Effects of Nonsteroidal Anti-Inflammatory Drug Therapy on Blood Pressure and Peripheral Edema

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used drugs with potential effects on systemic blood pressure. NSAIDs act by inhibiting synthesis of prostaglandins (PGs) from arachidonic acid via cyclooxygenase (COX)-1 and COX-2, the 2 isoforms of COX. NSAIDs may affect blood pressure via the renin–angiotensin pathway, alterations in sodium and water retention in the kidneys, inhibition of vasodilating PGs, and production of various vasoconstricting factors, including endothelin-1 and P450–mediated metabolites of arachidonic acid. In 2 meta-analyses, it was found that NSAIDs have small but significant effects on blood pressure, most notably in hypertensive patients on antihypertensive medication. NSAIDs cause small (<5 mm Hg) elevations in systolic blood pressure, and little or no change in diastolic blood pressure. The incidence rates of hypertension and peripheral edema were low, ranging from <1% to >9% of patients. The incidence and levels of hypertension associated with COX-2 inhibitors are within the range of those observed with nonspecific NSAIDs. Apparent differences between the COX-2 inhibitors celecoxib and rofecoxib may be functions of differences in study population susceptibilities to NSAID-mediated hypertensive effects. Patients at risk for hypertension should be monitored for changes in blood pressure during NSAID treatment. ©2002 by Excerpta Medica, Inc.

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used over-the-counter and prescribed drugs in the world. In developed countries, NSAIDs represent 4% to 9% of drug prescriptions.[1] Several studies have suggested an association between NSAIDs and hypertension. Under current definitions, as many as 43 to 50 million individuals in the United States may have hypertension, which places them at increased risk for heart disease and stroke.[2–5] A significant proportion of individuals who have hypertension or are at increased risk for hypertension, including the elderly and patients with rheumatoid arthritis, regularly use NSAIDs.[6,7] For example, in 1 study, >50% of individuals >60 years of age were diagnosed with hypertension, and 12% to 15% of these patients used both antihypertensive medication and NSAIDs.[7]

Increases in either systolic or diastolic blood pressure have significant, linear correlation with risk of cardiovascular and cerebrovascular disease.[3–5,8,9] In the past, emphasis was placed on increases in diastolic pressure as being the most significant predictor of risk for cerebrovascular and cardiovascular disease.[4,8] Recently, however, increased systolic pressure has become recognized as the more important predictor of risk for cerebrovascular and cardiovascular disease.[2,3,5]

Given the prevalence and risks of hypertension and the frequency of NSAID use, any effect of NSAIDs on blood pressure may have significant implications for the health of patients. This article will review the potential mechanisms and evidence for effects of NSAIDs on blood pressure and peripheral edema.

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MECHANISMS BY WHICH NONSTEROIDAL ANTI-INFLAMMATORY DRUGS MAY AFFECT BLOOD PRESSURE

Prostaglandins (PGs) act locally in the kidney to maintain homeostasis by regulating sodium and water reabsorption, particularly in the thick ascending loop of Henle and the collecting duct. PGE_2 mediates the response to antidiuretic hormone in the collecting duct and thick ascending loop of Henle by reducing sodium reabsorption.[10–12] In addition, PGs may inhibit production of renal endothelin-1 in the renal vasculature, thereby decreasing sodium and water reabsorption.[7]

NSAIDs increase sodium and water retention by increasing the tubular reabsorption of sodium (Figure 1).[7] Estimates of the frequency of sodium retention and associated edema in patients taking NSAIDs range from 2% to 5%[13] to up to 25% of patients.[11] NSAID-associated sodium retention and edema formation are more likely in patients already at risk for these problems.[1] Data also suggest that the increased sodium retention seen with NSAIDs may be associated with a decreased response to diuretics.[1,10] Sodium retention appears to be mostly cyclooxygenase (COX)-2 mediated, as indicated by studies that show similar levels of sodium retention in patients treated with nonspecific NSAIDs and in patients treated with COX-2–specific inhibitors (coxibs).[13–16]

Prostacyclin (PGI_2) is a vasodilator, synthesized in endothelial cells primarily by a COX-2–dependent pathway.[14,17] Vasodilatory PGs, such as PGI_2, may be produced to counteract vasoconstricting signals, such

