Cyclooxygenase-inhibiting nitric oxide donators for osteoarthritis

John L. Wallace¹, Serena Viappiani² and Manlio Bolla²

¹Farncombe Family Digestive Health Research Institute, McMaster University, Hamilton, Ontario, L8N 3Z5, Canada
²NicOx Research, 06906 Sophia-Antipolis, France

Nonsteroidal anti-inflammatory drugs (NSAIDs) remain the most commonly used medications for the treatment of the symptoms of many chronic inflammatory diseases, including osteoarthritis. Unfortunately, the toxicity of NSAIDs substantially limits their long-term use. Some newer NSAIDs, namely selective cyclooxygenase (COX)-2 inhibitors, exhibit greater gastrointestinal safety, and concomitant use of anti-secretory drugs can also reduce NSAID-induced gastropathy. However, NSAIDs also adversely affect the cardiovascular system.

A new class of anti-inflammatory drugs, COX-inhibiting nitric oxide donators (CINODs), has been designed to exert similar anti-inflammatory effects as NSAIDs, but with an improved safety profile. CINODs release nitric oxide, providing protective effects in the gastrointestinal tract and attenuating the detrimental effects on blood pressure normally associated with NSAIDs. We provide an outline of the rationale for CINODs and their activity, in addition to an overview of the pre-clinical and clinical profile of the most advanced CINOD, naproxcinod.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a mainstay for the treatment of several chronic inflammatory conditions, including osteoarthritis (OA). Traditional NSAIDs (tNSAIDs), which non-selectively inhibit both cyclooxygenase (COX) isoforms, have long been recognized for their ability to cause serious gastrointestinal (GI) damage (Box 1). Selective COX-2 inhibitors were developed with the goal of being much more GI-sparing than tNSAIDs. However, in the aftermath of the withdrawal of rofecoxib (Vioxx™) from the marketplace, it has become clear that these drugs, and possibly also tNSAIDs, can cause serious cardiovascular (CV) adverse effects (Box 2). This is problematic for physicians when their patients are in need of long-term anti-inflammatory and analgesic therapy in the presence of CV co-morbidities [1]. Further complicating the issue is the finding that co-administration of low-dose aspirin, in an attempt to counteract lack of anti-thrombotic actions of selective COX-2 inhibitors, abolishes any advantage these drugs offer in terms of GI safety [2]. There remains, therefore, a need for potent and safe anti-inflammatory and analgesic agents that can be used on a long-term basis.

The purpose of this opinion article is to provide the scientific background and pharmacological profile of a new class of anti-inflammatory drugs, the COX-inhibiting nitric oxide (NO) donators (CINODs). CINODs inhibit COX (COX-1 and/or COX-2; Table 1) and release NO in the vasculature and GI tract. Besides exhibiting reduced GI toxicity, CINODs control inflammation and pain without increasing blood pressure (BP), a clinically important adverse effect of tNSAIDs and selective COX-2 inhibitors.

The first member of the CINOD class, naproxcinod, is an investigational new drug approaching the completion of its Phase III clinical development program, the aim of which is to confirm in OA patients the findings observed in the previous phases of development, including efficacy and favourable BP profile.

NSAIDs and NO

NSAIDs inhibit the activity of COX enzymes, thereby reducing the conversion of arachidonic acid into prostaglandins (PG) and thromboxane. Two isoforms of COX have been identified. COX-1 is constitutively expressed, while COX-2 is inducible. Partial NO synthase activity is retained in COX-2 [3]. COX-2 activity accounts for most of the synthesis of PGs at sites of inflammation, but this includes both the prostanoids that promote inflammation and those that exert anti-inflammatory effects, the latter contributing extensively to the resolution of inflammation [3]. COX-2 is also constitutively expressed and/or rapidly induced in some healthy tissues, such as the vasculature, stomach, kidney and brain, where it has important regulatory properties [4,5]. Thus, selective inhibition of COX-2 can cause serious perturbations of several physiological processes.

