Expert Opinion on Pharmacotherapy

ISSN: 1465-6566 (Print) 1744-7666 (Online) Journal homepage: informahealthcare.com/journals/ieop20

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To cite this article: George Pavlou, Margaritis Kyrkos, Evaggelos Tsialogiannis, Nectarios Korres & Eleftherios Tsiridis (2012) Pharmacological treatment of heterotopic ossification following hip surgery: an update, Expert Opinion on Pharmacotherapy, 13:5, 619-622, DOI: 10.1517/14656566.2012.662342

To link to this article: https://doi.org/10.1517/14656566.2012.662342

Published online: 09 Mar 2012.

EXPERT OPINION

Pharmacological treatment of heterotopic ossification following hip surgery: an update

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Heterotopic ossification is a frequent complication following total hip arthroplasty and acetabular surgery. Formation of ectopic lamellar bone in tissues that exhibit no potential for ossification can lead to associated pain and decrease in function. Prophylaxis and treatment protocols aim to reduce the incidence, by both the use of nonsteroidal anti-inflammatory drug (NSAID) regimens and localized radiotherapy. New therapeutic modalities including bone morphogenetic proteins (BMP) inhibitors like Noggin, BMP type 1 receptor inhibition, nuclear retinoic acid receptor-gamma agonists (RAR-γ), and free radical scavengers are currently under investigation.

Keywords: heterotopic ossification, hip surgery, pelvic surgery, trauma, hip reconstruction

Expert Opin. Pharmacother. (2012) 13(5):619-622

1. Introduction

Heterotopic ossification (HO) frequently complicates hip and acetabular surgery, with a reported incidence ranging from 43% to as high as 73% [1]. The presence of HO can potentially jeopardize any intended surgical benefits by reducing range of joint motion and causing impingement pain. The pathophysiology is still poorly understood, but over recent years a better understanding has been established. Traumatic HO as seen in post-surgical patients is thought to be secondary to the osteoblastic differentiation of mesenchymal stem cells that is probably triggered by local inflammatory mediators, cell death and upregulation of osteogenic growth factors. High levels of bone morphogenetic protein (BMP) 4 are thought to play a key role, with inhibition shown to prevent HO proliferation in animal models [2]. The role of prostaglandin (PG) E_2 has also been implicated in HO formation following hip surgery, in addition to several risk factors including history of HO in the contralateral hip, arthritis, ankylosing spondylitis, diffuse idiopathic skeletal hyperostosis, osteonecrosis, Paget's disease, male sex, and technique and approach of hip arthroplasty surgery [3]. The use of NSAIDS remains the mainstay of pharmacological treatment of HO, and radiation therapy has been used with comparable results. The aim of this editorial is to update the reader on current and new pharmacological therapeutic modalities for the treatment of HO.

2. Pharmacologic treatment of heterotopic ossification

2.1 Non-selective COX inhibitors

Indomethacin inhibits PGE_2 via COX-1 downregulation and osteoprogenitor cell differentiation to osteoblasts. Extensive studies have shown this treatment modality to be efficacious: a treatment dose of 25 mg three times daily given traditionally for a period of 6 weeks has been shown to be effective for prophylaxis [1]. There is now evidence to suggest that the duration of treatment can be reduced to a minimum of 7 days, thus conferring the added benefits of reducing the recognized side effects of

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indomethacin. Combined protocol regimens have had promising results. Using both radiotherapy (RT) and indomethacin together has shown greater efficacy than use of indomethacin alone. A prospective study of 96 patients enrolled to receive either a single dose of RT and indomethacin versus indomethacin alone demonstrated significantly reduced incidence in the former group [4]. These combined protocols demonstrate excellent efficacy, with an overall reduction in the incidence of HO [5]. Indomethacin prophylaxis remains the gold standard, but should be used with caution due to the potential side-effect profiles of renal impairment, gastrointestinal bleeding, perioperative bleeding, and bony nonunion caused by a reduction of thromboxane A_2, which is essential for platelet aggregation. There is now evidence to suggest that combined protocols with RT could be used reducing overall length of treatment to 15 days, thus lowering potential drug complications. The authors recommend a dosage of 700 cGY as part of their combined protocol for reducing HO in hip resurfacing procedures [5].

2.2 Selective COX-2 inhibitors

The use of selective COX-2 inhibitors has been well researched, demonstrating efficacious results compared with nonselective COX inhibitors. The potential advantages include a reduced side-effect profile and less intra- and postoperative bleeding [6]. Studies so far have demonstrated reduced incidence of gastrointestinal bleeding [7]. More recently, concerns have been expressed over potential cardiovascular complications, with increased risk of myocardial infarction with the use of selective COX-2 inhibitors [8]. Recent publications lend weight to current established literature suggesting that COX-2 inhibitors are efficacious in the prophylaxis of HO [7,9]. There is still, however, a lack of evidence to support selective COX-2 inhibitors as a first-line treatment over indomethacin for the treatment of HO. They could be used in patients who are known to have gastrointestinal disorders or peptic ulceration who cannot tolerate nonselective NSAIDs, but should be used with caution in patients with a cardiac history.

