Editorial

Hypertension in the Patient with Arthritis: Have We Been Underestimating Its Significance?

The practice of rheumatology seems to be increasingly linked with cardiovascular medicine. The revelation that rheumatoid arthritis (RA) and inflammation per se is a significant risk factor for cardiovascular disease (CVD) and that the C-reactive protein concentration in serum is a useful index for that risk has led to a flurry of investigation and new knowledge relevant not only to our clinical discipline but also to cardiovascular medicine[1-4]. Nonsteroidal antiinflammatory drug (NSAID)-induced hypertension has been recognized for many years; these drugs increase blood pressure on average by a few mm Hg, but with occasional individuals show marked increases[5]. Some NSAID such as indomethacin have been identified as more likely to lead to this effect. Those patients with hypertension prior to exposure to NSAID, whether treated or not, are noted to be more susceptible. NSAID ameliorate the effects of diuretics, beta–blockers, and angiotensin converting enzyme inhibitors, but are less likely to interfere with calcium channel blockers[5]. It was hoped that cyclooxygenase-2 (COX-2) selective inhibitors (CSI) in contrast to NSAID would not cause or exacerbate hypertension, but this is not the case[6].

Against this background, in this issue of *The Journal*, Singh and colleagues have attempted to model the impact of increases in systolic blood pressure (SBP) on the rate of cardiovascular events in patients with osteoarthritis (OA) and RA in the USA[7]. This is a worthy topic because of the coprevalence of hypertension and arthritis and the known consequences of hypertension, namely increased risk of adverse cardiovascular events. Further, as our population ages, both conditions are becoming more prevalent and this is on a background of increasing rates of other risk factors for CVD, particularly obesity, hyperlipidemia, diabetes mellitus, and smoking in women.

The coprevalence estimate of Singh, *et al* relies on data from the Third National Health and Nutrition Examination Survey (NHANES III) in the USA, undertaken between 1988 and 1994. This information is dated and probably underestimates the numbers involved in 2003. However, the survey estimates that 30 million US citizens have OA or RA and over one-third (almost 12 million) of these will be receiving pharmacologic therapy for hypertension. Should the blood pressure of these arthritis patients increase further, perhaps as a result of the arthritis medicines rheumatologists prescribe, what will be the health and economic consequences? This is the question that Singh, *et al* address.

Singh, *et al*'s analysis and predictive model relies not only on NHANES III but also cardiovascular risk prediction models based on the Framingham Heart Study database and estimates of the costs associated with CVD treatments in the USA. Using quite complicated statistical methodologies, the investigators calculate the probability of occurrence of stroke or ischemic heart disease over one year in each individual in the NHANES III survey, incorporating all known risk factors such as age, plasma lipid concentrations, systolic blood pressure (SBP), current smoking status, history of diabetes mellitus, and electrocardiograph evidence of left ventricular hypertrophy.

The key predictions from the model were:

- About 7100 and 35,700 additional ischemic heart disease and stroke events would be expected to occur in the OA/RA population over one year as a result of a 1 and 5 mm Hg increase in SBP, respectively
- These increases would lead to a direct economic burden in the OA population of $114 to $569 million in Year 2000 dollars for a 1 and 5 mm Hg increase in SBP, respectively

Singh, *et al* conclude that we rheumatologists may have underestimated the population and individual consequences of small rises in SBP associated with our arthritis medication prescriptions in our arthritis patients. They argue that their results are likely to be quite conservative, given results from various other recent studies, where for example:

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- An increase of 3 mm Hg in SBP increased the frequency of congestive heart failure by 10–20%[8], an outcome not modeled in Singh *et al*'s study
- An increase of 3 mm Hg in SBP increased the risk of stroke and angina by 15–20% and 12%, respectively[9]
- A reduction of 20 mm Hg in raised SBP in the elderly with isolated systolic hypertension was associated with a reduction of cardiovascular event occurrences by 34%[10]. This contrasts sharply with Singh, *et al*'s forecasts of a 30% increase in occurrence of these events associated with a 20 mm Hg increase of SBP in the arthritis population with hypertension

Singh, *et al*'s main point is that rheumatologists and other physicians should take more care in selection of the arthritis medications for our patients with hypertension or cardiovascular risk factors, as even small increases in SBP will have quite startling effects on the rates of ischemic heart disease and stroke and the associated economic burdens. The reasonable assumption is that the increases in blood pressure in the hypertensive arthritis population, whether drug-induced or not, will translate into increased numbers of cardiovascular endpoints analogous to the increases seen in the general population.

Medicines that rheumatologists prescribe are important causes of hypertension. Glucocorticosteroids result in a dose-response relationship for salt and water retention that translates into a clinical risk for peripheral edema, hypertension, and cardiac failure. Prednisone is widely prescribed in RA patients and frequently NSAID and CSI are coprescribed, presumably increasing the risk for these adverse effects. Cyclosporin A, also in a dose-related way, induces hypertension, the mechanism being functional and structural effects on the proximal convoluted tubule[11]. These effects of prednisone and cyclosporin A are not confined to the elderly or those with controlled cardiac failure. Further, it is not unusual that a patient with RA might be prescribed NSAID or a CSI, cyclosporin A, and low-dose prednisone, thereby complicating and most likely compounding the risk for cardiovascular adverse effects.

