Editorial

Hypertension, Nonsteroidal Antiinflammatory Drugs, and Lessons Learned

Newer guidelines have suggested that in patients over 50 years of age, systolic blood pressure (BP) is more important than diastolic BP as a cardiovascular risk factor[1]. Also, the chance of developing hypertension (HTN) over their remaining lifetime in normotensive people at age 55 years is as high as 90%. A reduction of 5 mm Hg in systolic BP decreases mortality by 7% (the reduction is greater for cardiovascular mortality).

In a study of 463 people with rheumatoid arthritis (RA), BP was not always measured in the charts of patients. Nineteen percent had no BP recorded, 37% of those with readings had HTN, and the BP was uncontrolled (worse than 140/90) in 77%[2]. Nonsteroidal antiinflammatory drugs (NSAID) are most apt to increase systolic BP. It appears that rheumatologists are not doing a good job with respect to adequate recognition and treatment of HTN.

In this issue of *The Journal*, Wolfe, *et al* discuss the prevalence of self-reported HTN and edema in the National Data Bank for Rheumatic Diseases among traditional NSAID users and coxib users[3]. The following key messages will be highlighted in this editorial: where these findings fit in with other studies of BP destabilization with NSAID; the potential biases of the Wolfe, *et al* study; the high prevalence of HTN in our arthritis patients; and the role of this information leading to good clinical practice.

For over 2 decades, the possibility of NSAID aggravating BP has been recognized[4,5]. In fact, much of the work on captopril, an early angiotensin converting enzyme (ACE) inhibitor, was done to determine why it was attenuated with NSAID, as well as to determine its prostaglandin effects[6-8]. NSAID alter prostaglandins (PG) and result in decreases in PGI_2 and changes in urinary measurements of PGE and $PGF_1\alpha$[9]. This change can result in renovascular vasoconstriction and resultant decreased renal blood flow and can cause or aggravate HTN in some patients who are dependent on the renin system[10,11].

Patients using NSAID at risk for HTN include those with baseline HTN or borderline BP elevations, the elderly, and likely those with compromised renal compensatory mechanisms[4]. Two metaanalyses were published comparing various traditional NSAID and their effects on BP[4,5]. The average incremental increases in mean arterial pressure were small, but this was because most subjects did not have significant BP aggravation; however, hidden in the mean values were those who had large and significant BP elevations. Indomethacin was most likely to increase BP, and sulindac (an inactive prodrug at the kidney) did not have any elevations in BP. The take-home message was that patients are usually lucky, but occasionally significant HTN will occur, particularly in high risk individuals.

As the first 2 coxibs differentiated themselves in the marketplace, research was undertaken to compare these agents head to head in the area of HTN. Consistently, celecoxib showed less effects on BP than rofecoxib[12,13], but discussions regarding dose equivalence and timing of BP readings followed. HTN as a side effect is uncommon in healthy normotensive individuals, so differences between coxibs can also be hidden or magnified, depending on the patient population studied. Thus, trials comparing normotensive patients would rarely show BP differences, whereas in elderly hypertensive subjects, the between-drug differences would be more obvious[14,15]. From one large study, one could conclude that clinically important increases in BP in hypertensive patients were found in 15% of rofecoxib 25 mg od users compared to 7% of celecoxib 200 mg od users, with the majority of effects observed being those on systolic BP[13].

One interpretation of these results would be to follow BP carefully, particularly early on, in patients with HTN using coxibs. Options to be considered in those with worsening BP control could be stopping the NSAID, switching to another drug, lowering the dose of NSAID, and/or

See Blood pressure destabilization and edema among 8538 users of celecoxib, rofecoxib, and non-selective NSAID, and nonusers of NSAID receiving ordinary clinical care, *page 1143*

increasing hypertensive medications if the benefit of the NSAID merits continued treatment.

