An Underrecognized Challenge in Evaluating Postmarketing Drug Safety

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The withdrawal of the cyclooxygenase (COX)-2-specific inhibitor rofecoxib (Vioxx; Merck) has generated a high-profile debate in the medical and lay press over when a signal suggesting the potential for harm from this drug was first apparent and what steps the medical community, the US Food and Drug Administration, and the pharmaceutical sponsor took and should have taken to address this issue.1,2 This debate, however, has glossed over a fundamental problem that the withdrawal of the drug serves to highlight—not how best to deal with a potential signal once it is described, but rather how to identify such important and initially unanticipated effects after a drug is marketed.

What Is Known About a Drug When It Is Marketed?

The contemporary processes of drug discovery and marketing include both basic studies and drug exposure in humans, generally in no more than several thousand patients. These studies establish a putative mechanism of action of the new compound, although, as discussed below, new molecular mechanisms of actions often are discovered after a drug has been marketed. Efficacy must be established in rigorous controlled clinical trials, with well-defined patient populations, inclusion and exclusion criteria, predefined end points, and appropriate statistical analyses. Other important pieces of information include major mechanisms of drug metabolism and excretion and the potential for both pharmacokinetic and pharmacodynamic drug interactions. An important result of this premarketing workup is that adverse effects that commonly occur during the administration of a drug become well recognized. If these effects are common or serious, then the drug may in fact not be suitable for marketing.

What Is Not Known About a Drug When It Is Marketed?

The basic science and clinical trial experience that precedes the marketing of a new drug allows regulators to craft a label to guide use of the drug. Experience teaches that real-world use may result in a side effect profile quite different from that anticipated from the premarketing portfolio. Thus, drugs may be used at higher doses than recommended, for longer periods than recommended, or in combinations that have not been fully explored. An example is the antihypertensive mibefradil that was widely recognized as a potent inhibitor of multiple pathways of drug metabolism and a potent bradycardic agent. After being marketed, however, the drug generated an unexpectedly high incidence of serious adverse reactions, such as bradycardiac and interacting drugs are one example; cerivastatin and fibrates are another.8 This line of reasoning also implies that less bizarre adverse drug effects that occur after drug administration may not be recognized.

The rofecoxib episode emphasizes that drugs not only may produce unusual adverse drug effects that ultimately could be recognizable by an individual clinician, but also may significantly increase the risk of a common adverse event in a particular population. The distinction is important because by definition the latter event is not detectable by an individual practitioner. The effect of rofecoxib to increase cardiovascular events was detected in a trial in patients at risk for colon cancer; because questions about the cardiovascular safety of the drug had been raised previously, the trial tracked prespecified cardiovascular end points.2,9 Rofecoxib is not the first drug in which this type of adverse effect has been documented. Arguably, one of the first and most compelling demonstrations of this phenomenon was in the Cardiac Arrhythmia Suppression Trial (CAST), which identified a marked increase in sudden death among patients treated with sodium channel blockers as compared with patients treated with placebo after acute myocardial infarction.10 A similar outcome has been observed with other antiarrhythmic drugs,11,12 as well as with a series of drugs targeted for symptom relief in heart failure.13–15 A common feature of the antiarrhythmic, heart failure, and rofecoxib episodes is that the adverse drug effect was detected only through the mechanism of a well-controlled, randomized clinical trial. Another common feature

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was that clinical reports and or basic science studies antedating the controlled clinical trial suggested but by no means confirmed that risk might be present.

An extension of these concepts might be that only some patients would be at risk for a particular adverse effect. It would be even more difficult to identify such a subset, although this is one hope of modern genomics and proteomics. It also is entirely conceivable that certain patient subsets would show unexpected benefits from drug therapy in unexpected settings. Examples include the potential for aspirin to slow the development of Alzheimer disease or prevent colon cancer, effects only recently appreciated.

The problem of how to first identify a potential adverse drug reaction has analogies to the problem of detecting drug interactions. The identification of important drug interactions after marketing depends on their being recognized and reported. To the extent that either of these is less than 100% effective in identifying unrecognized drug interactions, unrecognized interactions must be occurring, possibly frequently, in our polypharmacy community. The withdrawal of mibefradil is one example. Another striking example is the first case report to describe torsades de pointes at usual doses of terfenadine, resulting from concomitant ketoconazole. This recognition occurred only after tens of millions of prescriptions had been written, and arguably because a clinical pharmacologist, a physician with a heightened sensitivity to the issue of unusual drug effects, happened to be involved in the index case.

**Is Specificity in Drug Action Highly Desirable?**

A common mantra in the drug development community is that new drug agents should specifically and selectively, with nanomolar potency, target a singular molecular entity, chosen by an understanding of the disease process to be treated. The advantage of this approach is that common nonspecific adverse effects such as headache or nausea, commonly seen with drugs acting in the micromolar range, can be reduced. It also is hoped that by interacting with only specific target molecules, new drug entities would achieve not only safety, but also high degrees of predictable efficacy in appropriately selected patients. The example of imatinib (Gleevec; Novartis Pharmaceuticals), which has striking efficacy in some forms of chronic leukemia, demonstrates the promise of using an understanding of the molecular basis of disease to develop new and highly effective therapies. The rofecoxib episode and other examples suggest, however, that specificity of drug targeting also may carry with it liabilities.