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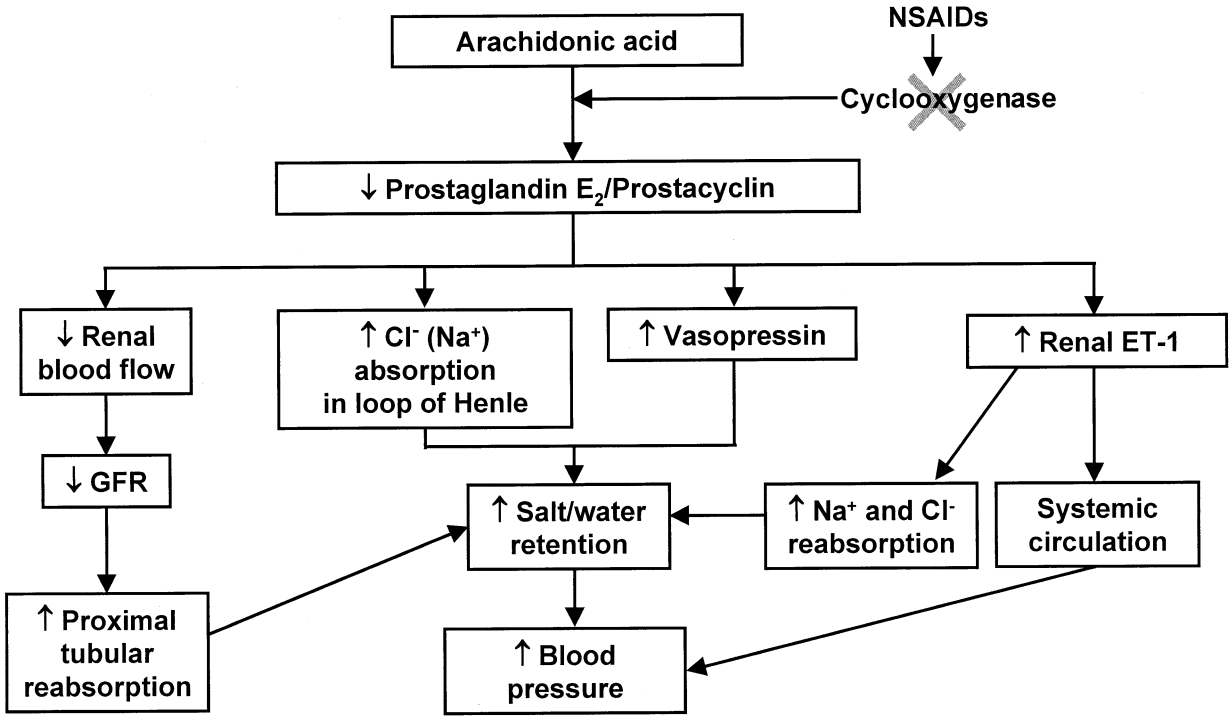

FIGURE 1. Potential mechanisms of nonsteroidal anti-inflammatory drug (NSAID)–induced systemic hypertension. Cl^- = chlorine; ET = endothelin; GFR = glomerular filtration rate; Na^+ = sodium. (Adapted from *Drugs Aging.*[7])

as increased sympathetic tone, plasma angiotensin II, or vasoconstrictive prostanoids (thromboxane A_2). In addition, PGs inhibit vascular endothelial production of endothelin-1, a factor that acts to increase peripheral vascular resistance.[6,18] Treatment with NSAIDs may inhibit production of PGI_2 and may reduce the PG-mediated inhibition of endothelin-1 production, resulting in increased peripheral resistance.[7]

PGs can also regulate renal function and hemodynamics through their effects on the renin–angiotensin system (RAS). PGI_2 acts on juxtaglomerular cells, effecting the release of renin and leading to increased synthesis of angiotensin II and release of aldosterone under conditions of actual or effective hypovolemia.[1,10] Aldosterone causes increased sodium and water reabsorption and excretion of potassium. RAS also stimulates release of the antidiuretic hormone, which causes increased water reabsorption in the collecting duct. Thus, PG-mediated release of renin may cause an increase in blood pressure through the combined effects of vasoconstriction by angiotensin II and increases in volume through the effects of aldosterone and antidiuretic hormone. Therefore, under certain conditions, NSAIDs may inhibit the RAS and reduce blood pressure.[19]

