Commentary

COX-2: where are we in 2003?

The role of cyclooxygenase-2 in bone repair

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Abstract

Prostaglandins are important mediators of bone repair, and cyclooxygenases are required for prostaglandin production. Data from animal studies suggest that both non-specific and specific inhibitors of cyclooxygenases impair fracture healing but that this is due to the inhibition of COX-2 and not COX-1. Although these data raise concerns about the use of COX-2-specific inhibitors as anti-inflammatory or anti-analgesic drugs in patients undergoing bone repair, clinical reports have been inconclusive. Because animal data suggest that the effects of COX-2 inhibitors are both dose-dependent and reversible, in the absence of scientifically sound clinical evidence it is suggested that physicians consider short-term administration or other drugs in the management of these patients.

Keywords: bone repair, cyclooxygenase-2, fracture healing, non-steroidal anti-inflammatory drugs, prostaglandins

Introduction

Bone repair is a complex process involving the participation of several cell types, signal transduction pathways and biochemical events [1]. Because it is initiated by a skeletal injury, which induces an inflammatory response, chemical mediators of inflammation are also involved in this process [2]. Prostaglandins, a class of compounds known to mediate inflammation and shown to have effects on bone formation and resorption, are essential in bone repair [3].

Prostaglandin synthesis is initiated with the release of arachidonic acid from membrane phospholipids. The subsequent conversion of arachidonic acid to prostaglandin H_2 (PGH_2) is catalyzed in two steps by cyclooxygenase [4]. Synthase enzymes then convert PGH_2 to specific prostaglandins such as PGD_2, PGE_2, $PGF_2\alpha$, prostacyclin and thromboxane. Thus, cyclooxygenase activity is essential for normal prostaglandin production and is the rate-limiting enzyme in the synthetic pathway. The two recognized forms of this enzyme, cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) are encoded by two separate genes [5,6]. COX-1 is constitutively expressed by many tissues and functions as a so-called 'housekeeping' enzyme maintaining homeostatic levels of prostaglandins for the normal function of several organs, in particular the stomach [7]. In contrast, COX-2 is induced by an array of stimuli including inflammation, injury and mechanical stress [8,9].

The role of COX-2 in bone repair has received recent attention because drugs that inhibit prostaglandin production have been shown to inhibit experimental fracture healing [10–12]. Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed drugs worldwide and are indicated in the treatment of several forms of arthritis, menstrual pain and headache. Their ability to decrease inflammation by inhibiting cyclooxygenase has improved the quality of many people's lives but their use has been limited by gastrointestinal side effects such as dyspepsia, abdominal pain, and, in some instances, gastric or duodenal perforation or bleeding. The development of COX-2 inhibitors (coxibs) was a response to the need for drugs that inhibit prostaglandin production without side effects [13]. Because most NSAIDs inhibit

COX-1 = cyclooxygenase-1; COX-2 = cyclooxygenase-2; coxib = COX-2 inhibitor; NSAIDs = non-steroidal anti-inflammatory drugs; PG = prostaglandin.

COX-1 and COX-2 with almost equal potency, it was hoped that the development of COX-2-selective drugs would be better tolerated and equally efficacious in managing inflammation. However, whereas the selectivity of this group of compounds might allow inflammation to be inhibited with minimal effects on certain homeostatic mechanisms, their role in bone metabolism and repair remains unclear.

Review of the evidence

To determine the role of COX-2 in bone repair, investigators have studied fracture healing in animal models of COX-2 inhibition or deletion. Although several studies have been reported at scientific meetings, only two have been published in the peer-reviewed literature [10,12]. Simon *et al.* [10] treated rats with the non-selective NSAID indomethacin and the two most widely prescribed coxibs, celecoxib and rofecoxib. They showed that all three drugs inhibited fracture healing, but the effects were more profound when coxibs were used. They also demonstrated impaired fracture healing in mice homozygous for a null mutation in the COX-2 gene. However, whereas the doses of indomethacin and celecoxib used in the rats were roughly equivalent to those used in patients, the dose of rofecoxib was nearly eight times that used to manage inflammation and four times that used to manage acute pain. Moreover, whereas the use of these drugs in the management of acute pain is typically short term (a few days to two weeks), their continuous usage in these experiments was a departure from clinical practice.

