Abstract

BACKGROUND: In this era of increasing use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) for treatment of painful/inflammatory disorders, it is necessary to review the effect of these drugs on bone and cartilage metabolism. Inflammation is an essential component of the healing process in bone, and cyclooxygenase (cox-1 and cox-2) enzymes play important roles in fracture repair. Therefore, there is concern that NSAIDs, which have anti-inflammatory and analgesic properties that are mediated by inhibition of cox-1 and cox-2 may delay the healing of bone injuries. Also as newer drugs, selective cox-2 inhibitors are being developed to avert the gastrointestinal symptoms of the non-specific NSAIDs, it is imperative that these substances are studied for any deleterious effect on bone and cartilage metabolism.

Methods: Literature on the subject was reviewed using manual library search, articles in journals and internet search. The search words were: NSAIDs and bone metabolism, cyclooxygenase inhibitors and bone metabolism. The search was done using medscape, ortolink and pubmed search engines. The search covered a period of 35 years (1970-2005).

Results: NSAIDs can either reversibly or irreversibly block the cyclooxygenase pathway thereby inhibiting prostaglandin synthesis. These cox inhibitors especially the cox-2 have been found to inhibit the production of prostaglandins which are necessary in bone healing. Prostaglandins play a role in both osteoblastogenesis and bone resorption, and so, cox inhibitors suppress these functions.

Conclusion: NSAIDs especially the cox-2 inhibitors should be avoided following fractures or implant surgery. They should be reserved for other painful inflammatory disorders in which bone resorption and formation mediated by prostaglandins are not required.

Keywords: Cyclooxygenase inhibitors, Prostaglandins, Nonsteroidal Anti-Inflammatory Drugs, Bone

INTRODUCTION

The use of nonsteroidal anti-inflammatory drugs (NSAIDs) which are the cyclo-oxygenase inhibitors continue to expand at a remarkable rate due to the broad spectrum of clinical applications for these medicaments. The use of NSAIDs is particularly prevalent in patients with a variety of musculoskeletal conditions and injuries. Reports of impaired bone healing associated with these NSAIDs are a particular cause for concern for the orthopaedic surgeons. The aim of the study is to elucidate how NSAIDs affect bone and cartilage metabolism and to recommend ways to avert the problems in management of fractures.

CYCLOOXYGENASES

Cyclo-oxygenase (cox) enzymes (also referred to as prostaglandin H synthase or prostaglandin endoperoxide synthase), catalyses the rate limiting steps in prostaglandin (PG) and thromboxane (Tx) syntheses as shown in fig 1.

Cox-1 was first purified and characterized in the 1970s and the gene was isolated in 1988. The discovery of and cloning of gene sequence of the second cox enzyme, cox-2 in 1991 initiated a revolution in our understanding of prostaglandins and their functions in normal physiology and diseases. Two isoforms, cox-1 and cox-2 exist in higher organisms. They are highly similar in structure and enzymatic activity. The main differences between the two lie in their genetic regulation and biological roles. Cox-1 expression is constitutive in most cell types and is thought to carry out 'house-keeping' roles in the various tissues. In contrast, cox-2 expression is induced in response to inflammatory and proliferative stimuli.

The relative roles of these enzymes in bone remodeling have been recently resolved in studies with mice genetically deficient for cox-1 or cox-2. Mice lacking cox-2 but not cox-1 expression display reduced bone resorption in response to parathyroid hormone or 1,25-
hydroxylvitamin D3. Cox-2 is also required for wear debris-induced osteoclastogenesis and osteolysis in an in vivo mouse Calvaria model. In addition to bone resorption, cox-2 may also have a role in bone formation. Systemic or local injection of prostaglandin E2 stimulates bone formation. Increased lamellar bone formation in response to mechanical strain is mediated by cox-2. Although both cox-1 and cox-2 have been identified in osteoblasts, the differential roles of the two cyclooxygenases in bone formation remain unclear.

Figure 1: Prostaglandin and Thromboxane syntheses

PROSTAGLANDINS
Prostaglandins are the cyclo-oxygenase metabolites of arachidonic acid and include PGD2, PGE2, PGF2, PGI2 and Tx A2. They are synthesized and released upon cell stimulation and act on cells in the vicinity of their synthesis to exert their actions.