In general, the greatest attenuation of antihypertensives from NSAID is observed with ACE inhibitors, and less with beta blockers, calcium channel blockers, and diuretics. One must be aware of the other renal effects of combining some of these medications with NSAID, such as worsening renal insufficiency, and in the case of ACE, angiotensin II, potassium-sparing drugs, and beta blockers, a risk of hyperkalemia. In a study of NSAID in the elderly, it was concluded at 2 weeks that BP elevations were similar between rofecoxib, naproxen, and celecoxib (funded by Merck)[15]. This study was small (n = 67) and the subjects were elderly but normotensive, so worsening BP would be rare in these patients. Thus trial design can play a role to minimize or magnify drug differences. It is unknown what role the design of Wolfe's study, which was funded by Pfizer, may have played in shaping conclusions about the effects of BP, as even in rofecoxib trials sponsored by Merck, which were based on normotensive subjects, rofecoxib seemed to have a slightly increased mean BP with a dose-response relationship when compared to other NSAID such as naproxen (where a majority of data had been obtained in phase III and IV studies[16,17]).

The database in Wolfe's study consists of 9226 patients (77% with RA), of whom 8538 were eligible for this study[3]. The prevalence of HTN was high (about 45%) and it was lowest in the users of traditional NSAID, possibly due to their younger age, but comparable with the prevalence of HTN in a recent study of RA of 37%[2]. Fluid retention for most of the patients in Wolfe, *et al* was clinically irrelevant (frequently reported but not leading usually to discontinuation or changing of medications) and thus will not be discussed.

Any study has limitations. The patients may or may not be generalizable to a specific practice, but the large sample size ensures some degree of "certainty" regarding the observations. A major limitation of the Wolfe, *et al* study is self-reporting of HTN and its exacerbation. However, the authors tried to confirm whether changes in BP medications were made. Indeed, 91% of self-reported HTN patients were using antihypertensive medications, and 75% reported changes in dose when they had an exacerbation of their BP control. The pooling of traditional NSAID data is not straightforward as past studies have suggested that the effects of BP are different with several traditional NSAID[4,5]. Also, this methodology would not necessarily justify the separation of coxibs as a class. Treatment biases are not easily determined in data sets. For instance, a large Canadian data set suggested that severe asthma exacerbation was less in asthmatics taking beta blockers[19]. Of course, beta blockers can exacerbate asthma, but it is likely that only those with the most mild disease would be prescribed beta blockers, so the observation is confounded by mild disease. Similarly, the unknown biases of prescribing patterns may have affected the results. Wolfe's Table 7 displays the crude HTN rates with specific NSAID. Indomethacin had only 20% increases in HTN and sulindac had 43%, which is in direct contrast to previous metaanalyses of randomized controlled trials with these agents, and reveals a quirk in the data. One wonders if mostly younger normotensive patients were prescribed indomethacin and hypertensive patients received sulindac, as sulindac is known to be an NSAID that does not have BP effects. Thus the attribution of HTN worsening in that group could be due to other factors. Thus one becomes less certain as to the conclusions of the individual coxibs, although the age and morbidity of the users of celecoxib and rofecoxib were similar. One explanation could be that physicians were aware of results of trials showing exacerbation of HTN with rofecoxib and thus were more likely to measure BP in that group (detection bias). They tried to adjust for this by subsetting the data into years before and after the greater awareness of BP effects of rofecoxib. In the Wolfe, *et al* study the efficacy of the NSAID treatment was not measured, so the tradeoffs of risks and benefits of any drug cannot be determined. Results demonstrated more HTN exacerbations in the rofecoxib group. We do not know the dose comparability between rofecoxib and celecoxib.

So what should a clinician do with this knowledge? We must be aware that HTN is common and underdiagnosed and undertreated in our patients, and that in hypertensive patients, NSAID may aggravate their HTN control. One can decide that some drugs are more or less apt to destabilize BP, but good clinical practice would warrant a common sense approach: being aware, monitoring BP, particularly early in chronic NSAID users, and responding to significant elevations of BP.