Alternatively, renal PGs may provide a counterregulatory mechanism to normalize renal function under high-renin conditions by (1) enhancing renal vasodilation (to counter the vasoconstriction caused by the renin pathway) and glomerular filtration rate, and (2) inhibiting aldosterone secretion.[11] Thus, NSAIDs would counteract the renal vasodilatory effects of PGs, as well as the inhibition of aldosterone secretion, and thereby could increase blood pressure. These theoretic effects of NSAIDs on RAS have been examined in experimental models and in clinical studies. Laboratory experiments have shown that COX-2 expression in the kidney is upregulated under conditions causing release of renin, such as low-sodium diet or treatment with angiotensin II inhibitors.[20,21] As expected, NSAID-induced inhibition of PG synthesis leads to a decrease in plasma renin activity in animal models under these experimental conditions.[19,21,22] In an animal model of renal vascular hypertension, COX-2 inhibition reduced plasma renin and ameliorated hypertension.[19] The clinical relevance of these findings is not clear, however. A meta-analysis of clinical studies did not indicate any significant changes in plasma renin activity during therapy with NSAIDs,[6] suggesting that NSAIDs do not affect blood pressure via the renin–angiotensin pathway under normal conditions. On the other hand, 1 study found that intravenous aspirin significantly reduced plasma renin activity and decreased blood pressure in patients with renovascular hypertension.[23] In these patients, the effects of PGs on the release of renin may be more important than direct effects on renal physiology.

Finally, inhibition of PG synthesis can increase production of alternative metabolites that may have hypertensive effects. When COX is inhibited, arachidonic acid (the substrate for COX) can undergo metabolism by an alternative metabolic pathway involving cytochrome P450 enzymes.[24] The products of this pathway include epoxyeicosatrienoic acids and 20-hydroxyeicosatretraenoic acid, which have renal and vasoconstrictive effects that may induce hypertension.

For example, when 20-hydroxyeicosatretraenoic acid formation is inhibited in rats, arterial pressure is reduced and sodium reabsorption is increased.[25] Small studies in humans have shown higher levels of cytochrome P450 metabolites of arachidonic acid in hypertensive patients.[26]

CLINICAL EVIDENCE FOR NONSTEROIDAL ANTI-INFLAMMATORY–MEDIATED EFFECTS ON BLOOD PRESSURE

An association between therapy with NSAIDs and elevated blood pressure has been found by several epidemiologic studies.[27–29] Some of the clinical trials aimed at establishing this association demonstrated an increase in blood pressure with NSAID therapy, whereas other studies did not support such findings. These differences may be statistical aberrations or may arise from real differences in NSAID type or patient populations. Meta-analyses provide a tool to increase statistical power by pooling studies with similar designs—2 such meta-analyses were performed, and notably, neither meta-analysis included trials with elderly patients.

An analysis of pooled data from 54 trials with a total of 1,324 patients found that NSAIDs increased blood pressure slightly in normotensive subjects (1.1 mm Hg), and to a greater degree in hypertensive subjects (3.3 mm Hg).[30] In this study, different NSAIDs had different degrees of effect on blood pressure. The greatest increase in blood pressure was seen with naproxen and indomethacin; the effects of sulindac and aspirin were most similar to those of placebo. The other meta-analysis used data from 50 randomized studies with 771 patients. The findings of this study were similar to those of the first meta-analysis: mean blood pressure was increased by an average of 5 mm Hg in subjects treated with NSAIDs, and the increase in mean blood pressure depended on the hypertensive status of the patients.[6] The effect was greatest in hypertensive subjects treated with antihypertensive medication. In addition, normotensive subjects on hypertension treatment had higher increases in blood pressure than subjects with uncontrolled hypertension or normotensive subjects receiving no hypertension treatment.[6] In this study, the effects of NSAID treatment on fluid–electrolyte balance, plasma renin, or PG excretion were not statistically significant, suggesting that NSAIDs may affect blood pressure primarily via changes in peripheral vascular resistance or cardiac output. Aspirin and sulindac had little or no effect, whereas piroxicam, indomethacin, naproxen, and ibuprofen had the greatest effect (Figure 2).[6] This may be because of differences in how these drugs interact with COX. Sulindac, for instance, may be a weaker inhibitor of renal synthesis of vasodilatory PGs than other NSAIDs.[7,10]

The results of reported meta-analyses support the hypothesis that treatment with NSAIDs may lead to increases in blood pressure. Because the effect of NSAIDs on blood pressure was greatest in hypertensive individuals and in those treated with antihypertensive medication, these results suggest that NSAIDs may exert their effects via physiologic mechanisms that affect blood pressure and via interaction with antihypertensive medications.

CYCLOOXYGENASE-2 INHIBITORS AND BLOOD PRESSURE

NSAIDs induce changes in blood pressure by inhibiting PG synthesis. The effects of coxibs on blood pressure should therefore depend on the role of COX-2 in synthesis of renal and vascular prostanoids. The relative contribution of COX-1 and COX-2 enzyme isoforms in production of PGs important for regulation of blood pressure is not known, but data from clinical trials suggest that COX-2 inhibitors have similar effects on blood pressure as traditional NSAIDs.