Prostaglandins are potent local regulators of bone cell function and may play a critical role in both physiologic and pathologic changes in the human skeleton. PG particularly the type E affects bone remodeling in both formation and resorption. The bone resorptive activity of PGE was first noted in vitro in bone organ cultures and then in vivo in animals receiving systemic as well as local injections of PG. This is associated with the occurrence of an increase in the number of osteoclasts. Interleukin-1 induces cox-2 in osteoblasts to release PGE2 in addition to bone resorption. PGE2 added exogenously also induces bone formation. This was first noticed as a reversible increase in the bone cortex of infants with congenital heart diseases who were receiving PGE as a preventive measure. This bone forming activity of the E type of PG was then confirmed in young rats receiving daily subcutaneous injections of PGE. Histological examinations indicated that PGE2 reduced bone resorption and increased the number of osteoblasts in these animals.
CYCLO-OXYGENASE INHIBITORS
Cox enzymatic activity is the target of widely used NSAIDs. Cox-2 selective NSAIDs are currently being used in the hopes of limiting inflammation without adverse gastrointestinal and renal effects.2

Researchers at Stanford University medical Center 18 have found that selective cox-2 inhibitors - a class of medicaments widely prescribed for painful inflammatory conditions interfere with the healing process after fracture or cementless joint implant surgery. Cox-2 inhibitors include Rofecoxib, Celecoxib block production of this enzyme and thus impede new bone growth that normally helps heal a fracture or stabilize a joint implant.18

Nonspecific NSAIDs which inhibit cox-2 production as well as cox-1 include aspirin, ibuprofen, naproxen have been confirmed years ago to inhibit bone growth and healing but Stanford study is among the first to show that cox-2 inhibitors have the same effect.18 In a work done by Reuben et al, the study revealed that the short term perioperative administration of Celecoxib, Rofecoxib, or low dose ketorolac(110mg/day) had no significant deleterious effect on non union following spinal fusion surgery. In contrast, higher doses of ketorolac (120-240mg/day), history of smoking and 2 level vertebral fusions resulted in a significant increase in the incidence of non union following spinal fusion surgery.19

MECHANISMS OF COX INHIBITION
Based upon their inhibitory mechanisms, cox inhibitors can be grouped into four classes (table 1).2 All but the first class are reversible inhibitors in that once the drug is removed; cox activity is restored, albeit at different rates depending upon the compound.

The first class which include aspirin and recently developed cox specific aspirin- like molecules irreversibly inactivate cox activity by acetylating an active site serine. Aspirin is considered cox-1 selective since doses 10-100 fold higher than those required for cox-1 are necessary to acetylate the cox-2 active site.

The second class of inhibitors consists of reversible competitive inhibitors of both enzymes. These compounds compete with arachidonic acid for binding to the cyclo-oxygenase active site. The third class of cox inhibitors exhibit a slow time-dependent inhibition of both cox isoforms. The delayed kinetics of inhibition by this class probably reflects the time necessary for formation of a salt bridge between the carboxylate of the drug and arginine 120 (cox-1 numbering). The fourth class of cox inhibitors selectively inhibit cox-2. They contain larger side groups which penetrate the larger binding pocket of cox-2 but their size prevents them from entering the smaller pockets of cox-1.2

Table 1: Four modes of COX inhibition by NSAIDS

<table>
<thead>
<tr>
<th>Mode of inhibition</th>
<th>Selectivity</th>
<th>Examples</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Covalent modification</td>
<td>COX-1</td>
<td>Aspirin</td>
<td>Acetylation of active site serine</td>
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<tr>
<td></td>
<td>COX-2 (APHS)</td>
<td>APHS</td>
<td></td>
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<tr>
<td>Reversible competitive</td>
<td>COX-1 and 2</td>
<td>Ibuprofen</td>
<td>Compete with Arachidonic acid for active site</td>
</tr>
<tr>
<td>inhibition</td>
<td></td>
<td>Mefenamate</td>
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</tr>
<tr>
<td>Slow time-dependent</td>
<td>COX-1 and 2</td>
<td>Indomethacin</td>
<td>Salt bridge formation with Arginine 120</td>
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<tr>
<td>inhibition</td>
<td></td>
<td>Flurbiprofen</td>
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<tr>
<td>Time-independent cox-2</td>
<td>COX-2</td>
<td>Celecoxib</td>
<td>Large side groups to occupy extra side pocket in cox-2</td>
</tr>
<tr>
<td>inhibition</td>
<td></td>
<td>Rofecoxib</td>
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X = Acetoxphenyl hept-2- ynyl sulphide