JANET E. POPE, MD, MPH, FRCPC,
Associate Professor of Medicine,
Division of Rheumatology, Department of Medicine,
The University of Western Ontario,
London, Ontario, Canada

Address reprint requests to Dr. J.E. Pope, Rheumatology Centre, St. Joseph's Health Centre, 268 Grosvenor Street, Box 5777, London, ON N6A 4V2. E-mail: janet.pope@sjhc.london.on.ca

REFERENCES

1. Chobanian AV, Bakris GL, Black HR, et al. National Heart, Lung,and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003;289:2560-72.
2. Nguyen-Oghalai TU, Fyr CW, Criswell LA. Inadequate detection and treatment of hypertension in rheumatoid arthritis [abstract]. Arthritis Rheum 2003;48 Suppl:S320.
3. Wolfe F, Zhao S, Reynolds M, Pettitt D. Blood pressure destabilization and edema among 8538 users of celecoxib, rofecoxib, non-selective NSAID and nonusers of NSAID receiving

ordinary clinical care. J Rheumatol 2004;31:1143-51.
4. Pope JE, Anderson JJ, Felson DT. A meta-analysis of the effects of nonsteroidal anti-inflammatory drugs on blood pressure. Arch Intern Med 1993;153:477-84.
5. Johnson AG, Nguyen TV, Day RO. Do nonsteroidal anti-inflammatory drugs affect blood pressure. A meta-analysis. Ann Intern Med 1994;121:289-300.
6. Fujita T, Yamashita N, Yamashita K. Effect of indomethacin on antihypertensive action of captopril in hypertensive patients. Clin Exp Hypertens 1981;3:939-52.
7. Covi G, Minuz P, Capuzzo G, Lechi C, Delva P, Lechi A. Reduction of the antihypertensive effect of captopril induced by prostaglandin synthetase inhibition. Int J Clin Pharmacol Res 1984;4:47-52.
8. Seto S, Aoi W, Iwami K, et al. Effect of propranolol and indomethacin on the depressor action of captopril in patients with essential hypertension. Clin Exp Hypertens A 1987;9:623-7.
9. Quilley J, Duchin KL, Hudes EM, McGiff JC. The antihypertensive effect of captopril in essential hypertension: relationship to prostaglandins and the kallikrein-kinin system. J Hypertens 1987;5:121-8.
10. Higashimori K, Gante J, Holzemann G, Inagami T. Significance of vascular renin for local generation of angiotensins. Hypertension 1991;17:270-7.
11. Ashida T, Nishioeda Y, Kimura G, et al. Effects of salt, prostaglandin, and captopril on vascular responsiveness in essential hypertension. Am J Hypertens 1989;2:640-2.
12. Whelton A, Fort JG, Puma JA, Normandin D, Bello AE, Verburg KM. SUCCESS VI Study Group. Cyclooxygenase-2-specific inhibitors and cardiorenal function: a randomized, controlled trial of celecoxib and rofecoxib in older hypertensive osteoarthritis patients. Am J Ther 2001;8:85-95. Erratum in: Am J Ther 2001;8:220.
13. Whelton A, White WB, Bello AE, Puma JA, Fort JG. SUCCESS-VII Investigators. Effects of celecoxib and rofecoxib on blood pressure and edema in patients ≥ 65 years of age with systemic hypertension and osteoarthritis. Am J Cardiol 2002;90:959-63.
14. Nietert PJ, Ornstein SM, Dickerson LM, Rothenberg RJ. Comparison of changes in blood pressure measurements and anti-hypertensive therapy in older, hypertensive, ambulatory care patients prescribed celecoxib or rofecoxib. Pharmacotherapy 2003;23:1416-23.
15. Schwartz JI, Vandormael K, Malice MP, et al. Comparison of rofecoxib, celecoxib, and naproxen on renal function in elderly subjects receiving a normal-salt diet. Clin Pharmacol Ther 2002;72:50-61.
16. Bombardier C, Laine L, Reicin A, et al. The VIGOR Study Group. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. N Engl J Med 2000;343:1520-8.
17. Weir MR, Sperling RS, Reicin A, Gertz BJ. Selective COX-2 inhibition and cardiovascular effects: a review of the rofecoxib development program [review]. Am Heart J 2003;146:591-604.
18. Senthilselvan A. Prevalence of physician-diagnosed asthma in Saskatchewan, 1981 to 1990. Chest 1998;114:388-92.