NSAID and CSI are the most widely used medications in arthritis patients and are well known to induce increases in SBP, particularly in already hypertensive patients. Salt and water "retention," most likely linked to inhibition of renal prostaglandin production, some of which is COX-2-dependent, seems the most plausible mechanism for NSAID and CSI-induced hypertension, although other mechanisms may contribute[12]. This property of increasing blood pressure relates in uncertain ways to NSAID or CSI-induced decrements in renal function, notably glomerular filtration rate[13]. A key question arising from Singh, *et al*'s study: Should the inherent propensity of individual NSAID and CSI to increase SBP direct our selection of drug? Singh, *et al* argue in the affirmative in the case of arthritis patients with hypertension. These investigators do not single out particular NSAID or CSI, but the study was supported by Pfizer, Inc., whose COX-2 inhibitor, celecoxib, is claimed to be less likely to induce hypertension than rofecoxib, and this possible contrast is used in Pfizer's marketing, but is contested by their competitors.

Both celecoxib and rofecoxib can increase SBP, especially in already hypertensive individuals, and this is noted in the respective labels. The increases on average are in the region of a few mm Hg, but some individuals display quite marked increases in blood pressure. There is a dose-response relationship for this effect so that comparative trials need always to be examined very closely to ascertain whether the comparisons are reasonable[14,15]. Thus celecoxib 200 mg once daily was less likely to cause hypertension and raised blood pressure than rofecoxib 25 mg daily in a study by Whelton, *et al*[14]. On the other hand Schwartz, *et al*'s study in healthy elderly subjects on a salt replete, controlled diet compared celecoxib 200 mg bd, rofecoxib 25 mg daily, naproxen 1000 mg daily, and placebo. Both CSI and naproxen increased blood pressure significantly by a few mm Hg, but there was no difference between treatments[15]. In contrast, in a study of celecoxib 200 mg bd in ambulatory OA patients with hypertension controlled by lisinopril, celecoxib was not different from placebo in effect on SBP[16]. There is some lack of consistency between studies, suggesting careful attention to the populations studied, the methodologies employed, and doses of CSI chosen[12].

At a clinical level, selection of a CSI will take into account a number of factors, concomitant hypertension being one of these. The advisability of prescription of an NSAID or CSI in this circumstance will depend on the type and severity of arthritis and previous responses to therapy of an individual patient. If an NSAID or CSI is indicated, the lower the dose needed to provide relief the less likely there will be a hypertensive response. Increased monitoring of blood pressure will always be in order in these patients, independent of which CSI or NSAID is selected. Adjustment of antihypertensive therapy may also be needed if hypertensive responses are noted.

Meanwhile, individual susceptibility to NSAID or CSI-induced hypertension has not been explained. Pharmacokinetic factors that might explain greater exposure of some individuals to drug and also link with induction of hypertension have not been identified, but have received insufficient attention to reject this possibility confidently. Systematic work linking plasma NSAID or CSI concentrations throughout the fluctuations associated with the dosage interval and linked to surrogate mechanisms of potential relevance such as the inhibition of the COX-2 isoenzyme and finally to blood pressure readings would seem a useful research direction. The careful investigation of individuals who demonstrate very large effects of NSAID or CSI on their blood pressure would be worthy of more intense study in this way.

We have become more aware recently of the older clinical observation that NSAID and CSI can precipitate cardiac failure. This had most commonly been ascribed to "salt and water" retention induced by NSAID or CSI. This drug group appears to represent a significant risk for induction of cardiac failure, not only in those with controlled cardiac failure but also for "first episode" of cardiac failure in the elderly[17,18]. Hypertension, especially of acute onset, is likely to be instrumental in the pathogenesis of acute cardiac failure.

The "interplay" between risk factors for ischemic and thrombotic CVD is becoming complex but more relevant to clinical rheumatologists. We must be more aware of our patient's risk factors including hypertension, obesity and diet, diabetes mellitus, family and smoking history, plasma lipid profile, along with a recognition of the risk of uncontrolled inflammation per se.

Concomitant drug therapy, particularly related to the cardiovascular system, is a pertinent consideration also. Assessment of the adequacy of cardiovascular drug therapy with respect to prophylaxis against adverse primary or secondary cardiovascular outcomes has become an important matter to review. Thus, the coprescription of low-dose aspirin, beta-blockers, angiotensin-converting enzyme inhibitors, hypolipidemics, and other drugs relevant to CVD increasingly needs to be addressed and reviewed when advising and treating patients with rheumatic conditions. Another important and contentious issue here is the possible risk associated with CSI in patients with various levels of cardiovascular risk. This matter was raised by the incidental finding of a significant contrast between rofecoxib 50 mg per day and naproxen 1500 mg per day in the rate of myocardial infarction and thrombotic events in RA patients[19]. This issue has been the subject of much analysis and comment, but resolution concerning the true risks of thrombotic vascular disease of CSI in patients with risk factors awaits the results of large randomized controlled studies now in progress[20-22].

We can quibble perhaps with the estimates of Singh, *et al* given the indirect methodology and reliance on complex statistical and mathematical approaches, but the message is valid and important, namely, even small increases in SBP, especially in our hypertensive patients, are of great consequence in terms of rates of ischemic heart disease and stroke and the accompanying costs. It therefore is reasonable for us to take this issue seriously. It also follows that we will need to be more vigilant in monitoring our patient's blood pressures and more careful in the selection and review of the medicines we and others prescribe.

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