2.3 Aspirin

The results of aspirin in the prevention of HO are mixed. A large prospective study of 2649 patients found that aspirin was ineffective in preventing HO formation [10]. More recently, a retrospective study comparing first-stage bilateral total hip arthroplasty patients treated with aspirin versus coumadin demonstrated a significant reduction in the prevalence and severity of HO with aspirin [11]. On comparing hip surface replacement procedures, aspirin appears to decrease incidence and severity of HO to a level similar to that seen in total hip arthroplasty when compared to coumadin alone [12]. The result of aspirin as a prophylaxis against HO are encouraging, with the added advantage that aspirin is used in many centers for thromboembolic prophylaxis after surgery. Aspirin may thus negate the requirement for other pharmacological treatments and could be used as a dual therapy for both HO and thromboembolic prophylaxis.

2.4 BMP type 1 receptor inhibition and BMP antagonist, noggin

The role of BMP in the development of HO has yet to be fully understood. Osteogenic differentiation is regulated by BMP type II receptors (BMPRII, ActRIIA, ActRIIB) that activate BMP type I receptors (activin receptor-like kinase [ALK] 2, 3, 6), which in turn phosphorylate SMAD-1,5,8 to subsequently translocate into the nucleus regulating genes related to growth and differentiation. Antagonists of BMP receptors could therefore be potential therapeutic targets for downregulation of osteogenic differentiation and therefore HO proliferation. *In vitro* and *in vivo* models suggest that small-molecule inhibition of BMP type I receptors can downregulate BMP signaling, and thus may be useful in treating HO syndromes. Furthermore, heterozygous mutations in the *ACVR1* gene encoding for the BMP type I receptor ALK2 have been shown to be key in the genetics of fibrodysplasia ossificans progressiva (FOP) and therefore offer potential future therapeutic targets to inhibit excess bone formation [13]. BMP-4 is involved in physiological skeletogenesis and disease such as FOP. Manipulating BMP antagonists like noggin may protect against HO formation. *Ex vivo* delivery of noggin via retroviral [14] or adenoviral 2 vectors suppressed BMP-4 expression and the subsequent experimental HO in a dose-dependent manner. Currently, the use of BMP type 1 receptor antagonists offer no clinical use in HO prophylaxis, but do offer a novel target for future development.

2.5 Nuclear retinoic acid receptor γ agonists (RAR-γ)

Inflammation induces endochondral HO following surgical insult. The RAR pathway is a strong inhibitor of chondrogenesis, and subsequently of HO formation. RAR-γ are expressed on both chondrogenic cells and mature chondrocytes. Evidence from animal models indicates that RAR-γ agonists cause reduction in BMP signaling, lowering downstream Smad 1/5/8 phosphorylation and overall Smad levels [15]. It is also possible that RAR-γ agonists inhibit HO formation by increasing Wnt/β-catenin signaling, and thus could form a basis for future anti-HO therapy. Transient delay in fracture repair and negative effects on the growth plate are downsides, hence not yet tested in human trials. Further research needs to be conducted before this modality offers any hope for use in a clinical setting.

2.6 Free radical (FR) scavengers and etidronate disodium

FRs, produced by oxidative stress as a result of hypoxia, induce tissue trauma that is related to HO formation. Based on the latter assumption, FR scavengers like the combined allopurinol and N-acetylcysteine (A/A) may prevent HO formation. Limited *in vivo* data indicate that A/A is superior to indomethacin [16] and equivalent to methylprednisolone

in preventing experimentally induced HO in rodents [17]. Two randomized, controlled trials comparing etidronate disodium versus placebo were reviewed recently by Haran and colleagues in *Cochrane Reviews,* showing that etidronate disodium delays rather than prevents HO mineralization [18]. Limited data on FR scavengers and etidronate disodium limit their use, and further research is required to demonstrate potential benefits.

3. Expert opinion

Numerous modalities for the prevention of HO following total hip arthroplasty have been studied in the literature. Considerable evidence indicates that the gold standard of treatment remains the use of indomethacin in divided 25-mg doses, beginning in the immediate postoperative period. Treatment duration is variable, but is suggested to be ≥ 7 days. Combination protocols using both indomethacin and RT have shown results superior to monotherapy alone and could potentially reduce the duration of therapy. The use of selective COX-2 inhibitors has been demonstrated to be as efficacious as nonselective COX inhibitors. The theoretical advantages of the COX-2 inhibitors are their improved side-effect profiles, which makes them more appealing for clinical use. Their use, however, has been limited, since published data demonstrated increased cardiovascular risk and morbidity. A combination of careful surgical technique with minimal trauma to soft tissues, pulsed lavage, and rapid rehabilitation has considerably diminished the incidence of clinically relevant HO related to total hip arthroplasty, and should be used as standard practice alongside pharmacological prophylaxis.

More recent *in vitro* and animal model evidence in delineating the genetic and cellular pathways of HO formation have led to a better understanding of the complex interactions required for osteogenic differentiation and regulation. ALK2 receptor inhibition, retro- or adenoviral delivery of noggin, RAR-γ agonists, FR scavengers, and etidronate disodium offer potential exciting therapeutic targets for HO following hip surgery. Development of pharmacotherapy applicable to human clinical use remains the ultimate goal; but in view of the complexity, feedback mechanisms, potential inhibitory side effects of osteogenesis, and long-term toxicity, it is likely that any targeted treatment will remain under investigation.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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