Editorial

The Cardiovascular System in Rheumatic Disease: The Newest "Extraarticular" Manifestation?

While the primary manifestations of most rheumatic diseases are musculoskeletal pathologies, they are frequently associated with systemic symptoms and other organ involvement. The cardiovascular system has increasingly become one of the extraarticular systems of great interest and a focus for patient care and research in rheumatology. In particular, there has been great interest in the development of atherosclerosis in association with inflammatory arthritis.

Epidemiological studies have highlighted that cardiovascular disease (CVD) prevalence is increased in many inflammatory rheumatic conditions including lupus[1], rheumatoid arthritis[2], giant cell arteritis[3], and possibly ankylosing spondylitis[4]. Inflammation appears to play a key role in promoting CVD in the general population, and it is now accepted that atherosclerosis has important inflammatory underpinnings[5]. However, there are also reports of excess CVD mortality in male patients with osteoarthritis (OA)[6], and it is widely accepted that CVD risk factors are frequently elevated in patients with OA[7].

Patients with rheumatic conditions are frequent users of nonsteroidal antiinflammatory drugs (NSAID). And given that many of these patients will have coexisting CVD, it is of prime importance to consider the optimum treatment of CVD in the rheumatic diseases. The recent withdrawal of several coxibs has drawn attention to the potential for cardiovascular side effects of both selective and nonselective NSAID as a class of agents. A recent clinical pharmacology study has stimulated several epidemiologists to assess a potential interaction between ibuprofen and aspirin. One such study, by Hudson and colleagues, is included in this issue of *The Journal*[8].

CLINICAL PHARMACOLOGY

Careful clinical pharmacology studies can offer insight into clinical experience when relevant patient groups are treated with one or several medications at typical dosages. Early studies had suggested a possible interaction between ibuprofen and aspirin[9]. Catella-Lawson and colleagues investigated this in healthy volunteers[10]. These investigators tested the effects on *ex vivo* platelet aggregation of a variety of nonselective and selective NSAID or acetaminophen plus aspirin. They varied the timing and frequency of the dosing of these agents. When ibuprofen 400 mg was taken 2 hours before uncoated aspirin 81 mg, it blocked aspirin's ability to inhibit platelet aggregation over the entire dosing interval of 24 hours. However, when the uncoated aspirin 81 mg was taken 2 hours before ibuprofen 400 mg, aspirin inhibited platelet aggregation throughout the entire 24-hour period. Equally important was their finding that when enteric-coated aspirin 81 mg was given 2 hours before ibuprofen 400 mg taken 3 times daily, aspirin also inhibited platelet aggregation during the 24-hour period. No interactions were observed when aspirin was taken with diclofenac, rofecoxib, or acetaminophen.

There are important limitations to this study: platelet aggregation studies were conducted *ex vivo*, all subjects were healthy, and relatively few persons were enrolled; nevertheless, this set of elegant studies yields powerful data suggesting a potential interaction between ibuprofen and aspirin. The authors point to some possible mechanisms for this interaction, including competitive inhibition by ibuprofen of the acetylation site in the platelet cyclooxygenase-1 enzyme: Without access to this site, aspirin is unable to irreversibly inhibit thromboxane A_2 production in the platelet.

This finding has been followed by 2 further studies with other selective NSAID. In these investigations, meloxicam, celecoxib, and valdecoxib were shown to have little effect on aspirin's antiplatelet function[11,12].

Do these clinical pharmacology experiments offer insights that translate into clinical recommendations? One would anticipate that they might, but proving the relevance of their observations has been quite difficult. In this situa-

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tion where the timing and frequency of drug dosing appears to be very important, a clinical trial would be the best way of testing this hypothesis. However, concerns about the potential harm of these drug interactions plus the current concerns over CVD side effects of NSAID may prohibit such a trial. Thus, we look to observational drug epidemiology studies, pharmacoepidemiology, to provide evidence.

PHARMACOEPIDEMIOLOGY

The present study by Hudson and colleagues[8] on potential interaction between ibuprofen and aspirin was conducted in Quebec, Canada, where a large provincial healthcare information system was used that includes prescription medications and over-the-counter aspirin, resulting in a very thorough study database. Persons with overlapping prescriptions for aspirin and ibuprofen were compared with those taking only aspirin. (The authors describe that over 90% of aspirin use is through prescriptions in Quebec.) The authors describe a graded risk of myocardial infarction associated with different durations of ibuprofen use — ever hazard ratio (HR) 1.01 (95% CI 0.58, 1.76), ≥ 30 days HR 1.13 (95% CI 0.54, 2.39), and ≥ 60 days HR 1.83 (95% CI 0.76, 4.42).

