Commentary

Patients, their doctors, nonsteroidal anti-inflammatory drugs and the perception of risk

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Abstract

This article is about risk. Risk is probably the most misunderstood component in determining therapeutic intervention; however, it is probably the most relevant issue to consider in the context of expected benefit. The rarity of quantitative risk–benefit assessment and the lack of comparative risk–benefit when alternative therapies exist for a given condition leads to inadequate decisions. Without some quantitation of the risks associated with specific therapies, doctors and patients cannot make optimal risk–benefit calculations. Patients may abandon effective therapies for which benefits may still outweigh risks, or opt for therapies with less well-publicized potential adverse events of even greater frequency or severity. When only small incremental benefits accrue to patients from the use of a given therapy, on the other hand, even very rare serious events may play a role in decision-making by patients, by their health care providers and by regulatory authorities.

Risk is inherent to essentially all drug therapy. Any pharmacological therapy is likely to have some risk of adverse effects in some patients. If an adverse event is mild and reversible it generally is not a significant issue in the choice of drug therapy for clinicians or patients. If the potential adverse event is considered severe and/or serious, however, it becomes more relevant to therapeutic decision-making [1]. If any risk were unacceptable then new drug development would halt [2]. This is often not very clear to patients, to oversight government committees or even at times to practicing clinicians. The recent firestorm associated with the extensive risk assessment of the COX-2 selective inhibitors (coxibs) has clearly demonstrated the dilemma. Patients rely upon their health care providers to prescribe therapies that will benefit them and will not place them at risk for a drug-induced adverse event. Even with the empowered general public of the twenty-first century there is still the implied contract with the physician that they are able to determine the appropriate and safe therapy for a patient's specific problem. Conveying risk to the patient while allowing them to understand the decision-making process leading to the use of the specific therapy remains daunting. The issue of the relative risk for a therapeutic in the context of its relative benefit should nonetheless continue to drive this process of assigning drug therapy to patients.

A generic and daunting vulnerability in drug development worldwide is the lack of quantitative risk–benefit assessment and the lack of comparative risk–benefit when other therapies exist for a given condition. Without some quantitation of the risks associated with specific therapies, doctors and patients cannot make an optimal risk–benefit calculation. Patients may forgo effective therapies for which benefits may still outweigh risks; or may opt for therapies with less well-publicized toxicities of even greater frequency or severity. When only small incremental benefits accrue to patients from the use of a given therapy, on the other hand, even very rare serious events may play a role in decision-making by patients, by their health care providers and by regulatory authorities. It is critical that serious drug toxicity be adequately quantitated to inform the process of decision-making regarding medical therapy. Frequent but trivial adverse effects are well studied and communicated currently in drug labeling. It is the rare but serious or severe adverse effects that represent the unmet challenge today.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly used classes of drugs. Unfortunately the effect size on pain is relatively modest, and in clinical trials of severe postoperative pain most patients require rescue medications. During the last decades of the twentieth century when these drugs were developed, careful studies of drug safety were relatively small and therefore it took a decade or more for the medical community to understand the uncommon but serious risks of chronic NSAID use on the gastrointestinal tract and blood pressure. Despite the current

coxib = COX-2 selective inhibitor; FDA = Food and Drug Administration; NSAID = nonsteroidal anti-inflammatory drug.

widely disseminated risk information, these drugs are among the most widely used over-the-counter medications. The risk–benefit perception in the medical community and of the public remains a positive one to justify such broad use of these drugs. Interestingly, only with the development of the coxibs have high-quality randomized, prospective, controlled long-term safety databases become available on naproxen, ibuprofen and diclofenac as well as on the newer coxibs.

The precedent for 'large simple safety trials' has been set [3,4]. The value of such studies is highlighted by the identification of cardiovascular risk of high-dose rofecoxib in the VIGOR trial, in which rofecoxib 50 mg/day was observed to have a fivefold higher risk of a nonfatal myocardial infarction as compared with naproxen [4] in rheumatoid arthritis patients. In the CLASS trial, which was a large simple trial to assess the risk of celecoxib 800 mg/day, no such cardiovascular risk was identified compared with ibuprofen or diclofenac [3]. Placebo control in these studies was absent since arthritis patients cannot go untreated for the extended duration of chronic safety studies. Cardiovascular risk was not the primary endpoint in either of these large studies. It is only with careful, large, long-term safety studies that uncommon and or unanticipated risks can be adequately studied.

Gastrointestinal risk of NSAIDs took decades to understand. Not so with coxibs. Within several years of approval, multiple large safety trials were completed comparing several of these drugs with nonselective NSAIDs. Risk perceptions associated with coxibs (selective NSAIDs) have essentially replaced the slowly accumulated previous concerns of risk associated with the nonselective NSAIDs. It is very difficult for physicians and patients to manage competing risks when shaping risk–benefit perceptions. This remarkable fact has escaped major public awareness.

The NSAID story demonstrates that risk assessment is not a static process. It begins before a human is exposed to a new experimental drug and continues throughout drug development into postmarketing broad exposure once approved. It is impossible to identify all possible risks for all possible users based on exposure in several hundred to several thousand subjects during drug development. Although critics of drug development believe that many typical examples of patients are not included in studies of a potentially new therapy, it would be unethical to enroll very sick patients who are most vulnerable to possible adverse events before a drug is found to be effective. If the Food and Drug Administration (FDA) held back approvals until study had occurred in patients on all possible cotherapies and with all possible comorbidities, drug development would not be feasible. Knowledge of a new drug once approved may be extensive by current guidelines but ultimately imperfect at the time of FDA approval.