NO is synthesized from l-arginine by the enzyme NO synthase (NOS), which exists in three isoforms, namely the constitutively expressed endothelial (eNOS or NOS3) and neuronal (nNOS or NOS1) forms, and the mainly inducible isoform (iNOS or NOS2). NO activates soluble guanylyl cyclase, which in turn converts GTP into cyclic (c)GMP, the second messenger responsible for most NO signalling. NO is a key regulator of blood flow [6–9] and an important modulator of platelet and leukocyte activation, adhesion and aggregation. Inhibition of NO synthesis leads to an increase in systemic BP [10,11]. This underscores the importance of vascular NO generation in controlling BP, and a growing amount of evidence indicates that NO signalling is a key factor in counteracting the onset and development of several CV diseases including hypertension, myocardial infarction and stroke. NO also prevents atherogenesis by inhibiting vascular smooth muscle cell

Corresponding author: Wallace, J.L. (wallacejohn@mcmaster.ca).
Box 1. Mechanisms of NSAID-induced gastric mucosal injury

NSAIDs cause gastric damage through at least two distinct mechanisms: direct epithelial damage, due to their acidic properties, and a reduction of mucosal prostaglandin (PG) synthesis, with a resulting decrease in mucosal defence [51]. Chemical masking of the carboxylic acid group, or improved formulations (coated or slow-release formulations), have addressed the irritant effects of NSAIDs but have had little impact on the incidence of clinically important gastric injury and bleeding [51]. It is the suppression of PG synthesis by NSAIDs, even when administered systemically, that seems to be the predominant mechanism through which these drugs induce damage in the stomach. Reduced gastric PG synthesis results in several events that contribute to the generation of mucosal damage, including leukocyte adherence to the vascular endothelium in the gastrointestinal (GI) microcirculation, reduced mucosal blood flow and reduced gastric mucus and bicarbonate secretion [51]. The induction of gastric injury by NSAIDs in an otherwise healthy stomach requires inhibition of both COX-1 and COX-2 [52]. The latter is expressed at very low levels in the normal stomach but is rapidly upregulated after suppression of COX-1 activity or irritation of the mucosa and makes an important contribution to mucosal defense and repair [5,53].

COX-2 inhibitors have, indeed, proven to induce less upper GI damage than traditional NSAIDs in patients who are considered to be at low risk for GI ulceration (for review, see Ref. [54]). In patients with co-morbidities or other factors that increase the risk of GI ulceration (e.g. advanced age), the benefits of a selective COX-2 inhibitor over tNSAIDs are substantially diminished. It is also important to bear in mind that any GI benefit of a selective COX-2 inhibitor is lost if these drugs are taken concomitantly with low-dose aspirin [2]. The co-administration of a tNSAID with proton pump inhibitors can be as effective as the use of a selective COX-2 inhibitor in terms of reducing the incidence of upper GI tract adverse events [55]; however, the long-term use of proton pump inhibitors also carries some risk to the patients, such as an increased susceptibility to certain infections and an increase in the risk of hip fractures [56]. Whether or not proton pump inhibitors reduce the incidence of NSAID-induced injury in the small intestine, which is the site of most bleeding caused by this class of drugs [57], is unclear.

proliferation and preventing low-density lipoprotein oxidation and macrophage activation [12].

In the GI tract, NO-dependent modulation of blood flow contributes to mucosal defence against luminal irritants. NO also modulates other components of mucosal defence, such as mucus and bicarbonate secretion, and epithelial permeability and the mucosal healing processes [9]. Inhibition of leukocyte adherence within the mucosal microcirculation seems to be an important action with respect to NO-mediated protection against NSAID-induced damage [13]. NO also regulates mitochondrial respiration, acts as a free radical scavenger and antioxidant, mediates neurotransmission and modulates vascular permeability. Among the various activities of NO that are not dependent on cGMP activation, the modulation of activity of transcription factor nuclear factor (NF)-κB represents a potential target for controlling inflammation [14,15]. This mechanism might account for the ability of NO to suppress the release from and/or expression of pro-inflammatory mediators in several cells including mast cells [16], macrophages [17] and vascular smooth muscle cells [12].

Rationale for CINODs

CINODs have been designed to provide the anti-inflammatory and analgesic efficacy of tNSAIDs with improved tolerability and safety, particularly in the GI and CV systems (Figure 1). The CINOD technology involves chemical modification of the structure of a tNSAID or selective COX-2 inhibitor (Table 1). With respect to naproxcinod and other nitrate esters, the nature of the ‘linker’ that connects the NSAID to the NO-releasing moiety is very important. Enzymatic cleavage of the CINODs is required for them to inhibit COX. In vivo, CINODs exhibit full COX inhibition and anti-inflammatory and analgesic properties comparable to those of the reference NSAID [18,19]. However, CINODs show significantly improved GI tolerability [18,20–22], probably because of the release of NO. Thus, NO derived from CINODs has been shown to improve gastric mucosal blood flow, to inhibit leukocyte adhesion in the GI microcirculation and to inhibit caspase-1 and caspase-3 activity, which are involved in epithelial-cell apoptosis [20,21,23]. Moreover, the NO derived from CINODs has been shown to promote healing [24–26].