A small (N = 40) 7-day study of normotensive subjects on a low-salt diet showed no significant differences in systolic or diastolic blood pressure among groups taking (1) a nonspecific NSAID (naproxen 500 mg bid); (2) 1 of 2 doses of celecoxib (200 mg bid or 400 mg bid); or (3) placebo.[15] Both types of NSAIDs were associated with decreases in water, sodium, and potassium excretion. Similar results were found in a 14-day study of normotensive older adults randomized to receive: (1) a nonspecific NSAID (indomethacin 50 mg tid), (2) the COX-2 inhibitor rofecoxib (50 mg qd), or (3) placebo.[14] Diastolic blood pressure increased slightly in all groups: 1.7 mm Hg in the indomethacin group, 2.6 mm Hg in the rofecoxib group, and 1.6 mm Hg in the placebo group; these increases were not statistically significant.[14] Systolic blood pressure also showed slight and nonsignificant increases in all groups. Significant decreases in urinary sodium excretion were seen in both active treatment groups.

The slight increases in systolic blood pressure with coxibs appear to be consistent over time. Results from 2 large, long-term (52-week) osteoarthritis studies indicated a slight, dose-related increase in systolic blood pressure associated with rofecoxib therapy. Patients treated with the higher dose of rofecoxib (25 mg qd) had a <3 mm Hg increase in systolic blood pressure over the course of a year (Figure 3A).[11] The change in diastolic blood pressure over the same period was smaller (<1 mm Hg) and not statistically significant (Figure 3B).

These results indicate that slight increases in systolic blood pressure may be associated with treatment with NSAIDs. The effects seem to be the same, regardless of the type of NSAID used, and no significant alteration in systolic and diastolic blood pressure should be anticipated if patients are switched from a nonselective NSAID to therapeutic doses of COX-2 inhibitors. In a small number of patients, however, the increase in blood pressure with prolonged therapy with nonselective NSAIDs or COX-2 inhibitors may be significant, resulting in development of hypertension. In 4 large studies that analyzed efficacy and safety of COX-2 inhibitors in the treatment of either osteoarthritis or rheumatoid arthritis, data were provided on the frequency of hypertension as an adverse event. Unfortunately, in most studies, hypertension

Drugs	N	Trials
Piroxicam	27	4
Indomethacin	395	33
Ibuprofen	63	5
Tiaprofenic acid	11	1
Diclofenac	4	1
Naproxen	39	2
Flurbiprofen	40	4
Sulindac	85	7
Aspirin	105	8

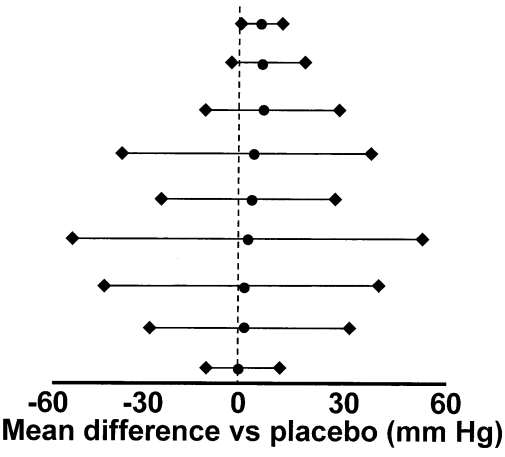

FIGURE 2. Hypertension with nonspecific nonsteroidal anti-inflammatory drugs: meta-analysis of randomized, placebo-controlled trials. (Adapted from *Ann Intern Med.*[6])

