Treatment strategies for osteoarthritis patients with pain and hypertension

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Abstract: Out of 100 patients with osteoarthritis (OA), almost 40 have a concomitant diagnosis of hypertension. Nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors may trigger a rise in blood pressure (BP), which is more marked in patients with established hypertension. NSAIDs and COX-2 inhibitors attenuate the antihypertensive effect of several antihypertensive agents. Frequent BP controls are needed in treated hypertensive patients who are concomitantly receiving NSAIDs or COX-2 inhibitors because even a small increase in BP may be associated with an important rise in the risk of major cardiovascular complications. In meta-analyses, an increase in systolic BP of 5 mmHg was associated with a 25% higher risk of cardiovascular events. These data have been confirmed in randomized studies with rofecoxib and celecoxib, where a modest increase in BP was associated with a significantly higher risk of cardiovascular disease. There is emerging evidence that the COX-inhibiting nitric oxide donator (CINOD) class is promising in the treatment of patients with OA. Naproxcinod, the first CINOD investigated in clinical trials, is composed of the traditional NSAID naproxen covalently bound to the nitric oxide (NO)-donating moiety butanediol mononitrate (BDMN). The molecule has the potential to provide a sustained release of NO. In clinical studies, naproxcinod prevented the BP rise in normotensive and hypertensive patients observed with naproxen. The BP benefit of naproxcinod over naproxen was greater in patients concomitantly receiving angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. These investigational data suggest that naproxcinod is a valuable alternative to NSAIDs and COX-2 inhibitors for treatment of OA patients.

Keywords: cardiovascular disease, hypertension, naproxcinod, nitric oxide, rheumatoid arthritis

Introduction

Osteoarthritis (OA) is the most frequent musculoskeletal disease and the most frequent cause of pain and loss of functional and work ability [Woolf and Pfleger, 2003]. Owing to the progressive aging of the population and the growing burden of obesity, the incidence of OA is expected to consistently rise over the next decades. In addition to age and obesity, trauma and physically demanding occupations are additional determinants of the risk of OA, particularly at the level of hand, knee and hip [Lohmander *et al.* 2007]. OA imposes a significant financial burden both on patients and healthcare systems and it has been estimated that the cost of patients with OA is twice as much as that of patients without OA [Rabenda *et al.* 2006; Gabriel *et al.* 1997].

OA and hypertension frequently coexist in the same patients [Singh *et al.* 2002]. The *Third National Health and Nutrition Examination Survey* (NHANES III) showed that OA is diagnosed in approximately 21% of the 115.9 million US adults aged ≥ 35 years that have OA [Singh *et al.* 2002]. NHANES III also estimated that a concomitant diagnosis of hypertension is present in 40% of these subjects [Singh *et al.* 2002].

As shown in Figure 1, other cardiovascular risk factors including diabetes, hypercholesterolemia and renal impairment are more frequent in patients with OA than in people without OA. Data in Figure 1 are derived from NHANES III [Singh *et al.* 2002]. Such a cluster of cardiovascular risk factors may be expected to affect the

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†Serum creatinine levels >1.5mg/dl;

*Serum creatinine levels ≥3.0mg/dl

Figure 1. Prevalence of cardiovascular risk factors in subjects with and without osteoarthritis. LDL, low-density lipoprotein.

overall cardiovascular risk in these patients. Addressing this issue, Singh and colleagues estimated the potential impact on the risk of cardiovascular disease and the associated costs of treatment in relation with a given rise in systolic blood pressure (SBP) in patients with OA [Singh *et al.* 2003]. Estimates were based on patient-level data from NHANES III in patients with OA and rheumatoid arthritis, and the Framingham equations for risk calculation. Using validated models, these authors estimated that increases in SBP of only 1–5 mmHg are associated with 7100–35,700 additional coronary artery disease and stroke events per year, with associated costs of between US\$114 million and US\$569 million [Singh *et al.* 2003]. The authors concluded that in cases where two different drugs for OA would have similar anti-inflammatory efficacy but a different effect on systolic BP, considerations of incremental cardiovascular risk may become relevant [Singh *et al.* 2003].

