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Indomethacin-Induced Delayed Fracture Healing

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Summary. A patient with an ankle joint fracture-dislocation was preoperatively treated with indomethacin. As in previous animal experiments, indomethacin was found to have an inhibitory effect on bone formation. It is suggested that indomethacin should be used with caution if periosteal fracture healing is anticipated.

Zusammenfassung. Die Autoren haben einen Patienten mit einer Knöchelfraktur mit Syndesmosensprengung bei Ulceration und anschließender Infektion des Ulcus Indomethacin über 9 Wochen gegeben, um die Frakturheilung zu verzögern. Anschließend wurde eine operative stabile Osteosynthese durchgeführt.

Die histologische Untersuchung des während der nach 9 Wochen nach dem Unfall entnommenen Callusgewebes zeigte verminderte Osteoblastenaktivität. Es bestand lediglich eine fibröse Verbindung zwischen den Knochenenden.

Die Autoren empfehlen daher

1. mit der Gabe von Indomethacin bei Frakturen vorsichtig zu sein,
2. auf Wunsch durch Indomethacin bedingte Frakturverzögerung zu erzielen, um anschließend doch noch eine genaue Reposition durchführen zu können. Die Knochenregeneration sollte dann jedoch durch einen Knochenspan angeregt werden.

Introduction

Fracture-dislocations of the ankle joint usually lead to the development of posttraumatic oedema, which often delays operative reduction and internal fixation. The longer the operation is postponed, however, the more difficult an exact operative reduction will be owing to callus formation.

In animal experiments antiphlogistic doses of indomethacin have been shown to retard callus formation [3, 4]. In order to inhibit callus formation and facilitate operative reduction, we accordingly gave indomethacin to a patient with a recent fracture-dislocation of the ankle joint.

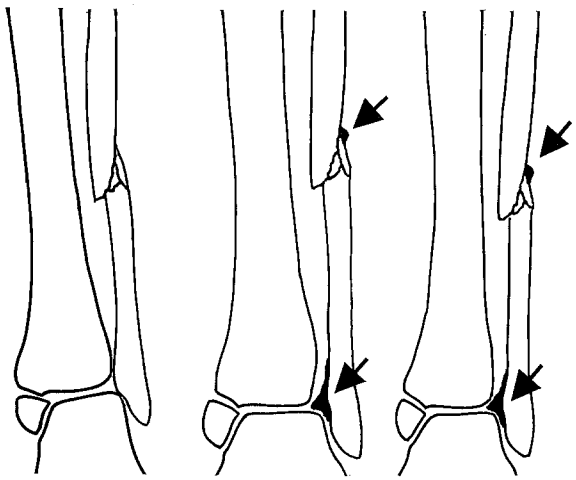

Fig. 1. Drawing of AP X-rays of left ankle fracture-dislocation with rupture of distal tibio-fibular syndesmosis. Left to right: The day of injury, and after 4 and 9 weeks of indomethacin treatment. Arrows indicate woven-fibred bone formation

Case Report

The patient was a 64-year-old man who had sustained a fracture-dislocation of his left ankle joint in which the distal tibio-fibular syndesmosis was ruptured (Fig. 1). On the proximal, lateral side of the leg there was a superficial skin excoriation. Because of swelling of the soft tissues the ankle and leg were temporarily immobilized in a plaster cast. When the cast was removed 1 week later it was found that the excoriation had developed into an ulcer and a swab culture revealed haemolytic staphylococci. The ulcer healed slowly and the operation had to be postponed for 9 weeks during which the ankel was immobilized in a plaster cast below the knee. The patient was given indomethacin (Confortid, Dumex, Copenhagen, Denmark) 25 mg per os three times daily, at 8 a.m., 1 p.m. and 6 p.m.

Upon operation both the fibular and medial malleolar fractures were found to be united by fibrous tissue. The fractures were reduced and the fracture-dislocation rendered stable by internal fixation. Cancellous bone chips from the iliac crest were autografted onto both fractures. The indomethacin medication was discontinued on the day of the operation.

The postoperative period was uneventful.

Laboratory Procedures

X-rays

Roentgenological examination at 4 weeks following injury showed barely visible callus formation at the fibular fracture and in the distal, ruptured tibio-fibular syndesmosis. No further callus formation was visible in later X-rays. Callus formation at the fibular fracture was visible in X-rays taken 10 weeks after the operation.

Indomethacin Assay

Blood samples for indomethacin assay were drawn on the 51st day following injury at 8 a.m. before the patient took his first daily dose, at 10 and 12 a.m. and at 6 p.m. before he took the last dose.

The serum samples were frozen and stored until assayed for indomethacin by Dumex, Copenhagen, Denmark [1]. The indomethacin concentrations in the four samples were 0.1, 0.3, 0.3 and 0.4 μg/ml respectively.

Histological Examination

During the operation bone tissue was removed for histological examination from the iliac crest just posterior to the anterior superior iliac spine, from both fractures and from the ruptured syndesmosis. The tissue for histiological study was fixed in 4% formaldehyde, decalcified and embedded in Epon. Epon sections, 3 μm thick, were cut and stained with haematoxilin and eosin after dissolving the resin in 1% potassium hydroxide in absolute ethanol. The stained sections were assessed qualitatively and the bone surface activity of the iliac crest [2, 7] both qualitatively and quantitatively, by mixed-image planimetry and mixed-image longitudimetry [5, 6].

On histological examination of the bone biopsy from the iliac crest, the amount of cancellous bone was 20% as assessed by mixed-image planimetry (normal). The active bone formation surface was 0.4% of the total cancellous bone surface and the active resorption surface was 0% of the total calcified surface as assessed by mixed-image longitudimetry. This indicated a low surface activity (normal mean values about 4 and 0.5% respectively [2]).

The fracture gap in the medial malleolus was filled with connective tissue and numerous multinucleated osteoclasts were observed in Howship's lacunae on the fractured bone ends.

Microscopy of the hard tissue removed from the ruptured syndesmosis revealed woven-fibred bone tissue formation. Sparsely woven-fibred bone tissue was also observed near the fibular fracture. In addition many osteoclasts were observed on a small detached bone fragment where the lacunae appeared empty, indicating necrosis.

Discussion

A displaced fibular fracture usually heals even without external immobilization. In the present case, however, the fracture did not unite in spite of external immobilization for 9 weeks. This is in accordance with our findings in animal experiments, where indomethacin clearly retarded woven-fibred bone tissue formation and hence primitive, disordered osteoblastic activity [3, 4].

In the roentgenograms slight callus formation was noted 4 weeks after injury, but then came to a stop. Possibly the osteogenetic signal produced by the fracture gradually subsided because of the antiosteogenetic effect of indomethacin. Since active osteoclasts and osteoblasts were observed on histological examination, the inhibitory effect of indomethacin treatment on osteoclastic and osteoblastic activity was not complete. However, the indomethacin dosage and serum levels were quite low. It is not clear whether the low differenciated ordered osteoclastic and osteoblastic surface activity in the iliac crest of our patient was indomethacin-induced.

Since callus formation and uneventful fracture healing followed when the indomethacin treatment was discontinued and osteogenesis was once more activated by cancellous bone autografts, a defective osteogenetic cell lineage can be ruled out.

Our limited clinical experience permits no definite conclusions. Two suggestions may be made:

1. Indomethacin should be used with caution when periosteal fracture healing is anticipated.

2. The drug can be used in special cases to postpone fracture healing until the desired moment. However, fracture healing should then be reactivated by grafts of fresh autologous cancellous bone chips.

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