After the CAST episode, considerable efforts were made to develop drugs that prolonged cardiac repolarization, which at the time was believed to be a potentially antiarrhythmic drug action. These efforts resulted in the development of a series of compounds with potent $I_{Kr}$-blocking properties, and the potency and specificity of these agents (eg, dofetilide) did in fact reduce the incidence of noncardiac adverse effects. Nevertheless, marked QT prolongation and torsades de pointes are clearly an issue with $I_{Kr}$ blockers. Importantly, it is not block of this potassium current itself that generates this adverse effect; rather, by prolonging action potentials, $I_{Kr}$ block “engages” other arrhythmogenic currents, the activation of which then results in the long QT–related arrhythmia. Among antiarrhythmics, the “dirtiest” drug, amiodarone, appears to be the most effective. Although amiodarone is an $I_{Kr}$ blocker and consistently prolongs QT interval, it also likely includes effects that prevent torsades de pointes among its panoply of pharmacological actions.

Similarly, targeting COX-2 does appear to reduce the incidence of nonspecific toxicities, including gastrointestinal hemorrhage by nonselective COX inhibitors. An unexpected consequence of targeting COX-2 may well have been the inhibition of desirable cardiovascular effects, such as prostacyclin generation, mediated by COX-2 activation; this would also leave “unposed” COX-1–mediated generation of the prothrombotic eicosanoid thromboxane $A_2$. Both examples suggest that specificity of drug targeting within a complex biological system can result in unanticipated toxicity not directly attributable to the pharmacological effect, but rather to the effect of perturbing the system itself. As with antiarrhythmics, the nonselective agent aspirin clearly carries a more favorable cardiovascular risk profile than that of the highly selective agent.

Indeed, the same sort of thinking applies to other major classes of drugs commonly used in cardiovascular therapy. Carvedilol appears to confer greater mortality benefit as compared with other $\beta$-blockers, an advantage that has been attributed to nonselective receptor blockade, pharmacological effects beyond adrenergic receptor blockade, or both. The benefits of angiotensin-converting enzyme inhibitors in hypertension may be attributable not only to the inhibition of angiotensin II generation, but also to enhanced bradykinin generation. The highly beneficial effects of statins on low-density lipoprotein cholesterol and cardiovascular end points have been similarly attributed to effects beyond HMG-CoA reductase inhibition, the target molecule for which these agents were developed initially. The common lesson here may be that introducing perturbations into a complex biological system carries with it risks that initially may be unanticipated on the basis of a contemporary understanding of biology. As a corollary, drugs with multiple mechanisms of action may in fact carry advantages that are not well appreciated by the target molecule screening strategy.

**Identifying Unexpected Drug Actions: A Key First Step in Drug Safety**

The examples of rare unusual adverse drug effects and of drug-related increased incidence of common adverse effects have the shared feature that they are recognized either by astute clinicians or by appropriately conducted prospective clinical trials. Once these signals are identified, they can be pursued, understood, and validated at the basic and clinical science levels. Thus, the key first step in pursuing postmarketing adverse drug effects is actual identification of a signal that the phenomenon exists; current sources for this first signal include basic or clinical investigation or postmarketing surveillance.

One approach to assessment of a potential safety issue is a placebo-controlled trial, but ethical issues are associated with mounting such trials unless a reasonable possibility exists that either placebo- or drug-treated patients could derive benefit. Another approach is postmarketing surveillance, but it is not
clear how that would aid in the key first step of identifying a potential adverse effect. Approaches such as pharmacoepidemiological studies have been hugely helpful in testing hypotheses that may be unapproachable in other ways, and these studies can address rare and common events, as well as drug interactions.25–27 Unfortunately, hypothesis-free examination of large databases to find new adverse (or even desirable) drug effects has not been a stated goal of any stakeholder in the drug development, regulatory, or clinical communities. To date, clues to identifying heretofore unappreciated adverse (or beneficial) drug actions or interactions have come from understanding basic mechanisms of drug actions or from unexpected results of placebo-controlled trials often mounted for other reasons. Another approach could be the development of new database tools to automatically search large electronic medical records in an unbiased fashion. Given the roles that serendipity and continuing basic and clinical investigation play in identifying such adverse effects, it would be extraordinarily naïve of practicing physicians, regulators, or the pharmaceutical industry to assume that each “event” such as terfenadine-induced torsades de pointes, rofecoxib-associated stroke, or statin-associated rhabdomyolysis is unusual. The rofecoxib episode is likely the largest drug withdrawal in history. The analogy to airplane crashes and the National Transportation Safety Board has been made previously.28 Just as the National Transportation Safety Board investigates not simply to determine cause in a particular accident, but to improve overall air safety, there is a clear and pressing need for an appropriately funded, independent agency with a mandate to learn from each drug toxicity episode, not simply to improve the safety of a small group of drugs but to improve the system we use to deliver therapies to patients.28

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