CINODs also exhibit an improved CV safety profile in animal studies as compared to tNSAIDs and COX-2 inhibitors. This is probably owing to their ability to inhibit platelet aggregation [27,28], reduce systemic BP [29–31] and preserve vascular, cardiac and renal function in settings of hypertension or myocardial dysfunction [30,32].

Naproxinod

Naproxinod is a CINOD that is in the late stages of Phase III clinical trials. Because the results from the completed trials are confirming the rationale behind the CINOD strategy, the preclinical and clinical pharmacological characterization of naproxinod will serve as a model here.

Preclinical pharmacodynamics

Naproxinod is effective in several animal models of arthritis and pain, with similar potency to naproxen. In the carrageenan-induced paw edema model, oral naproxinod dose-dependently reduced paw swelling [18,22,33,34]. Naproxinod was also as effective as naproxen in a model of experimental arthritis, whether given preventatively or
after the arthritis had been established [19,35], and reduced Brewer's yeast-induced fever in rats in a dose-dependent manner [33].

These anti-inflammatory, analgesic and anti-pyretic properties of naproxcinod derive from its ability to inhibit both COX-1 and COX-2 in vivo, subsequent to its metabolism to release naproxen. Dose-dependent inhibition of COX-1 (systemic thromboxane synthesis) was detected after single or repeated administration of naproxcinod to rodents [25,36]. Naproxcinod also inhibited accumulation of COX-2-derived PGE2 in inflammatory exudates, with similar potency to naproxen [22,25]. The degree of COX inhibition by orally administered naproxcinod correlated well with plasma concentrations of naproxen [33,37].

**GI-sparing properties of naproxcinod**

Naproxcinod showed improved GI tolerability as compared with naproxen, both after single or repeated administration to rats [18,34]. Markedly less hemorrhagic damage was observed with naproxcinod in both the stomach and small intestine, and a significant reduction of bleeding was

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<th>CINOD technology</th>
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Figure 1. Mechanisms of action of CINODs. Inhibition of COX-1 and COX-2 by traditional NSAIDs (tNSAIDs) results in diminished gastric mucosal defence and repair, leading to mucosal injury and bleeding. The latter is exacerbated by the inhibition of platelet aggregation (owing to suppression of COX-1-dependent thromboxane synthesis). NSAIDs also cause a reduction in renal perfusion, promote elevations in BP and can exacerbate CV damage. NO released from CINODs could counteract many of the detrimental effects of NSAIDs while not interfering with their ability to produce the desired effects (i.e. reduced edema and pain). Via soluble guanylyl cyclase, NO acts to maintain mucosal blood flow, inhibit leukocyte adherence within the GI microcirculation, stimulate mucus and bicarbonate secretion and enhance healing of mucosal injury. NO exerts several cardioprotective effects and, as a potent vasodilator, diminishes the BP-raising effects of NSAIDs. In some circumstances, the NO released from CINODs could exert additional anti-inflammatory effects to those of the NSAID moiety, as a result of the ability of NO to act as an anti-oxidant and to inhibit the activation of nuclear transcription factor αB.
indicated by the attenuated reduction of hematocrit in the naproxcinod-treated animals [18].

The incidence of GI adverse effects of NSAIDs is elevated in patients with certain co-morbidities or other risk factors [38,39]. Naproxcinod has been tested in several animal models that mimic these clinical settings. In arthritic rats, daily administration of naproxcinod caused ~70% less gastric mucosal injury than an equimolar dose of naproxen (P < 0.01) [35]. Moreover, in animals receiving aspirin (which increases susceptibility to NSAID-induced gastropathy), naproxcinod elicited significantly less gastric damage than was seen with naproxen or a selective COX-2 inhibitor (celecoxib) [35]. In a model in which NO synthesis was chronically suppressed by administration of a NOS inhibitor, naproxen elicited extensive gastric damage, whereas naproxcinod significantly protected the stomach [29].

CV effects of naproxcinod

When incubated in vitro with rat aortic rings, naproxcinod is metabolized such that NO release occurs, resulting in a concentration-dependent relaxation. This occurred with aortic rings from hypertensive rats and from healthy controls with an EC₅₀ in each case in the low micromolar range [29,30]. The dependency of this relaxation on NO has been confirmed using selective inhibitors of the soluble guanylyl cyclase pathway [40].