This article joins several other pharmacoepidemiologic analyses on this issue (see Table 1). Many of the studies have found an increased risk associated with concurrent use of ibuprofen with aspirin, but several have not. Possible explanations for these apparently contradictory results include:

1. Chance: Small numbers of subjects make for less stable and less robust findings. Several of the studies are quite large and others much smaller. The 2 largest studies found no association.

2. Misclassification of exposure: Over-the-counter use of ibuprofen and aspirin is common and not accurately recorded.

3. Sequential effects of drug dosing: Attempting to study an interaction, which may be time-dependent, using retrospective data sources is very difficult. If the interaction is time-dependent, as suggested by Catella-Lawson's work, we would expect varying results based on how patients take these medications.

4. Confounding: A third factor, not well measured, might confuse the relationship. For example, an inhibitor of platelet sensitivity to aspirin, such as tobacco use[13], may be more common among persons who do not use ibuprofen. If this were the case, the inhibition of aspirin's effect by ibuprofen may be difficult to assess.

CONCLUSIONS

We are left with several important unanswered questions. Is the potential interaction between ibuprofen and aspirin clin-

Table 1. Epidemiologic studies of a potential interaction between ibuprofen and aspirin.

Study	Study Population	Study Design	Source of Drug Information	Outcome of Interest	Exposure of Interest	n	Events n	Results Adjusted*
Studies demonstrating a possible increased risk of CVD events with ibuprofen** and aspirin combinations								
MacDonald[14]	Tayside general practice	Cohort	Medicine monitoring unit — prescription dispensing	CVD mortality	ASA (reference)	6285	1350	HR (95% CI)
					ASA & ibuprofen	187	39	1.73 (1.05, 2.84)
					ASA & diclofenac	206	44	0.80 (0.49, 1.31)
Kimmel[15]	Hospital discharge after MI and community controls	Case-control	Retrospective survey including OTC meds	First hospitalized non-fatal MI	ASA (reference)	1059	288	OR (95% CI)
					ASA & NSAID users	366	74	0.83 (0.58, 1.17)
					ASA & frequent ibuprofen***	NA	NA	2.03 (0.60, 6.84)
Kurth[16]	Male primary prevention (Physicians Health Study)	Randomized controlled trial	Prospective survey via mailed questionnaire every 6–12 months	First MI	ASA (reference)	10,780	107	HR (95% CI)
					ASA & NSAID† (1–59 days)	195	26	1.19 (0.77, 1.85)
					ASA & NSAID† (≥ 60 days)	25	6	2.84 (1.24, 6.52)
Studies demonstrating no increased risk of CVD events with ibuprofen* and aspirin combinations								
Curtis[17]	Medicare patients post-MI (Cooperative Cardiovascular Project)	Cohort	Hospital discharge medications	1 year mortality	ASA (reference)	66,739	11,546	HR (95% CI)
					ASA & NSAID	2733	432	0.96 (0.86, 1.06)
					ASA & ibuprofen	844	118	0.84 (0.70, 1.01)
Patel[18]	Veterans Affairs patients	Cohort	Pharmacy records	MI	ASA (reference)	10,239	684	RR (95% CI)
					ASA & ibuprofen	3859	1348	0.61 (0.50, 0.73)
Garcia-Rodriguez[19]	Primary care (GPRD)	Nested case-control	Primary care prescriptions	MI & CVD mortality	ASA (reference)	3515	1119	OR (95% CI)
					ASA & NSAID	466	163	1.10 (0.89, 1.37)
					ASA & ibuprofen	132	46	1.08 (0.74, 1.58)

ASA: aspirin; HR: hazard ratio; CI: confidence interval; MI: myocardial infarction; RR: relative risk; NA: not available; OR: odds ratio; GPRD: general practice research database. * Adjusted for demographics and measures of CVD risk in all but the Patel study. ** Some studies did not examine ibuprofen separately. *** Frequent ibuprofen use was defined as ≥ 4 times/week). † Type of NSAID not known. Duration of NSAID use was estimated for each year of the study from the frequency of use in the preceding month.

ically relevant? While not all data support the interaction, there is substantial evidence, and many other therapeutic options to recommend against using ibuprofen in patients requiring cardioprotective aspirin. What are the other choices? Catella-Lawson's initial work[10] suggests that diclofenac and acetaminophen do not block aspirin's effect on platelets. As well, other studies suggest no strong interaction with meloxicam or celecoxib. However, we have little or no data about many other commonly used NSAID.

While this potential interaction may seem to be of only academic interest, many rheumatic disease patients are at an increased risk of cardiovascular events. Some of these patients are at an increased risk presumably because of chronic systemic inflammation, while others are at an increased risk because of older age, elevated body mass index, and/or reduced physical activity. These issues make many of our patients good candidates for aspirin and should make us think twice before suggesting coprescription of ibuprofen.

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