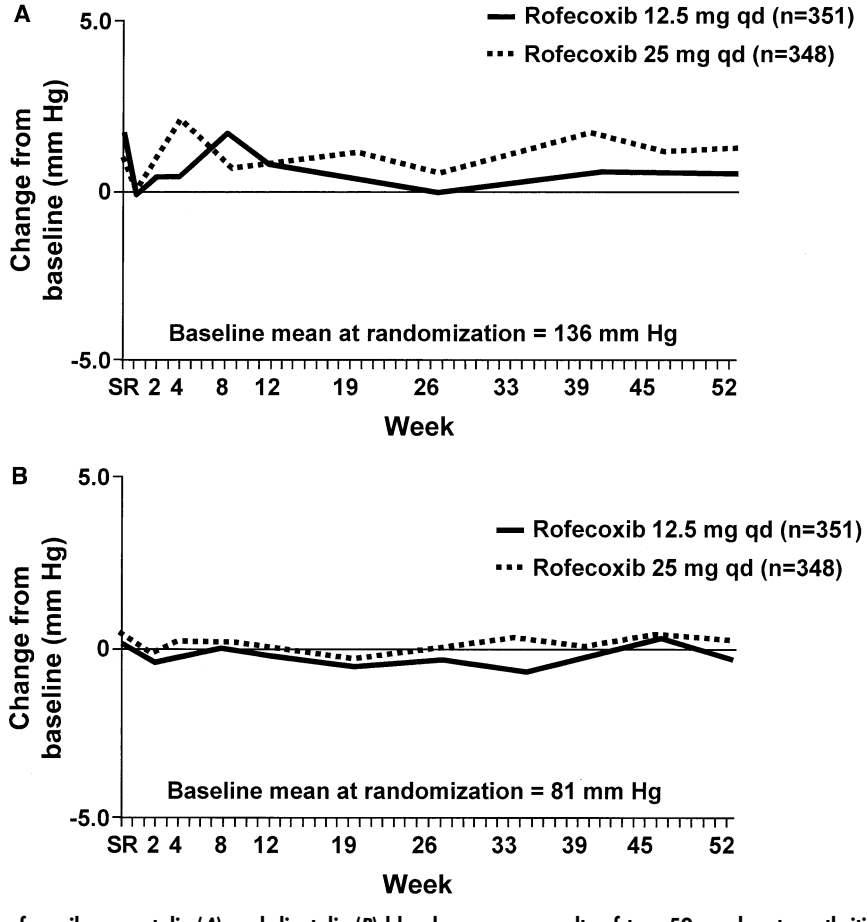

FIGURE 3. Effects of rofecoxib on systolic (*A*) and diastolic (*B*) blood pressure: results of two 52-week osteoarthritis clinical trials. R = randomization visit; S = screening visit. (Adapted from *Am J Nephrol.*[11])

was not defined by a threshold value or a prespecified percent change in blood pressure. Instead, adverse-events data for hypertension rates incidence were based on spontaneous reports by investigators, limiting their utility. Given these constraints, the rate of reported hypertension in patients treated with the COX-2 inhibitors rofecoxib and celecoxib in these studies was within the range of variability exhibited by nonspecific NSAIDs.

Rofecoxib at 3 doses (12.5 mg/day, 25 mg/day, and 50 mg/day) was compared with ibuprofen (2,400 mg/day), diclofenac (150 mg/day), and placebo in an

