Critical Reviews in Oncology/Hematology 100 (2016) 25–31

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Is the cardiovascular toxicity of NSAIDS and COX-2 selective inhibitors underestimated in patients with haemophilia?

Ana Boban[a,b,*], Catherine Lambert[a], Cedric Hermans[a]

[a] Haemostasis and Thrombosis Unit, Division of Haematology, Haemophilia Clinic, Saint-Luc University Hospital, Brussels, Belgium
[b] Division of Haematology, Department of Internal medicine, University Hospital Zagreb, Medical School of Zagreb, Croatia

Contents

ARTICLE INFO

Article history:
Received 27 July 2015
Received in revised form 31 January 2016
Accepted 8 February 2016

Keywords:
Cardiovascular disease
Coxibs
Haemophilia A
Haemophilia B
NSAID

ABSTRACT

Joint pain secondary to chronic arthropathy represents one of the most common and debilitating complications of haemophilia, often requiring analgesic care. When compared with nonselective non-steroidal anti-inflammatory drugs (ns-NSAIDs), selective COX-2 inhibitors (coxibs) offer the major advantage of not increasing the bleeding risk, thus being a better choice of analgesics for haemophilia patients. However, several studies have highlighted the cardiovascular risks posed by coxibs and NSAIDs. Given the assumed protection against thrombosis conferred by the deficiency in coagulation factors VIII or IX, these precautions regarding the use of coxibs and NSAIDs have never really been taken into account in haemophilia management. However, contrary to what has long been suspected, haemophilia patients are indeed affected by the same cardiovascular risk factors as nonhaemophiliac patients. Further studies should be conducted to evaluate the impact of NSAIDs on cardiovascular risks and the prevalence of hypertension in haemophilia patients.

1. Haemophilic arthropathy management

Haemophilic arthropathy represents one of the most common and debilitating complications of haemophilia. The pathophysiology of haemophilic arthropathy is complex, multifactorial, and not yet fully understood. The hypothesis has been suggested saying that the process begins with intra-articular bleeding, either in a first episode or recurrent event, consequently triggering the inflammatory cascade, which then promotes angiogenesis (Acharya et al., 2011; Zetterberg et al., 2014). With recurrent bleedings, synovial angiogenesis both causes and enhances vascular reorganization, resulting in vascular rarefaction adjacent to the synovial surface, as well as increased vascular densities further away from the joint space. Simultaneously, due to the prolonged and frequent immobilization and avoidance of physical exercise observed in this population, the surrounding muscles become hypotrophic, thus weakening the joint. Together, this leads to susceptibility for joint re-bleeding. If recurrent bleeding still persists, the process develops into chronic inflammation, finally causing fibrosis, cartilage degeneration, and joint destruction. Inflammatory cells serve to release proteolytic and hydrolytic enzymes, which activate osteoclasts and

* Corresponding author at: Clinique d'Hémophilie, Service d'Hématologie, Cliniques Universitaires Saint-Luc, Avenue Hippocrate 10, B-1200 Bruxelles, Belgium.
E-mail addresses: bobanana@gmail.com, ana.boban@zg-kbc.hr (A. Boban), catherine.lambert@clin.ucl.ac.be (C. Lambert), Cedric.Hermans@uclouvain.be (C. Hermans).

http://dx.doi.org/10.1016/j.critrevonc.2016.02.002
1040-8428/

cause the erosion of joint cartilage and bone (Dunn et al., 2002). It would therefore seem that inflammation plays a major role in the pathogenesis of haemophilic arthropathy, from the first bleeding episode to the eventual destruction of the joint.

Haemophilic arthropathy predominantly presents clinically with pain, either acute or chronic, which has a significant negative impact on a haemophilia patient's quality of life (Witkop et al., 2015; Forsyth et al., 2015). Moreover, the joint pain frequently requires the intensive or prolonged use of analgesics. As many as three-quarters of adult haemophilia patients have been estimated to suffer from arthropathy requiring the use of pain-control medication (Eyster et al., 2007). In addition to this, it is difficult for both the patients and their physicians to make the difference between acute bleeding and an exacerbation of chronic arthropathy (Timmer et al., 2015). Yet, these two conditions require different approaches: replacement therapy of clotting factor concentrates for acute bleeding or anti-inflammatory agents for chronic arthropathy. In this setting, effective analgesics might help to identify chronic pain cases specifically, as well as to achieve better pain control and also reduce the amount of factor concentrates administered.

Choosing the best analgesic therapy for haemophilia patients can be challenging, requiring consideration of the estimated duration of analgesic therapy, which is usually long-term, along with the presence of co-morbidities and potential of some drugs to increase the bleeding risk. Acetaminophen (paracetamol) is the most commonly-prescribed drug in this setting, yet it does not possess the necessary anti-inflammatory capacity for managing chronic inflammation in damaged joints. Moreover, there is a concern regarding its hepatotoxic potential, even when adhering to the recommended doses and drug levels that were not previously considered hepatotoxic (van Veen et al., 2008). Alternatively, opioids are effective for both acute and chronic pain, although they do not possess anti-inflammatory capacities either, and even pose the risks of tachyphylaxis, dependency, or even drug abuse. Moreover, no specific literature currently exists on how to use opioids in pain management strategies for haemophilia (Holstein et al., 2012).