Effects of non-steroidal anti-inflammatory drugs on blood pressure

The non-steroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors are a diverse group of drugs that share an inhibitory effect on cyclooxygenase (COX), the rate-limiting enzyme which converts arachidonic

acid to the labile intermediate PGH_2 . In turn, PGH_2 is converted to thromboxane A_2 by thromboxane synthase, prostacyclin by prostacyclin synthase and other prostaglandins including PGE_2 and PGD_2 . The metabolism of prostaglandins is markedly altered by COX inhibition.

Mechanisms of the blood pressure raising effect

Although the exact mechanisms through which NSAIDs and COX-2 inhibitors may increase blood pressure (BP) levels are not completely known, experimental and clinical studies strongly suggest that these agents may trigger vasoconstriction and a marked antinatriuretic effect (Figure 2) [Simon *et al.* 2002; Morgan *et al.* 2000; Whelton, 2000; Brater, 1999].

By inhibiting COX, NSAIDs systematically reduce the production of several prostaglandins with vasodilating effect, including PGE_2 and PGI_2 . At the renal level the inhibition of prostaglandins results in a drop in the renal blood flow, with reduced glomerular filtration rate and consequent rise in urea and creatinine [Whelton, 2000]. Inhibition of prostaglandins may also trigger an increase in chloride absorption, with consequent sodium retention, edema and hypertension. The reduction of prostaglandins may induce a reduction of renin and aldosterone,

Figure 2. Putative mechanisms underlying the rise in blood pressure during treatment with nonsteroidal anti-inflammatory drugs (NSAIDs).

with consequent potassium retention and hyperkalemia. Finally, the reduction in prostaglandins leads to an increase in the effect of antidiuretic hormone (ADH), which contributes to water retention with hyponatremia [Whelton, 2000].

These adverse effects at a renal level are relatively rare in young and healthy people, in whom the kidneys are usually able to compensate for the effects of NSAIDs on sodium and water retention. Acute COX inhibition may reduce the urinary sodium excretion by 30% or more [Brater, 1999]. In the case of sustained COX inhibition in subjects with normal kidney function, a modest level of sodium and water retention, usually not accompanied by a rise in BP, is in most cases sufficient to re-increase sodium excretion, thereby preserving sodium and water hemostasis [Whelton *et al.* 2000]. This phenomenon may be impaired in patients with reduced kidney function, as well as in elderly people and in those with congestive heart failure (CHF), and this may result in considerable sodium and water retention, leading to a rise in BP in just a few weeks in these patients [Solomon *et al.* 2004; Whelton, 1999]. Fortunately, nephrotoxicity appears to be largely reversible after discontinuation of NSAIDs [Wilson and Poulter, 2006].

In a study from the United Kingdom, the risk of CHF was about 60% higher on average in NSAID users than nonusers [Garcia Rodriguez and Hernandez-Diaz, 2003]. Among the different NSAIDs, the risk was highest for indomethacin and lowest for diclofenac [Garcia Rodriguez and Hernandez-Diaz, 2003].

Another mechanism for the rise in BP induced by NSAIDs and COX-2 inhibitors seems to be the inhibition of the synthesis of prostacyclin, which is known to exert a marked vasodilatory effect which counteracts the vasoconstriction triggered, for example, by angiotensin II and endothelin. Inhibition of prostacyclin may thus induce systemic vasoconstriction with rise in peripheral vascular resistance.

Effects in healthy subjects

The *British Hypertension Society Guidelines* have included NSAIDs as potential causes of BP elevation and deterioration of previously achieved BP control [Williams *et al.* 2004]. In general, normotensive and otherwise healthy subjects who need a short course of NSAIDs usually show only a minor and transient rise in BP [Kurth *et al.* 2005].

An analysis of a Medicare elderly population showed a rate of new-onset hypertension of 22% in subjects not treated with NSAIDs or COX-2 inhibitors. The rate of new-onset hypertension was not significantly different in subjects treated with celecoxib (21%) or NSAIDs (23%), but it rose significantly to 27% among subjects treated with rofecoxib [Solomon *et al.* 2004]. Subjects with concomitant kidney disease or CHF showed a systematically higher risk of developing new-onset hypertension [Solomon *et al.* 2004].