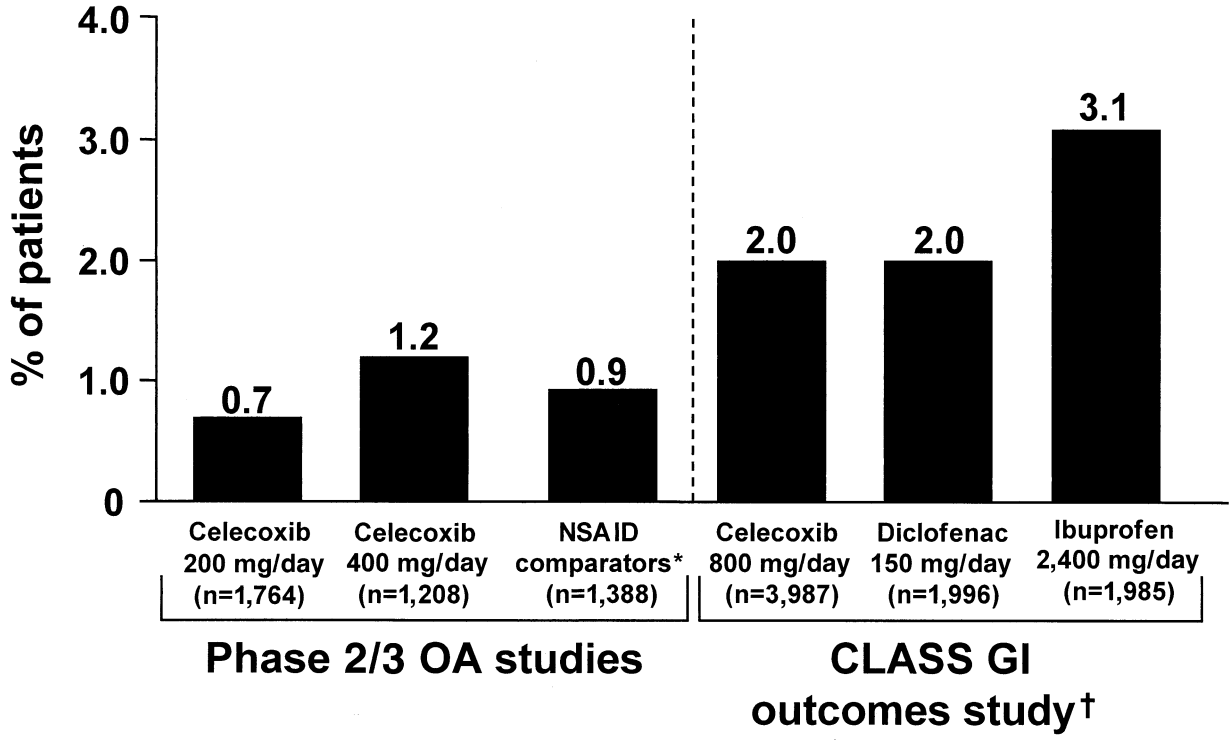

FIGURE 4. Hypertension incidence in celecoxib trials (investigator-reported data). *Naproxen, diclofenac. †Data from entire study period. CLASS = Celecoxib Long-term Arthritis Safety Study; GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug; OA = osteoarthritis. (Phase 2/3 OA studies data adapted from Celebrex [celecoxib] product information.[34,36] CLASS GI outcomes study data adapted from FDA Arthritis Advisory Committee Meeting.[33])

analysis that combined data from 9 phase 2 and phase 3 osteoarthritis studies, with a total of 5,433 subjects. The rate of hypertension in the rofecoxib groups appears to be dose related. Thus, the rate of hypertension in the 12.5-mg/day rofecoxib group was similar to the ibuprofen group (rofecoxib, 2.8%; ibuprofen, 2.9%), whereas the rate increased to 4.0% with rofecoxib 25 mg/day. The rate was highest (8.2%) among patients treated with the 50-mg/day dose, but this dose is not recommended for long-term therapy.[31]

Rofecoxib (50 mg qd) and naproxen (500 mg bid) were compared for efficacy and gastrointestinal toxicity in a large (8,076 subjects), multicenter, long-term study of older adults (>40 years of age) with rheumatoid arthritis (the Vioxx Gastrointestinal Outcomes Research [VIGOR] study).[32,33] The rate of hypertension in this study was higher than in the previous study, with 9.7% of the rofecoxib patients and 5.5% of the naproxen patients developing hypertension. It should be noted that the dose of rofecoxib used in this study was higher than the maximal recommended dose for long-term therapy (25 mg qd).

Celecoxib at 3 doses (200, 400, and 800 mg/day), naproxen, and diclofenac were compared for efficacy and safety in phase 2 and 3 osteoarthritis studies, with a total of 4,459 patients. All groups showed very low levels of hypertension: (1) 0.9% among patients randomized to nonspecific NSAIDs, and (2) 0.7% and 1.2% among those randomized to celecoxib 200 mg/day and 400 mg/day, respectively.[34] Compared with the other groups, the number of patients in the highest celecoxib dose group was too small (n = 99) for meaningful comparisons. However, results from the Celecoxib Long-term Arthritis Safety Study (CLASS) indicate that the incidence of hypertension with celecoxib is also dose related. In this trial, celecoxib (400 mg bid) and the NSAIDs ibuprofen (800 mg tid) and diclofenac (75 bid) were compared for efficacy and gastrointestinal toxicity in a large (8,059 patients), multicenter, long-term study of adults (>18 years of age) with osteoarthritis or rheumatoid arthritis.[35] The rates of hypertension were higher in this study than in trials with lower doses of celecoxib (Figure 4).[33,34] In CLASS, 2.0% of the patients in the celecoxib group, 2.0% of those in the diclofenac group, and 3.1% of those in the ibuprofen group developed hypertension.[36]

In summary, the effects of COX-2 inhibitors on blood pressure are generally small and comparable to those of nonspecific NSAIDs. However, given the linear relation of systolic blood pressure with risk of cardiovascular and cerebrovascular disease and the risk for development of hypertension in a small number of patients, the data suggest that patients at risk for hypertension should be monitored during treatment with these agents.

INCIDENCE OF EDEMA WITH COXIBS

Peripheral edema is frequently seen with hypertension. Factors that lead to edema are often associated with hypertension or are affected by it. For example, increased blood pressure will lead to greater loss of fluid to the extravascular space when increased capil-

lary permeability is present. Renal factors that lead to hypertension, such as increased sodium retention, may also lead to peripheral edema. Note, however, that the mechanisms leading to edema are not identical to the mechanisms leading to hypertension, because patients with edema may not have hypertension, and vice versa.

Peripheral edema is an occasional side effect associated with all NSAIDs.[1] The degree of edema is typically minor and reversible with discontinuation of the drug. Nonspecific NSAIDs and COX-2 inhibitors may have similar effects on sodium-retention–mediated processes, such as edema, because the increased sodium retention that has been associated with all NSAIDs appears to be mediated mainly by COX-2.[10,14] Similar frequencies of edema as an adverse event reported in several studies of NSAIDs and COX-2 inhibitors support this hypothesis.