On the other hand, non-selective non-steroidal anti-inflammatory drugs (ns-NSAIDs) possess both properties required by haemophilia patients: good analgesic effects and anti-inflammatory activity. On the other hand, physicians often avoid prescribing these agents to haemophilia patients due to their increased risks of bleeding complications, particularly affecting the gastrointestinal (GI) tract, and their inhibitory effect on platelet function. Clinically-relevant upper-GI bleeding has, in fact, been described as a major issue in adult patients with haemophilia, with the annual incidence reported to be 1.3%, 5–10 times higher than that of the general population (Eyster et al., 2007).

Currently, there are no evidence-based guidelines on pain management strategies for people with haemophilia. Still, as shown by a survey on pain management in haemophilia in Europe, the preferred first-line treatment for managing acute pain is paracetamol and NSAIDs, while the second-line therapy differs from study to study. For managing chronic pain, most centres recommend weak opioids with or without paracetamol. Selective COX-2 inhibitors (coxibs) are preferred in young adults with chronic pain (Holstein et al., 2012).

2. NSAIDS and coxibs

NSAIDs exert their pharmacological effect by inhibiting the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzymes, thereby blocking conversion of arachidonic acid to prostaglandin E2 (PGE2) and PGI2 (prostacyclin), which mediate pain. Furthermore, COX enzymes convert arachidonic acid to prostaglandins in the gastric lining, where they protect the gastric mucosa, as well as in the vascular-endothelial and smooth-muscle cells of blood vessels, where they lead to vasodilation and inhibit platelet aggregation. In the platelets, prostaglandins are further converted by thromboxane synthase to thromboxane A2 (TXA2), which, when released, stimulates platelet aggregation and vasoconstriction (Cannon and Cannon, 2012) (Fig. 1). This explains why, besides their analgesic, anti-inflammatory, and antithrombotic effects, NSAIDs exhibit significant GI toxicity.

For this reason, a novel group of NSAIDs was developed that would selectively inhibit COX-2 and not COX-1, thereby avoiding inducing GI complications, while still reducing pain and inflammation. Coxibs, selective COX-2 inhibitors, have demonstrated a safer drug profile in terms of GI complications when compared to ns-NSAIDs. Two large trials were conducted in order to address this issue. The Vioxx Gastrointestinal Outcomes Research (VIGOR) study assessed whether rofecoxib, a coxib, induced a lower incidence of clinically-major upper-GI events than the ns-NSAID naproxen in patients with rheumatoid arthritis. The results clearly indicated lower incidences of GI perforation, GI haemorrhage, and symptomatic peptic ulcers in the patients receiving 50 mg of rofecoxib, compared to those receiving 2×500 mg of naproxen (Bombardier et al., 2000). Another large study, the CLASS trial, found no statistically significant difference in terms of incidences of ulcer perforation, gastric-outlet obstructions, and upper-GI bleeding between groups receiving either celecoxib or diclofenac (Silverstein et al., 2000). Of note, while diclofenac is registered as a ns-NSAID and celecoxib as a coxib, the selectivity of diclofenac for COX-1 and COX-2 has been reported to be similar to that of celecoxib (FitzGerald and Patrono, 2001). The inhibitory potency and selectivity of NSAIDs for COX-1 and COX-2 does, in fact, highly vary between particular NSAIDs (Blain et al., 2002). Moreover, the degree of COX-selectivity of an NSAID should be interpreted cautiously, since it also varies between species, experimental models, and *in vitro vs. in vivo* studies (Blain et al., 2002). Finally, some authors have emphasized the difference in GI toxicity levels between different NSAIDs, stressing that no trials have yet been conducted applying optimal criteria in order to demonstrate the superiority of coxibs over ns-NSAIDs (Cryer and Feldman, 1998). There is now a debate as to whether GI toxicity is related more to ns-NSAIDs than to coxibs. By way of an explanation of the GI toxicity of coxibs, it has been demonstrated that even coxibs exhibit sufficient COX-1 inhibitory activity to cause potent inhibitory effects on gastric PEG2 synthesis (Blain et al., 2002).

3. Administering coxibs to haemophilia patients

The development of coxibs significantly changed the perspective towards using NSAIDS in haemophilia patients. Coxibs were welcomed with high expectations due to their properties that suit the haemophilia population's needs. Firstly, when compared to ns-NSAIDs, coxibs have demonstrated similar analgesic effects, yet offer the major advantage of not increasing the risk of bleeding, on account of the reduced or absent effect these agents have on COX-1, which is involved in platelet aggregation (FitzGerald and Patrono, 2001). Furthermore, coxibs possess anti-angiogenic and anti-inflammatory properties (FitzGerald and Patrono, 2001) that could be valuable in attenuating the angiogenesis and thus recurrent haemarthrosis present in haemophilia patients. The inflammatory response in this context is believed to be at least partly mediated by both types of COX enzymes, with COX-2 heavily involved in promoting inflammation (FitzGerald and Patrono, 2001). COX-2 is an enzyme stimulated by the inflammation stimuli, in contrast to COX-1, which is constitutive. COX-2 is thus markedly upregulated by cytokines, growth factors, and