In vivo, a BP-lowering effect of naproxcinod was observed in several rat models of hypertension, including a mechanical model (two kidney, one clip), a chemical model (inhibition of NOS) and spontaneously hypertensive rats (SHR). In SHR, daily oral dosing with naproxcinod for one week reduced systolic BP (from 220 ± 3 mmHg to 204 ± 2 mmHg; P < 0.05) [36,40]. In the other models, naproxen exacerbated the hypertension, whereas naproxcinod significantly reduced BP [29,30]. Importantly, naproxcinod did not affect BP in normotensive rats [30,36]. This indicates a role of NO in restoring a compromised vascular function in hypertensive states.

A model of cardiac damage after ischemia/reperfusion has been used to further investigate the potential beneficial effects of naproxcinod [32]. Isolated rabbit hearts were perfused with vehicle, naproxen or naproxcinod and subjected to low-flow ischemia and reperfusion. With vehicle treatment, left ventricular end diastolic pressure, indicative of ventricular congestion, gradually increased over the ischemic period. Naproxen [32] and celecoxib [41] dose-dependently exacerbated this effect. By contrast, naproxcinod dose-dependently reduced ventricular congestion.

An in vivo model of myocardial infarction confirmed the cardioprotective properties of naproxcinod [42]. Rats were treated daily for 5 days with vehicle, naproxen or naproxcinod and were then subjected to ischemia/reperfusion. Mortality was reduced from 36% in vehicle-treated rats to 11% with naproxcinod and to 22% with naproxen. A reduction of infarct size was more pronounced in the naproxcinod-treated than in the naproxen-treated group.

Pharmacokinetic studies

The pre-clinical pharmacokinetic profile of naproxcinod was studied in rats and mini-pigs. After oral administration of naproxcinod, marked GI hydrolysis to naproxen was observed and plasma availability of naproxen was lower (55% and 85% in rats and mini-pigs, respectively) than that observed after administration of an equimolar dose of naproxen [43].

Studies in healthy volunteers [44] have shown that after single oral administration of naproxcinod (375 mg and 750 mg) only a small percentage of the intact drug is found in the plasma, and it is undetectable by 12 hours after administration. The majority of naproxcinod is rapidly metabolised to naproxen. The mean relative plasma bioavailability (Frel) of naproxen after naproxcinod administration is 80–85% when compared with the availability of an equimolar dose of naproxen [44]. The GI uptake of naproxen after oral naproxcinod is also slower (tmax = 3 hours) than after oral naproxen (tmax = 2 hours). Overall, these differences in availability of the main metabolite (naproxen) do not seem to affect the efficacy of naproxcinod in reducing pain and inflammation in hip and knee OA (described later).

Clinical efficacy and safety

Published clinical data have confirmed that naproxcinod provides some improvement in gastric tolerability, while maintaining similar efficacy to the original NSAID. Efficacy in OA patients has been assessed in Phase II clinical trials and confirmed in the first Phase III studies. In a Phase II double-blind, placebo-controlled, crossover study conducted on a total of 970 patients with hip or knee OA, naproxcinod (750 mg twice daily for 6 weeks) significantly reduced the signs and symptoms of hip and knee OA (WOMAC™ score; www.orthopaedicscores.com), with similar effectiveness to an equimolar dose of naproxen (500 mg twice daily) [45]. Efficacy was confirmed in a further double-blind study on 672 patients with knee OA, where naproxcinod (375 mg and 750 mg, twice daily for 6 weeks) decreased signs and symptoms of OA with similar efficacy to 25 mg rofecoxib and 500 mg naproxen [46]. The first Phase III clinical trial in 918 knee OA patients has confirmed that both the 375 mg and 750 mg doses of naproxcinod were superior to placebo for the three co-primary endpoints (WOMAC™ pain and function subscales, and patient overall assessment of disease status) [47]. In mid-September 2008, top-line results from a second pivotal Phase III were announced (NicOx press release, September 15, 2008; www.nicox.com/upload/PR302results-150908 GB.pdf). A total of 1020 patients with OA of the knee were enrolled. This study confirmed that both doses of naproxcinod (750 mg and 375 mg twice daily) met the three co-primary efficacy endpoints (as earlier) at week 13 versus placebo (P < 0.001). In addition, naproxcinod (750 mg twice daily) was statistically non-inferior to naproxen (500 mg twice daily) on the WOMAC™ pain and function subscales at weeks 13 and 26 (NicOx press release, September 15, 2008; www.nicox.com/upload/PR302results-150908 GB.pdf).