The incidence of edema in 4 large studies comparing either rofecoxib or celecoxib with several nonspecific NSAIDs was within the same range. Note, however, that the occurrence of edema in these large multicenter studies was investigator-reported data, and the definition of edema differed between the rofecoxib studies and the celecoxib studies, limiting the utility of comparisons between these data.

In the phase 2/3 osteoarthritis studies and the large VIGOR study comparing rofecoxib with nonspecific NSAIDs, only lower-extremity edema was reported. The incidence of lower-extremity edema ranged from 3.4% to 6.3% among the treatment groups in the pooled phase 2/3 studies.[31] The incidence rates also decreased within this range in the VIGOR study. Lower-extremity edema was reported in 5.4% of rofecoxib 50-mg/day dose patients and 3.6% of naproxen 1,000-mg/day dose patients.[33]

In the phase 2/3 osteoarthritis studies and the large CLASS study of celecoxib, peripheral edema was defined to include both upper- and lower-extremity edema. The incidence of peripheral edema ranged from 1.9% to 3.0% among the treatment groups in the pooled phase 2/3 osteoarthritis studies comparing celecoxib with naproxen and diclofenac.[34] The incidence rates for this adverse event were slightly higher in the CLASS study. Peripheral edema was seen in 3.7% of celecoxib patients, 3.5% of diclofenac patients, and 5.2% of ibuprofen patients.[36]

BLOOD PRESSURE AND CYCLOOXYGENASE-2 INHIBITION: CLASS-RELATED EFFECTS

Effects of COX-2 inhibitors on blood pressure can be explained by their mechanism of action (ie, inhibition of PG synthesis). Because the effects are dose related, they probably reflect the degree of potency of COX-2 inhibition.

Because of the differences in methodology and patient populations, cross-study comparisons of different agents are always difficult, and no conclusion should be drawn based on trials that used only 1 of the agents of interest. For example, the incidence of hypertension was greater overall in the VIGOR and CLASS studies than in corresponding phase 2/3 studies.[14,32] Another factor is the weak reliability of investigator-reported data. Hypertension was not measured systematically in these studies and was reported as an adverse event by the investigators rather than defined as a primary endpoint. For the same reasons, data on the incidence of edema are also difficult to compare between these studies. To investigate systematically the effects of both COX-2 inhibitors on blood pressure or edema, it will be necessary to conduct a large trial on a population with a defined risk of hypertension.

Unfortunately, head-to-head comparison trials of COX-2 inhibitors were either small or had methodology problems. The largest of these trials randomized 810 older ($\geq$65 years of age) patients with osteoarthritis to 6 weeks of therapy with once-daily celecoxib 200 mg or rofecoxib 25 mg. All patients were taking antihypertensive therapy at time of enrollment. This patient population generally has diminished renal function that may be more dependent on PG activity. This renal impairment probably accounted for relatively high incidences of blood pressure elevations in this study. Clinically important changes in systolic blood pressure at any point during the study, defined as increases $>$20 mm Hg with an absolute value $>$140 mm Hg, occurred in 17% of rofecoxib-treated patients and 11% of the celecoxib-treated patients. Consistent with other results from studies, mean change from baseline in systolic blood pressure was small ($<$3 mm Hg) in both groups. Fewer than 2% of the patients had significant changes in diastolic blood pressure; the incidence of the diastolic endpoint (change $>$15 mm Hg with an absolute value $>$90 mm Hg) was similar in the 2 groups. It should be noted that the doses of COX-2 inhibitors used in this study are probably not equivalent—the dose of celecoxib represented the half-maximal long-term dose, whereas the maximal long-term dose of rofecoxib was used. Additionally, celecoxib has shorter half-life than rofecoxib, frequently necessitating twice-daily dosing—the maximal long-term dose of celecoxib is 200 mg bid. Considering that the timing of blood pressure measurements in relation to daily dosing was not specified, it is possible that many of the celecoxib-treated patients had blood pressure measurements at times when the effects of the drug were less than maximal.