In the Nurses Health Study I, in which more than 51,000 nurses were followed for 8 years, the relative risk of developing hypertension

progressively increased with the number of days per month of treatment with conventional NSAIDs [Dedier *et al.* 2002]. These data have been confirmed in the Nurses Health Study II, in which more than 80,000 nurses were followed for 2 years. The relative risk of developing hypertension also progressively increased with the number of days per month of treatment with conventional NSAIDs [Curhan *et al.* 2002]. In a pooled analysis of both Nurses Health Studies, the risk of developing hypertension also increased with the average daily dose of NSAIDs [Forman *et al.* 2005]. Notably, the same analysis removed the potential objection that headache may have confounded the relation between NSAID use and the rise in BP [Forman *et al.* 2005].

Effects in hypertensive patients

Compared with healthy normotensive subjects, hypertensive patients subjected to long-term exposure to NSAIDs may experience a greater, although variable, degree of BP elevation. In individual studies, increases up to 10/7 mmHg [Morgan and Anderson, 1993] (systolic/diastolic BP) and 12/5 mmHg [Morgan *et al.* 2001] have been reported.

A meta-analysis by Pope and colleagues included 1324 subjects, 92% of whom were hypertensive, for a total of 54 studies. Overall, NSAIDs induced a rise in mean BP that averaged 3.3 mmHg in the hypertensive patients and only 1.1 mmHg in the normotensive subjects. In the hypertensive group, the rise in mean BP was 4.8 mmHg with indomethacin, 6.1 mmHg with naproxen and 2.9 mmHg with piroxicam. A limitation of this meta-analysis was the inclusion of generally healthy and young people, with exclusion of elderly subjects and patients with CHF, i.e. the subsets more frequently subjected to BP rises with NSAIDs [Pope *et al.* 1993].

Another meta-analysis, carried out in 771 relatively young subjects (mean age 47.6 years) enrolled in 66 trials, showed a BP rise induced by NSAIDs of about 5.0 mmHg [Johnson *et al.* 1994]. Indomethacin, piroxicam and ibuprofen caused the greater rise in BP. Notably, NSAIDs antagonized the antihypertensive effects of beta blockers to a greater extent than that of vasodilators and diuretics [Johnson *et al.* 1994].

There is general agreement that NSAIDs may attenuate the BP lowering effect of several antihypertensive agents, probably with the exclusion

of calcium-channel blockers [Morgan *et al.* 2001; Polonia *et al.* 1995; Morgan and Anderson, 1993].

NSAIDs versus COX-2 inhibitors

Several controlled trials have compared different COX-2 inhibitors with traditional NSAIDs in their impact on BP. For example, the *Celecoxib Rofecoxib Efficacy and Safety in Comorbidities Evaluation* (CRESCENT) study was carried out in 404 patients with hypertension, diabetes and OA randomized to celecoxib 200 mg once daily, rofecoxib 25 mg once daily or naproxen 500 mg twice daily. Twenty-four-hour ambulatory BP monitoring was carried out at entry and after 6 and 12 weeks of treatment. The three agents were equally effective in reducing OA symptoms. Rofecoxib, but not celecoxib and naproxen, caused a significant increase in 24-hour SBP. Furthermore, all treatments destabilized the BP control, although such effect was more marked with rofecoxib [Sowers *et al.* 2005].

Whelton and colleagues reported the results of a comparative study between celecoxib and rofecoxib conducted in more than 1000 subjects with OA and hypertension who were concomitantly treated with fixed doses of antihypertensive drugs [Whelton *et al.* 2002]. In this study, rofecoxib induced a greater rise in BP compared with celecoxib, in patients treated with angiotensin-converting enzyme inhibitors (ACEIs) and beta blockers, but not in patients receiving calcium channel blockers [Whelton *et al.* 2002].