THE ROLES OF CYCLOOXYGENASES AND PROSTAGLANDINS IN BONE METABOLISM
Prostaglandins have been shown to play an important role in bone metabolism.20, 21 The rate limiting step in PG production is controlled by the cyclooxygenases cox-1 and cox-2. The current paradigm to explain the role of these enzymes is that cox-1 is constitutively produced and functions to maintain homeostasis whereas cox-2 acts as a stress response gene and is responsible for high levels of PG production during inflammation.22

The metabolites of cox activity have long been suspected to have a role in skeletal reparative processes. The levels of Prostaglandins E and F are increased between days 3 and 14 in tissues obtained from rabbit tibia fractures.23

Fracture healing is a complex process that requires the recruitment, proliferation and differentiation of mesenchymal stem cells into chondrocytes and osteoblasts. It involves both endochondral ossification whereby bone formation occurs through cartilage intermediate and intramembranous ossification in which bone forms directly from differentiated osteoblasts.24, 25 Healing occurs when the bone gap is bridged by woven bone and is completed with remodeling and formation of mature lamellar bone. The
elucidation of the roles of cox-1 and cox-2 in bone healing is of paramount importance given the widespread clinical use of cox inhibitors.

In a study by Zhang et al, they demonstrated that cox-2 is required for both intra-membranous and endochondral bone formation during bone repair while cox-1 does not have a critical role in these processes. Furthermore, they established that cbfa-1 and osterix (which are genes specifically required for osteoblast differentiation and bone formation) are regulated by cox-2. Also that decreased expression of these genes may contribute to defective bone repair in cox-2 mice. The study also showed that cox-2 knock out mice had persistence of mesenchymal cells at the fracture site, significant delay of ossification of cartilage tissue, remarkable reduction in osteoblastogenesis demonstrating a critical requirement of cox-2 in osteoblastogenesis. These findings demonstrate that the production of cox-2 metabolites during the inflammatory phase is required for efficient bone healing and that mesenchymal cell differentiation is a major target of cox activity. In another work, the administration of PGE2 has increased the rate of fracture healing in several animal models indicating also that the metabolites of cox maybe necessary for efficient bone healing. Multiple NSAIDs whose primary targets are the cyclooxygenases have been reported to inhibit fracture healing in animal studies. By inhibiting cox enzymes and the subsequent production of prostaglandins, NSAIDs not only achieve their desired anti-inflammatory effects but also inhibit the increased production of prostaglandins necessary for bone healing to occur.

A recent clinical study showed marked association between non-union of the femoral shaft and the use of NSAIDs. Human studies further demonstrate a significant reduction in the rate of spinal fusion in patients taking NSAIDs.

In a work by Gerstenfeld et al, it was noted that cox-2 specific anti-inflammatory drugs (coxibs) inhibit fracture healing more than non-specific NSAIDs and that the magnitude of the effect is related to the duration of treatment. However, after the discontinuation of treatment prostaglandin E2 levels are gradually restored and the gain of strength returns to levels similar to the control.

CONCLUSION

There is a reasonable theoretical explanation for delayed fracture healing following the use of NSAIDs. Retrospective reviews of outcomes for human patients also indicate that there is a valid concern with NSAID therapy. The possibility that NSAIDs may delay bone healing must be carefully weighed against their analgesic effect when medications for controlling pain associated with fractures are chosen. Therefore patients who have fracture or cementless implants should avoid NSAIDs particularly cox-2 inhibitors.

It is recommended that studies be carried out in this part of the world.

References