Other studies comparing the 2 COX-2 inhibitors failed to demonstrate any difference in hemodynamic effects. In 1 of those studies, 67 elderly patients (60 to 80 years of age) were randomized to (1) maximal daily doses of the 2 COX-2 inhibitors (25 mg qd rofecoxib or 200 mg bid celecoxib), (2) naproxen 500 mg bid, or (3) placebo.[37] After 2 weeks of therapy, the systolic blood pressure increased to a similar degree in the 3 active treatment groups: by 3.4 mm Hg in the rofecoxib group, 4.3 mm Hg in the celecoxib group, and 3.1 mm Hg in the naproxen group. The differences among the groups, or between any of the active treatments and the placebo, were not statistically significant. The changes in diastolic blood pres-

sure were smaller and not statistically significant. Another recently reported trial randomized 382 patients to therapy with (1) acetaminophen 4,000 mg/day, (2) celecoxib 200 mg/day, and (3) rofecoxib 12.5 mg/day and 25 mg/day. The incidence of edema and hypertension in this study was similar across treatment groups.[38] Finally, a double-blind trial randomized 1,082 patients with osteoarthritis (>40 years of age) to therapy with (1) rofecoxib (25 mg qd), (2) celecoxib (200 mg qd), or (3) placebo.[39] After 6 weeks of therapy, the incidence of systolic hypertension (>20 mm Hg increase with absolute value >140 mm Hg) was 9.6% in the rofecoxib group, 9.4% in the celecoxib group, and 3.3% in the placebo group. Therefore, although the dose of celecoxib in this study was less than the recommended maximal dose, no difference between the effects of the 2 coxibs on blood pressure was observed. This is probably because of the characteristics of the patient population, which was younger and likely less sensitive to inhibition of renal PGs.

CONCLUSION

NSAIDs have small but significant effects on blood pressure and edema. Incidence rates for increases in blood pressure associated with NSAID treatment ranged from <1% to >9%. However, the average increases in blood pressure associated with NSAIDs were small: usually <5 mm Hg. These results may represent a very small number of people showing a large change in blood pressure, with more people showing only a very slight change, or no change.[1] Thus, most people may be at a low risk for NSAID-mediated increases in blood pressure, with only a small subpopulation being at higher risk. Certain classes of patients may be more susceptible to hypertensive effects of NSAIDs, including patients with preexisting hypertension, other cardiovascular disease, renal problems, or liver problems, as well as elderly patients and patients with rheumatoid arthritis. These patients should be monitored, and NSAIDs should be used cautiously in these patients.

Several studies showed increases in blood pressure among patients treated with NSAIDs and concurrent treatment with antihypertensive medications, including both hypertensive and normotensive individuals.[6] NSAIDs may attenuate the effects of antihypertensive medication through a variety of mechanisms, including renal mechanisms and peripheral vasoactive mechanisms.[7,13] For example, NSAIDs may attenuate the effects of diuretics by increasing sodium and water retention. NSAIDs have been shown to attenuate the effects of diuretics, β blockers, angiotensin-converting enzyme inhibitors, vasodilators, central α_2 agonists, peripheral α_1 blockers, and angiotensin II blockers.[13] Doses of antihypertensives may need to be adjusted for patients on concurrent NSAID treatment.

Rates and levels of hypertension in patients treated with COX-2 inhibitors generally were within the range shown by nonspecific NSAIDs. This suggests that the COX-2–mediated effects on blood pressure may be more important than COX-1–mediated mechanisms. With the exception of 1 study, trials comparing the 2 approved coxibs did not show any significant differences in effects on blood pressure. The study that indicated differential hemodynamic effects of the 2 agents used the half-maximal dose of celecoxib and the maximal dose of rofecoxib, and it enrolled a patient population that may be particularly sensitive to inhibition of renal PGs and, therefore, to differences in dosing regimens. Overall, clinical trials suggest that the hemodynamic effects of COX-2 inhibitors are based on their primary mechanism of action and not on any additional, agent-specific pharmacologic activity. Similar to the effects of nonspecific NSAIDs, the effects of coxibs on blood pressure and edema may be more pronounced in patients who depend on PGs for maintenance of renal function, including elderly patients, those with hypertension, and those with reduced actual or effective circulatory volume.

In conclusion, NSAIDs may be associated with a small increase in risk for hypertension or edema. This effect appears to be present in similar levels with both nonspecific NSAIDs and COX-2 inhibitors. Although the average degree of increase in blood pressure is small, there may be a small subpopulation of patients at risk for a more substantial increase. The linear relation between systolic blood pressure and risk of cerebrovascular and cardiovascular disease may be consistent at all levels of blood pressure. Although a small change in systolic blood pressure in a person in the normal range may not be as medically significant as a change in a person in a higher range, recent evidence suggests that blood pressures in the high-normal range (systolic at 130 to 139 mm Hg and/or diastolic at 80 to 85 mm Hg) may be associated with an increased risk of cardiovascular or cerebrovascular disease.[5] Thus, patients who show even small changes in blood pressure that appear with NSAID treatment should be monitored and treated.

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