A large study was the *Therapeutic Arthritis Research and Gastrointestinal Event* (TARGET) study, in which 18,325 patients with OA were randomized to lumiracoxib 400 mg once daily, naproxen 500 mg twice daily, or ibuprofen 800 mg three times daily [Farkouh *et al.* 2004]. The primary cardiovascular endpoint, a composite of nonfatal and silent myocardial infarction, stroke, or cardiovascular death did not differ between lumiracoxib and either ibuprofen or naproxen, irrespective of aspirin use. In this study, the patients randomized to lumiracoxib had a significantly smaller increase in SBP and diastolic BP from baseline values when compared with other NSAIDs including ibuprofen [Farkouh *et al.* 2004].

Prognostic impact of blood pressure changes

There is general agreement that a direct, continuous and graded relationship exists between the

levels of BP and the risk of cardiovascular disease. In a large meta-analysis of 61 observational studies, for a total of about 1 million individuals, a direct and linear relation was found between BP and mortality from coronary artery disease or stroke, beginning from values as low as 115/75 mmHg [Lewington *et al.* 2002]. Even more important, the relation was highly consistent across different age groups [Lewington *et al.* 2002]. Two limitations of this meta-analysis were the inclusion of generally uncomplicated subjects without prior cardiovascular disease, and the fact that BP was measured only in one single visit in each subject.

The prognostic impact of serial changes in BP was investigated in meta-regression analyses of intervention studies carried out in patients with high BP or increased cardiovascular risk. Again, a clear association was found between the degree of BP reduction and the size of the outcome benefit [Staessen *et al.* 2001]. For example, a 5 mmHg drop in BP was associated with a 25% reduction in the risk of major cardiovascular events [Staessen *et al.* 2005]. An interesting point was that the beneficial outcome associated with BP reduction appeared to be quite rapid to occur. This aspect emerged in the *Valsartan Antihypertensive Long-term Use Evaluation* (VALUE) study. In this study, SBP was 3.8 mmHg lower in the amlodipine group compared with the valsartan group during the first 3 months of the trial [Julius *et al.* 2004]. This small BP difference between the groups was associated with a significantly lower incidence of cardiovascular events in the amlodipine group than in the valsartan group [Julius *et al.* 2004]. Over the following months the difference between the two groups in SBP progressively disappeared and the outcome differences between the two groups also disappeared [Julius *et al.* 2004].

We have recently concluded the *Studio Italiano Sugli Effetti Cardiovascolari del Controllo della Pressione Arteriosa Sistolica* (Cardio-Sis) trial, in which 1111 treated nondiabetic patients with SBP ≥ 150 mmHg were randomly allocated to a goal SBP of <140 mmHg (usual control) or <130 mmHg (tight control) [Verdecchia *et al.* 2009]. Open-label agents were used to reach the randomized BP goals. The primary study endpoint was the proportion of patients with new development or lack of regression of electrocardiographic left ventricular hypertrophy 2 years after randomization and the main secondary

endpoint was a composite pool of prespecified cardiovascular events and death. Over a median follow up of 2.0 years, the achieved BP was lower by 3.8/1.5 mmHg in the tight control group than in the usual control group. The primary endpoint of the study occurred less frequently in the tight than in the usual control group ($p = 0.013$). Also the secondary endpoint occurred less frequently in the tight than in the usual control group ($p = 0.003$).

These results suggest that, on a population basis, modest differences in BP are associated with a lesser risk of major clinical events even after a relatively short period. However, the clinical impact of small changes in BP in individual subjects is difficult to ascertain. BP measured in the physician's office may be biased for several reasons including the inherent errors in BP measurement and the alerting reaction to visit [Mancia *et al.* 1983]. Twenty-four-hour ambulatory BP provides a more reliable BP assessment [Verdecchia, 2000] and the prognostic impact of small changes in 24-hour ambulatory BP is superior to that of comparable changes in office BP [Dolan *et al.* 2005; Sega *et al.* 2005].

