Is it Time to Believe the Hype?*
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“Doctor, is my Motrin killing me?”

Twice in the past year, headlines across the nation have highlighted the publication of studies suggesting that non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the cardioprotective effects of aspirin (1,2). Based on these results, some experts have strongly recommended that patients avoid taking these medications in combination (3,4). These studies and the resultant publicity place clinicians in an uncomfortable position and raise the natural question whether the current evidence supports this degree of concern.

Non-steroidal anti-inflammatory drugs are among the most commonly used medications in the U.S., with over 70 million prescriptions written annually for more than 30 million daily users (5,6). Although the primary indication for these medications is analgesia, they also inhibit platelet aggregation in a manner similar to that of aspirin. The key difference between aspirin and NSAIDs, however, is that aspirin’s effects on platelet activity are irreversible, whereas those of NSAIDs are transient. In addition, the binding site of certain NSAIDs within the cyclooxygenase-1 enzyme lies in close proximity to the binding site of aspirin. The similarities in mechanism and proximity of the binding sites have led to three important, but so far unanswered, questions. First, in the absence of aspirin therapy, do NSAIDs provide any protection against myocardial infarction? Second, what is the effect of these medications when given in combination? Third, are certain NSAIDs, particularly ibuprofen, more likely to interfere with aspirin than others?

In this issue of the Journal, Kimmel et al. (7) present data from a case-control study of survivors of myocardial infarction (MI) that address these questions. They found that in the absence of aspirin therapy, NSAIDs are associated with markedly lower risk. Among patients not taking aspirin, those taking NSAIDs had a lower risk of MI than patients taking neither aspirin nor an NSAID (odds ratio [OR] 0.53; 95% confidence interval [CI] 0.42 to 0.67). Previous investigations examining this question had inconsistent results, with some suggesting benefit (8–10) but others showing no effect (2,11,12). The particular strength of the Kimmel et al. (7) study is that the investigators acquired information about NSAID use directly from patients. This design allowed the investigators to determine the frequency and timing of NSAID use in relation to the MI. Furthermore, they were able to account for both over-the-counter and prescription NSAIDs. Nevertheless, this finding is unlikely to change clinical practice for patients who can tolerate aspirin. Even with the addition of this article to the literature, randomized clinical trials supporting the use of aspirin are much more definitive than the evidence about NSAIDs. Accordingly, aspirin will remain the first choice for both primary and secondary prevention.

The more important issue is whether certain NSAIDs, particularly ibuprofen, interfere with the benefit of aspirin or may even be harmful when taken in combination with aspirin. The possibility of an adverse pharmacodynamic interaction was mainly of theoretic concern until Catella-Lawson et al. (13) demonstrated that in healthy volunteers, the administration of a single daily dose of ibuprofen two hours before aspirin prevented the irreversible platelet inhibition usually afforded by aspirin. In patients given ibuprofen before aspirin, thromboxane B2 levels were significantly higher and platelet inhibition was significantly compromised compared with patients who took aspirin before ibuprofen. Findings were similar among patients given ibuprofen three times a day for six days, even when aspirin was given before the first morning dose of ibuprofen. Of note, the degree of platelet inhibition achieved by taking ibuprofen three times a day appeared significantly greater than that observed among patients taking a single dose of ibuprofen, although the authors did not formally test this comparison. Finally, the administration of aspirin with either acetaminophen or another NSAID, diclofenac, resulted in normal or near-normal platelet inhibition. These findings supported the existence of a pharmacodynamic interaction between aspirin and ibuprofen; however, the clinical significance of this finding remained unclear. Nevertheless, the manufacturers of Tylenol (acetaminophen, McNeil Consumer and Specialty Pharmaceuticals, Fort Washington, Pennsylvania) have already begun to use the results of this study in advertisements.

Currently, four articles have examined the clinical impact of coadministration of aspirin and NSAIDs. MacDonald and Wei (1) analyzed data from a Scottish administrative pharmacy database. They found that patients with estab-
lished cardiac disease who had been prescribed the combination of aspirin and ibuprofen had an increased risk of all-cause and cardiovascular mortality compared with patients taking aspirin alone. They did not find evidence of increased risk among patients taking the combination of aspirin and diclofenac. As the authors noted, however, this study had significant limitations in that it included little information regarding the severity of cardiovascular disease, other comorbidities, and did not capture the use of over-the-counter NSAIDs.

