As I write this Editor’s Page, Vioxx has just been withdrawn from the market by Merck, Inc., because of an increased risk of cardiovascular (CV) events. Given the number of patients involved (it is estimated that Vioxx was prescribed approximately 10 million times per month in the U.S.), the magnitude of sales of the agent ($2.5 billion/year), the financial impact upon Merck stock (a fall of 27% amounting to $27 billion), and the serious nature of the side effects (myocardial infarction and stroke), it is not surprising that this action received major media attention. The withdrawal provoked the immediate release of papers in the New England Journal of Medicine by prominent CV authorities questioning whether similar action should be taken for all selective cyclooxygenase-2 inhibitors (COXIBs) and even calling for a Congressional investigation (1,2). Clearly, this matter has the potential for significant fallout in many areas.

Non-steroidal anti-inflammatory drugs (NSAIDs) are effective agents, but are limited by potentially serious gastrointestinal (GI) ulcers and bleeding. Vioxx was one of several COXIBs developed to exploit the anti-inflammatory effects of selective cyclooxygenase (COX) 2 inhibition while preserving the protective action of COX-1 on the GI mucosa. The VIGOR study (3), which documented the efficacy of Vioxx in reducing GI side effects, also yielded unexpected evidence of increased myocardial infarction and stroke. Although the relationship between the increased CV events observed and Vioxx was uncertain, a plausible explanation consisted of the unopposed prothrombotic effect of thromboxane A2 via the COX-1 pathway. Given the uncertainty regarding the findings from the VIGOR study, the apparent absence of similar adverse events from other studies, and the demonstrated GI benefit, the major alteration in prescribing recommendations was to urge that all patients with an indication for aspirin (usually for prophylaxis of CV disease) be given that agent with Vioxx. Two years after the VIGOR study was published, the Food and Drug Administration (FDA) instructed Merck to add a warning regarding the risk of CV disease to the package insert. Another two years passed until the results of a study of colon polyps documented the CV risk and resulted in the withdrawal of Vioxx from the market.

At this time the exact magnitude of the problem remains uncertain. The data that provoked the withdrawal were derived from a study of 2,600 patients without CV disease in whom the drug was being tested to prevent the recurrence of colonic polyps. It was reported that the incidence of CV events was approximately double (7 vs. 15 in 1,000 patients annually) in patients who received the drug. The incidence of events in patients with CV disease would be anticipated to be higher. Obviously, this is a serious problem and these figures of public health proportions.

Although it is unclear where, if anywhere, the primary responsibility for this chain of events lies, the finger pointing is well underway. Merck, of course, receives the most attention as a culprit because it developed, tested, and sold the drug and has a major incentive to generate dividends for stockholders. The FDA presents a prominent target for blame because it is charged with the responsibility of ensuring the safety of pharmaceuticals. Physicians are not spared culpability and are accused of being too ready to use new drugs with potential side effects, rather than older agents with longer track records. The politically correct might claim it is a systems problem, with the proper processes not being in place to enable these entities to do their jobs. It is likely that no one particular party is entirely responsible, and even likelier that if one is, it will never be clearly identified. However, each of these parties, as well as patients, will probably experience fallout from the Vioxx affair for years to come.

Patients, of course, will be the group most affected. They have been exposed to the risk of adverse CV events for some time. In addition, they have now lost access to a drug that was effective therapy for the inflammatory diseases for which it was used. Perhaps of greatest consequence, patients have again been given reason to worry about the quality and safety of their health care system. Coming on the heels of recent reports of medical errors, we can expect patients to increasingly question the wisdom of our recommendations and efficacy of our management.

The pharmaceutical industry will almost certainly feel the effects of the Vioxx affair for some time. Just as a plane crash casts a pall over the entire airline industry, so a major withdrawal will dull the luster of prior drug development accomplishments. Because the pharmaceutical industry operates on a financial incentive basis, it will be subjected to an intense examination of its behavior and motives. New drugs will be viewed with more skepticism and likely will be subjected to increased testing. I suspect that the marketing practices of the pharmaceutical companies will come under further scrutiny. Does the industry make new drugs appear excessively attractive in direct-to-consumer advertising? Is there adequate emphasis upon potentially serious side effects...
in marketing to physicians? For my part, the industry action that I most regret was the failure to perform a properly powered, prospective randomized clinical trial (RCT) immediately after the VIGOR study to resolve with certainty whether COXIBs carried an increased risk of CV events. One can assume that pharmaceutical companies will hasten to perform such definitive studies in the future, even for side effects whose relation to the drug seems remote.

As is nearly always the case in drug recalls, the FDA will almost certainly be in line for a close examination. It will likely be noted that Vioxx was approved before the VIGOR study was published, and that the FDA did not require Merck to perform an RCT to establish the absence of CV risk. However, at the time the COXIBs were viewed as an important breakthrough in addressing the prevalent and costly problem of serious GI side effects of NSAIDs. Moreover, the scrutiny given to new drugs is as great in the U.S. as anywhere in the world, if not greater. The professionals at the FDA are given the difficult task of establishing risk versus benefit in as cost-effective and timely a manner as possible. Most physicians I know feel our drug approval process is too slow and detailed, not too quick and superficial. We often lag behind other countries in new therapies. I can recall a neighbor having to go to Canada to receive a drug-eluting stent that was not approved in the U.S. Nevertheless, the FDA will likely become even more demanding in its safety requirements for new drugs, and take more drastic action whenever suspicions of serious side effects arise for existing agents. Because clear evidence of increased CV risk for Vioxx did not appear until 18 months of therapy, some will argue for this length of follow-up before approving new pharmaceuticals. This, in my opinion, would be a detrimental overreaction.

Finally, we as physicians will also be exposed to fallout from the Vioxx affair. Many feel that the superiority of COX-1 inhibitors over other NSAIDs was modest and that the drugs were overused. Some are already portraying physicians as too susceptible to marketing and too quick to adopt new therapies. Our judgment is being questioned in regard to the ability to assess the real advantages of one agent over another and our tendency to overutilize new drugs in situations for which their advantages are not applicable. However, as evidenced by the multiple megatrials prevalent in our field, I believe that cardiologists are more data driven and evidence based in their practices than most physicians. Nevertheless, I would not be surprised if patients did not check the Internet themselves more often to make sure we have not missed something, and if authorities do not continue to tighten the ground rules under which we receive marketing and educational efforts.

In looking back over the Vioxx affair, a number of impressions surface. First, things always appear clearer and more apparent in retrospect, but we live prospectively. Even knowing all the data now available, I cannot say that the actions taken were totally unreasonable. The uncertain risk of CV events was being balanced against the documented benefits for GI complications. Even after the VIGOR study was published, I continued to prescribe Vioxx to my own family. Second, perhaps we as physicians tend to overestimate the benefits and underestimate the risks of new therapies. If this is so, however, I believe it is primarily to provide the greatest benefits to our patients. Third, as stated before, I do wish that an RCT for CV risk had been performed. In regard to possible pressures to conduct safety trials for 18 months or longer or to withdraw drugs at the first evidence of possible adverse effects, I think these would be overreactions. Rather, I believe each case should be handled individually. There will, and probably should, be fallout from the Vioxx affair; of that I have no doubt. I hope the repercussions will be appropriate in magnitude and direction, and that we will emerge with a better system, not one that is worse.

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