Studies with NSAIDs and COX-2 inhibitors

Randomized intervention trials of NSAIDs or COX-2 inhibitors showed a clear-cut relation between small changes in BP and increased risk of major cardiovascular events. In the VIGOR study, where SBP increased by only 1.6 mmHg with naproxen and by 4.6 mmHg with rofecoxib, rofecoxib was associated with a 2.38 times higher risk of serious cardiovascular events [White, 2007; Bombardier *et al.* 2000].

The *Adenomatous Polyp Prevention on Vioxx* (APPROVe) trial was a comparative trial between rofecoxib and placebo in 2586 patients with a history of colorectal adenomas. In this study SBP increased by 3.4 mmHg with rofecoxib and decreased by 0.5 mmHg with placebo, while the risk of major cardiovascular events was 1.92 times higher with rofecoxib than with placebo ($p = 0.008$) [Bresalier *et al.* 2005].

Similar results were found in trials with celecoxib. In a nonprespecified post-hoc analysis of individual patient data from two celecoxib trials, the *Adenoma Prevention with Celecoxib* (APC) trial and the *Prevention of Spontaneous Adenomatous Polyps* (PreSAP) trial, Solomon and colleagues found a direct association between the rise in

SBP, which was of the order of 2–5 mmHg, and the incidence of adjudicated cardiovascular endpoints [Solomon *et al.* 2006].

A concern on the potential implications of BP rise induced by traditional NSAIDs or COX-2 inhibitors has been expressed in a recent American Heart Association Scientific Statement, which suggested that BP and renal function should be monitored in subjects taking NSAIDs or COX-2 inhibitors [Antman *et al.* 2007]. This is especially relevant when these drugs are administered to patients with coexisting hypertension, renal disease and heart failure [Antman *et al.* 2007].

COX-inhibiting nitric oxide donor class

The COX-inhibiting nitric oxide donor (CINOD) class has been developed for the treatment of patients with osteoarthritis with the aim of an increased cardiovascular and gastrointestinal safety profile over NSAIDs. The underlying concept is that the nitric oxide (NO) released by these drugs would produce the mentioned beneficial effects [Fiorucci, 2009; Fiorucci *et al.* 2007; Wallace *et al.* 2002, 2009]. NO would also enhance the blood flow in the gastric mucosa, with consequent increased mucous production, reduced healing time and final effect of gastroprotection [Fiorucci, 2009].

Several aspects regarding the pharmacokinetics of CINODs remain to be fully elucidated. In particular, it is unclear whether CINODs are cleaved before intestinal absorption, or whether they are absorbed intact and subsequently metabolized, possibly in the liver. The exact mechanisms of NO release also require further investigation. In particular, CINODs are able to release NO in biological fluids, not in inert media [Fiorucci, 2009], and this raises the possibility that biological enzymes can intervene in the process of NO release *in vivo*.

Aspirin, naproxen, diclofenac and flurbiprofen have so far been coupled to a NO-releasing moiety [Fiorucci, 2009].

Naproxcinod, the first CINOD to be studied in large clinical trials, is composed of the traditional NSAID naproxen covalently bound to the NO-donating moiety butanediol mononitrate (BDMN) [Schnitzer *et al.* 2005]. Figure 3 shows the molecular structure of naproxen and

Figure 3. Molecular structure of naproxen and naproxcinod.

naproxcinod. The molecule of naproxcinod is broken to produce naproxen and the NO-donating moiety. Plasma bioavailability of naproxen is reduced by about 15–20% after administration of naproxcinod in comparison with equimolar doses of naproxen [Fagerholm and Björnsson, 2005] and the gastrointestinal uptake of naproxen is also slower [Wallace *et al.* 2009]. After cleavage, the naproxen component of naproxcinod maintains its inhibitory activity on COX-1 and COX-2 while NO, released from the moiety is expected to exert its favorable biologic effects on the cardiovascular system. It is well established that NO produced by endothelial cells is capable to induce vasodilatation, inhibition of platelet aggregation and inhibition of vascular smooth muscle proliferation [Moncada and Higgs, 2006; Rees *et al.* 1989] (Figure 4). In the gastrointestinal mucosa, NO may trigger an increased blood flow with enhanced mucous production, thereby contributing to preserve gastric mucosal integrity [Wallace, 1996]. Naproxcinod is currently in a late stage of phase III clinical trials. A new drug application has been submitted to the US Food and Drug Administration in September 2009, and a marketing authorization application to the European Medicines Agency in December 2009.