More recently, Kurth et al. (2) published an analysis of data from patients enrolled in the Physicians Health Study. The authors found that patients randomized to receive aspirin who used NSAIDs were at increased risk of adverse cardiovascular events compared with patients who did not use NSAIDs. The increased risk appeared to be dose dependent, with the greatest risk found among the relatively small number of patients who used NSAIDs more than 60 days per year. These findings should be interpreted with caution given that it was a post-hoc analysis and provided no information about specific types of NSAIDs. Furthermore, the overall rate of myocardial infarction was low, with only six events among patients randomized to aspirin who took NSAIDs >60 days/year.

In the Kimmel et al. article (7), among patients with no history of coronary disease, the use of aspirin was associated with a lower risk of MI compared with patients who were nonusers (OR 0.79; 95% CI 0.63 to 0.98). This benefit was not observed in patients who took an NSAID in addition to aspirin (OR 1.28; 95% CI 0.85 to 1.94). In contrast, patients with established coronary disease who had used NSAIDs plus aspirin were at similar risk of MI compared with patients taking aspirin alone (OR 0.92; 95% CI 0.46 to 1.81). The root cause of this discordance is not immediately clear but may be the result of the relatively small number of patients with coronary disease, differing effects among specific NSAIDs, or residual confounding. It is somewhat reassuring, however, that their findings suggest that NSAIDs do not interfere with the benefits of aspirin when used for secondary prevention.

Finally, in our previously published analysis of elderly survivors of myocardial infarction, the mortality of patients prescribed aspirin and an NSAID at discharge was similar to that of patients prescribed aspirin alone (aspirin and NSAID: Hazard ratio [HR] 0.78; 95% CI 0.69 to 0.88, aspirin alone: HR 0.81; 95% CI 0.77 to 0.86, and neither medication: HR 1.00, reference) (10). Results were similar in an updated analysis when we compared the outcomes of patients prescribed aspirin and ibuprofen with patients prescribed aspirin alone (HR 0.84; 95% CI 0.70 to 1.01) (14).

Thus, although the existence of an adverse pharmacodynamic interaction is biologically plausible, current observational studies and post-hoc analyses provide neither consistent nor definitive evidence that this interaction has a clinically important effect on patient outcomes. Although these studies have appropriately raised serious concerns about the safety of combining aspirin with NSAIDs and ibuprofen in particular, they fall short of providing the level of evidence necessary to warrant a national public health alert. The only reason to change practice is because reasonable alternatives exist to ibuprofen and other NSAIDs for most patients. While this issue is being resolved, the most prudent approach would be to recommend non-NSAID analgesics as initial therapy for patients taking aspirin and avoid using ibuprofen in patients who require NSAID therapy. Nevertheless, clinicians should take the preferences of each patient into account. For patients who have a strong preference for ibuprofen and a need for aspirin, it is reasonable to reassure them that the preponderance of evidence does not clearly demonstrate that this combination is harmful.

How then will this controversy ultimately be resolved? It appears unlikely that governmental institutions or pharmaceutical companies will fund head-to-head comparisons of different NSAID and non-NSAID analgesics. Large, national observational databases would be helpful to address such issues. In this example, such a database should be able to: 1) identify the specific NSAIDs used; 2) account for both prescription and over-the-counter use; 3) provide detailed information regarding the timing and frequency of NSAID use; and 4) control for potential confounders by adjusting for the presence and severity of cardiovascular disease and other medical comorbidities. Unfortunately, we lack such a surveillance system, and in the absence of this information we do not know the importance of an interaction that could have substantial public health consequences.

We also lack a clear consensus on the strength of evidence regarding harm that is required to change practice. We need a process that takes into account the magnitude of the harm, the value of the medications involved, and the potential consequences of the change in practice. As the number and availability of medications grows, the potential for adverse drug-drug interactions rises dramatically. Although a certain number of these interactions will take the form of overt harm, others may manifest more subtly as interfering with benefit. Already interactions have been reported, including the coadministration of aspirin and angiotensin-converting enzyme inhibitors in patients with heart failure (15) as well as the use of atorvastatin and clopidogrel in patients with acute coronary syndromes (16). Undoubtedly, some of these interactions will be real, but others will represent spurious statistical inferences. The problem will be sorting truth from fiction, which will require defining and applying an appropriate scientific standard having both biologic plausibility and methodological rigor. Until such standards are established, these decisions will continue to be tried in the court of public opinion, with much uncertainty about the best course of action.
REFERENCES