Zhang *et al.* [12] reported the critical role of COX-2 in mesenchymal cell differentiation during skeletal repair. Using COX-1-null and COX-2-null mice, they demonstrated the essential role of COX-2 in both endochondral and intramembranous ossification. Moreover, the healing of stabilized tibia fractures in COX-2-null mice was significantly delayed compared with that in COX-1-null mice. The histology of the fractures in the COX-2-null mice showed a persistence of undifferentiated mesenchyme and a marked reduction in osteoblastogenesis resulting in a high rate of nonunions. In addition, to elucidate the mechanism involved in this reduced bone formation, osteoblastogenesis was studied in bone marrow stromal cell cultures obtained from COX-2-null and wild-type mice. Bone nodule formation was reduced by 50% in the COX-2-null cultures, but this effect was completely rescued by the addition of PGE_2.

The important question raised by these studies is whether patients who are undergoing a bone repair process can safely be treated with inhibitors of COX-2. Bone repair is an essential aspect of fracture healing but is also the process required for successful spinal fusion, joint arthrodesis or osteointegration of an orthopedic or dental implant. The favorable safety profile of COX-2-specific inhibitors has led to their use at higher doses, which renders them effective as post-operative and post-fracture analgesics. However, whereas the use of these drugs in the management of arthritic conditions seems appropriate, their use at higher doses to manage pain induced by skeletal surgery or a fracture has raised concerns.

On the basis of animal studies, COX-2 inhibitors would seem to be contraindicated in patients undergoing bone repair. However, there is a paucity of data from clinical studies, and those that do exist do not support the results in animals. Moreover, the few clinical reports that have addressed the role of NSAIDs or coxibs in patients requiring bone repair have been confounded by other factors [14] or have collected data in a retrospective fashion [15–17]. Among these, the most well done was a retrospective analysis of 288 cases of spinal fusion performed at a single center [15]. In this study, ketorolac was administered as a 15 mg intramuscular loading dose followed by 30 mg every six hours as needed. Ketorolac was given to 167 patients, and no NSAID was given to 121. Nonunion occurred in 5 of 121 (4%) nontreated controls and 29 of 167 (17%) patients receiving ketorolac (odds ratio 4.9). There was a dose-dependent relationship between nonunion rate and ketorolac use. Only one clinical study with a coxib has been reported, and this too was a retrospective investigation. Rueben *et al.* [17] examined nonunion rates in 106 patients undergoing posterior spinal fusion and receiving analgesic doses of rofecoxib. No effect on nonunion rate was noted.

Conclusions

The evidence supporting an essential role for COX-2 in experimental bone repair is strong. However, there are no randomized, controlled trials in patients. In the absence of these kinds of prospective study, it is tempting to translate animal data to our management of patients. However, before doing this, certain points must be considered. Most of the studies in animals have evaluated healing at fairly early time points. Because most patients heal fractures or fuse spinal segments over a period of several months, but require drugs to manage their pain for only a few days or weeks, it is unclear whether short-term inhibition of COX-2 is really significant to the quality or timeliness of the healing. Indeed, the study by Zhang *et al.* [12] showed that restoration of PGE_2 levels immediately rescues the effects of an absence of COX-2. Thus, withdrawal of the drug in a patient might lead to a restoration of prostaglandin synthesis and a normal bone repair process.

Another point relates to the use of indomethacin in the inhibition of heterotopic ossification in patients who have sustained a pelvic fracture. These patients are at risk for developing heterotopic ossification, which could impair hip function. Indomethacin inhibits heterotopic ossification

but does so without preventing healing of the pelvic fracture [18]. Although a critical analysis was not performed to detect a measurable effect on fracture healing in these patients, no clinically apparent problem was reported.

In the absence of randomized controlled studies, definitive statements concerning the use of NSAIDs or coxibs in patients undergoing a bone repair process cannot be made. However, on the basis of animal data and limited clinical information, some recommendations can be proposed. For now, although I would not dismiss the use of these drugs in the management of post-fracture or post-operative pain in patients requiring bone healing, I would advise that physicians and their patients be familiar with the information and make decisions accordingly. I would advise that if these drugs are used as analgesics in these settings, their administration be for fairly short periods of time, probably not to exceed 10–14 days. I would be less inclined to use these drugs if a patient had a comorbid condition that might prevent or delay bone repair, such as smoking, glucocorticoid use, metabolic bone disease, or diabetes. In patients who use standard anti-inflammatory doses of NSAIDs or coxibs, and who undergo joint replacement surgery with a prosthesis that requires bone ingrowth, I would recommend that these drugs be discontinued until osteointegration has occurred (approximately three to six months).

The ability to resolve the role of COX-2 inhibitors in bone repair with a randomized, controlled trial would be challenging. The recruitment of sufficient numbers of patients to achieve statistical power, the development of reliable methods to measure the bone repair endpoint, and the randomization of patients to treatment groups in an ethical experimental design require substantial thought and planning. Until such data are available, the role of COX-2 in human bone repair must be inferred from basic science reports.

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