Animal models

In animal models of OA, naproxcinod showed a similar efficacy to naproxen [Wallace *et al.* 2009]. Investigations in rodents showed a dose-related inhibition of COX-1 after both single and repeated administration [Muscara *et al.* 2000a].

Figure 4. Dual effect of naproxenod resulting from cyclooxygenase inhibition and nitric oxide (NO) release.

Most likely as a result of the sustained NO release, naproxenod reduced BP in spontaneously hypertensive rats and rats made hypertensive by L-NAME [Muscara *et al.* 1998] and protected isolated hearts of rabbits in ischemia-reperfusion models [Rossoni *et al.* 2004]. In a rat model of hypertension induced by partial occlusion of a renal artery (two-kidney, one-clip renovascular hypertension), naproxenod significantly reduced BP when compared with both naproxen and vehicle [Muscara *et al.* 2000b].

A convincing evidence that naproxenod effectively releases NO *in vivo* came from studies in which a dose response was observed between the dose of naproxenod and the circulating levels of NO [Rossoni *et al.* 2006]. As expected, naproxen did not cause any change in NO [Rossoni *et al.* 2006]. Another supporting evidence came from a study which showed a progressive increase in the levels of the second messenger cGMP, the specific signaling pathway of NO, with progressively higher doses of naproxenod [Berndt *et al.* 2004].

In animal experiments, naproxenod caused less gastrointestinal damage when compared with equimolar doses of naproxen [Davies *et al.* 1997; Muscara *et al.* 1998]. In a human study, it improved gastrointestinal tolerability and induced fewer gastroduodenal erosions when compared with naproxen [Hawkey *et al.* 2003]. In a model of arthritic rats, naproxenod reduced the degree of injury of gastric mucosa by

approximately 70% when compared with equimolar doses of naproxen [Fiorucci *et al.* 2004].

Effects on OA

In a series of randomized, double-blind, placebo-controlled studies conducted in patients with OA on different sites, naproxenod showed a similar potency to equimolar doses of naproxen [Karlsson *et al.* 2009; Lohmander *et al.* 2005; Schnitzer *et al.* 2005]. The dose of naproxenod 750 mg twice daily showed the best balance between efficacy and safety [Karlsson *et al.* 2009].

Gastroprotection in clinical studies

The solid evidence of gastroprotection that emerged from animal studies was partly confirmed in human investigations. In a study conducted in 31 healthy volunteers, the number of gastroduodenal erosions was 11.5 with naproxen and only 4.1 with naproxenod ($p < 0.01$) [Hawkey *et al.* 2003]. In a multicenter study, naproxenod significantly decreased the numbers of ulcers and erosions in stomach and stomach/duodenum combined when compared with naproxen [Lohmander *et al.* 2005]. However, the incidence of ulcers ≥ 3 mm, the primary endpoint of the study, was 9.7% with naproxenod and 13.7% with naproxen ($p = 0.07$), versus 0% with placebo. The incidence of a Lanza score > 2 , an overall measure of gastroduodenal damage and secondary endpoint of the study, was significantly higher with naproxen than with naproxenod (43.7% versus 32.2%; $p < 0.001$) [Lohmander *et al.* 2005].

Figure 5. Changes in systolic blood pressure (BP) with naproxcinod, naproxen and placebo in patients with osteoarthritis.

Figure 6. Time course of blood pressure (BP) in patients with osteoarthritis treated with naproxen, naproxcinod and placebo.

