a closed transverse mid-diaphyseal femoral fracture was generated by external blunt trauma to the femur after its stabilization by insertion of an intramedullary pin, as described in previous works (8-15).

Parecoxib sodium (1.06 mg/kg) was administered intra-peritoneally in both study groups, immediately after the surgical procedure and fracture, and once daily for one week. Fracture healing was evaluated radiographically 2 weeks after fracture in group A and 6 weeks after fracture in group B.

T test, chi-square test and cross-tabs were used, in order to explore the relationship between the radiographic confirmation of bone healing and time.

RESULTS

Bone healing and callus formation was 10% and 80% at 2 and 6 weeks after fracture respectively. This difference was found to be significant (t test, $p<0.001$).

There was no violation of the assumption of the chi-square test concerning minimum expected cell frequency, as minimum expected count was

9 (>5), and Pearson chi-square test value had to be corrected by Yates' Correction for Continuity, because a 2 by 2 table was used. The conducted analysis confirmed the significance of the difference ($p<0.001$) that was also found by t test for possibilities (by means of z criterion) in bone healing between the second and the sixth week after fracture and administration of parecoxib.

Bone healing can be predicted as a function of time by the equation: $f(x)=y=17.5x-25$, where y is the percentage of bone healing, and x is time in weeks after fracture.

DISCUSSION

Parecoxib and other cyclooxygenase inhibitors prevent the healing of fractures by inhibiting prostaglandin synthesis and angiogenesis. As COX inhibitors are used as analgesics for bone fractures and for the relief of post-traumatic and postoperative pain in orthopaedics, it is of crucial meaning to investigate whether this inhibitory effect on bone reconstruction is reversible, and if it is safe to use these drugs in Orthopedics.

According to our previous studies, parecoxib, given in a high dose and for a short duration after bone trauma, seems to have a transient inhibitory early effect on bone healing in rats. Our present results confirm the reversibility of the inhibitory effect of parecoxib on bone healing, and offer a model for the prediction of long term bone healing in rats after treatment with parecoxib.

According to our model for the prediction of bone healing in rats treated with parecoxib for one week after fracture, no bone healing can be expected until the middle of the second week after fracture, while bone healing will be completed in all subjects by the beginning of the eighth week after operation and fracture.

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