The potential protective activity of NO in the gastric mucosa was assessed during the Phase I and II programs for naproxcinod. First, the GI safety profile of naproxcinod 750 mg twice daily was assessed versus naproxen 500 mg twice daily or placebo in 31 healthy volunteers in a
randomized, double-blind, crossover study. After 12 days of treatment, the mean number of gastroduodenal erosions was 11.5 in the naproxen group versus 4.1 in the naproxcinod group \( (P < 0.01) \) [48]. These results were only partially confirmed in a double-blind, placebo-controlled, crossover study in patients with OA treated for 6 weeks with naproxcinod or naproxen. A 30% lower incidence of gastroduodenal ulcers (>3 mm diameter) in the naproxcinod group did not achieve statistical significance \( (P = 0.066) \). However, statistically significant benefits of naproxcinod versus naproxen were achieved for most of the secondary endpoints [45].

Besides efficacy in OA, the effects of naproxcinod on systolic BP have been assessed via post-hoc analysis in two Phase II randomized controlled trials (involving 672 and 543 patients) with symptomatic hip or knee OA. For 6 weeks, patients took naproxcinod (375 mg or 750 mg twice daily), naproxen (500 mg twice daily), rofecoxib (25 mg once a day) or placebo. At the end of the treatment period, naproxcinod had decreased systolic BP by 2.1 mmHg, whereas rofecoxib caused an increase of 3 mmHg. These opposite effects on BP were especially evident in the hypertensive subpopulation [49]. These results were confirmed and extended in a Phase III study in which 918 knee OA patients received naproxcinod or naproxen twice daily for 13 weeks. The naproxcinod 750 mg and 375 mg groups showed mean changes in BP from baseline versus naproxen of \(-2.89 \ (P = 0.0154)\) and \(-1.82 \text{ mmHg} \ (P = 0.1207)\), respectively, and in diastolic BP of \(-1.79 \ (P = 0.0193)\) and \(-1.55 \text{ mmHg} \ (P = 0.0386)\), respectively. By week 13, more patients on naproxcinod had a decrease in BP as compared with patients on placebo or naproxen [47].

**Perspectives for OA patients**

Management of OA is essentially symptomatic, with the aim of reducing pain and improving quality of life. It relies on anti-inflammatory therapy, such as NSAIDs and corticosteroids. Several guidelines have been issued recently from different professional associations trying to assist physicians in deciding how best to manage patients with symptomatic OA, many of whom have a range of co-morbidities and are, therefore, more at risk of substantial adverse effects of NSAIDs [50]. NSAIDs cannot easily be substituted, so classification of patients on the basis of their risk profile is mandatory for optimizing therapy. Although there are some therapeutic options for the treatment of patients with increased GI risk (e.g. selective COX-2 inhibitors, proton pump inhibitors), the situation is more complicated when CV risk is present. Clearly, there remains an unmet need for efficacious but safer NSAIDs in the treatment of OA.

CINODs have been designed with the goal of fulfilling this need, at least in part. Despite the fact that naproxcinod did not meet the primary endpoint in terms of improved GI tolerability over naproxen in OA patients, it has exhibited better GI tolerability in healthy volunteers [48,49]. In addition, NO might be beneficial in controlling BP, which is increased during treatment with NSAIDs and selective COX-2 inhibitors. Pre-clinical data for naproxcinod indicate at least a non-worsening effect in hypertensive animal models, and the available clinical evidence confirms a non-detrimental effect versus placebo.

**Conclusions**

CINODs could be considered to be a product of translational research, in which knowledge of the physiological role of NO and its signalling pathways has triggered the development of NO-donating NSAIDs as therapeutic agents for improving care in an area of medical need. Gaseous NO is approved for inhalation therapy in conditions such as newborn respiratory distress syndrome and is being evaluated for other conditions such as pulmonary arterial hypertension. In this case, however, the action of NO is maintained only while the gas is administered. The CINODs afford NO activity for a longer period of time, and the results on BP in the Phase III trials indicate that this technology provides long-lasting NO-mediated effects.

The clinical development of naproxcinod still has to be completed before its potential in humans can be fully validated; however, the available pre-clinical and clinical data are encouraging.

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