BP in clinical studies

White and colleagues have recently published the results of a large clinical study in which 916 patients with OA of the knee were randomized to naproxcinod 375 mg and 750 mg twice daily, naproxen 500 mg twice daily or placebo. Duration of follow-up was 13 weeks. SBP decreased from baseline to week 13 by 2.9 mmHg more with naproxcinod than with naproxen (95% confidence interval -5.2 to -0.6 ; $p=0.015$) (Figure 5). Furthermore, SBP decreased 0.8 mmHg more with naproxcinod than with placebo (95% confidence interval -3.3 to 1.6 ; $p=0.505$) [White *et al.* 2009]. A subset of 207 patients with OA and hypertension were concomitantly treated with ACEIs or

angiotensin II receptor blockers (ARBs) alone or with diuretics. In these subjects, there was an average difference in SBP of 6.5 mmHg in favor of naproxcinod 750 mg over naproxen 500 mg (Figure 6). The proportion of patients with a SBP rise >10 mmHg was 22% with naproxen 500 mg and 14% with naproxcinod 750 mg (22% versus 14%; $p=0.04$) [White *et al.* 2009]. Overall, in this study naproxcinod eliminated the rise in SBP seen with naproxen and showed a similar effect on BP to that of placebo.

Clinical studies with 24-hour ambulatory BP

In a randomized, double-blind, crossover study, 121 hypertensive subjects who were naïve to NSAIDs and COX-2 inhibitors received

naproxenod 750 mg bid and naproxen 500 mg bid in random order for 2 weeks each, with a 2-week placebo period interposed between each of the two active treatment periods. A 24-hour ambulatory BP monitoring was carried out at the start and the end of each active treatment period. BP was lower with naproxenod than with naproxen and the difference between the two treatments in the changes of 24-hour BP, averaged (intention-to-treat analysis) a least squares (LS) mean difference of -2.4 mmHg (95% confidence interval [CI] -4.16 to -0.71 ; $p=0.006$) in SBP in favor of naproxenod 750 mg, and a LS mean difference of -1.8 mmHg (95% CI -3.13 to -0.50 ; $p=0.008$) in favor of naproxenod 750 mg in diastolic BP. Most of the advantage of naproxenod over naproxen was observed in the first 8 hours after oral intake [Townsend *et al.* 2007], with a LS mean difference of -4.4 mmHg (95% CI -6.40 to -2.49 ; $p<0.0001$) in favor of naproxenod 750 mg in SBP.

In another study, 118 patients with OA of hip or knee and controlled essential hypertension were randomized to naproxenod 375 mg bid or naproxen 250 mg bid. Treatment was force titrated to the next highest dose at 3-week intervals (naproxenod 750 and 1125 mg bid; naproxen 500 and 750 mg bid). Twenty-four-hour ambulatory BP monitoring was performed at baseline and at the end of each period. Naproxenod resulted in persistently lower levels of 24-hour SBP, the primary endpoint of the study. In an intention-to-treat analysis, the overall difference between the treatments in the mean change in the average 24-hour SBP was 3.8 mmHg (SE 1.47) in favor of naproxenod ($p=0.011$) [Townsend *et al.* 2009].

These findings indicate that naproxenod does not display the profile of a traditional antihypertensive drug, but that of a NSAID provided with the remarkable safety feature of releasing NO, thereby avoiding the increase in BP commonly seen with NSAIDs.

Conclusion

Hypertension and other cardiovascular risk factors are common among patients with OA. In particular, the prevalence of hypertension is about 40%. Even modest increases in BP in these patients, in the order of those induced by traditional NSAIDs and COX-2 inhibitors, may significantly increase the risk of major

cardiovascular complications and death. NSAIDs and COX-2 inhibitors may destabilize BP control by reducing the BP lowering effect of some antihypertensive agents including the ACEIs, the ARBs and the beta blockers. The CINOD class is being developed as an alternative to traditional NSAIDs and COX-2 inhibitors in order to combine the cyclooxygenase-mediated anti-inflammatory activity of the NSAID component with the systemic vasodilatation and potential gastrointestinal protection induced by the NO component. Naproxenod, the first CINOD to be investigated in clinical trials, showed a similar effect to placebo on BP and less of an effect when compared with equimolar doses of naproxen in patients with OA.

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Conflict of interest statement

None declared.

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