There are guidelines to require a reasonable safety assessment before marketing drugs. The International Conference on Harmonization, an ongoing conference including the FDA as well as European and Japanese drug regulatory agencies, has issued a guidance document that discusses safety assessment in drug development. Drugs for chronic use should be supported by safety analysis in at least 300–600 subjects for 6 months and in 100 subjects for 1 year. Frequent adverse events (>1%) can be identified before approval. Based on the 'rule of 3s' [5], if no events are seen in 300 exposures then the true event rate is below 1/100 or 1% (with 95% certainty). For an event that has a relatively high background rate, such as heart disease or cancer, a few events in a database of several hundred subjects may not be adequate to signal a drug-related serious toxicity. It can be quite difficult to assess the meaning of differences in low frequency events that are not a prespecified endpoint of any given study. For instance, is there a true difference in risk of a life-threatening adverse event between placebo and drug therapy if rates seen in clinical trials are 0.4% and 0.8%, respectively? In studies based on minimal current guidelines for drug development one could not know whether these results were random events. Yet if reflective of a true doubling of risk, this finding would be of significant concern for life-threatening events such as myocardial infarction or sepsis. It would require a well-controlled study of a very large number of subjects over time to interpret these results. For events that have extremely low spontaneous background rates, such as acute liver failure, a single event indicates a probable drug effect but will probably not be seen in the first several hundred to several thousand of exposures in pre-approval clinical trials. It would take tens of thousands of subjects exposed to a therapy to robustly assess rare, serious, but important, drug-related risk.

There is research underway to identify early or surrogate markers for serious toxicity to deal with this dilemma but such research will take years to impact drug development [6]. In summary, without large outcome studies involving many thousands of subjects for months to years, it is currently impossible to numerically assess small but potentially important risks of drug therapy.

Beyond the premarketing assessment of safety, additional safety information comes mostly from pharmacovigilance. Pharmacovigilance is defined as 'all observational (non-randomized) postapproval scientific and data gathering activities relating to the detection, assessment and understanding of adverse events' [7]. This includes the use of pharmacoepidemiologic studies.

In 2004 the FDA published a series of draft guidances for pharmaceutical companies to use both before and after initiating drug marketing. The Code of Federal Regulations that governs the regulation of new drugs has required drug manufacturers to collect postmarketing safety information that is available on their marketed product and to submit such reports to the FDA. In addition, any person can report an

adverse event directly to the FDA through the MEDWATCH system, which has evolved from a paper system years ago to an Internet-based computerized database system. Reports take only several minutes to complete and submit [8]. All reports are now entered into a computerized database called the Adverse Event Reporting System, which has over 6 million reports and is growing by about 300,000 reports per year. This is a passive/voluntary reporting system that is designed to identify signals for unexpected adverse events. The term 'signal' does not have a highly specific meaning but generally refers to the identification of an adverse event that may be reported at a rate in excess of what would be expected. A single report can constitute a signal for extremely rare events such as acute liver failure or rhabdomyolysis. With a common problem such as cardiovascular disease, however, such uncontrolled passive reporting offers little to no value. There are attempts being made to develop a statistical study of the Adverse Event Reporting System database through datamining programs that may allow for rapid postmarketing quantitative assessment of unanticipated risks [9,10]. Large outcome trials that recruit patients at some risk, however, may currently be required to understand the possible causal effects of some therapies.

Commonly used NSAIDs and coxibs do not alter the natural history of any disease for which they are labeled. Interestingly, however, celecoxib was approved for use in familial adenomatous polyposis based on the surrogate endpoint of decrease in the number of adenomatous polyps in relatively short-term studies [11]. One should not underestimate the importance of palliation, especially when there are limited options, each of which is associated with serious adverse events. For NSAIDs the risk for gastrointestinal bleeding is relatively low, particularly if used on an 'as needed' basis. With the extraordinarily large use of these drugs, however, absolute rates for these potential events are high [12].

Premarketing understanding of major biologic effects of new therapies and large carefully performed studies of new therapies simultaneously with widespread use offers the best approach to rapid development of the most accurate risk–benefit assessment. The media has unfortunately not advanced the public's understanding of the complex challenge of risk assessment and risk–benefit calculation by suggesting that the regulatory bodies around the world have not been doing their job of oversight; that all pharmaceutical companies making these products have sold these medicines without conscience, knowing that there was risk, and worked hard to keep that information from health care providers, the regulatory agencies and the public to preserve their profits; and that providers have not been doing their jobs as advocates for the patients in terms of providing safe and effective therapies.

Interestingly, careful analysis of existing data using the nonplacebo-controlled randomized controlled trials of the CLASS and TARGET studies as well as extensive epidemiologic studies using healthcare databases was presented to an FDA advisory committee in February 2005 [13,14]. These data suggest that ibuprofen, naproxen and diclofenac all possess similar hazard rates as two of the coxibs, celecoxib and lumiracoxib, when used for up to 1 year. The risk over longer term use is less well understood, however. It took polyp prevention studies of 2–3 years duration to indicate that risk may increase over long-term chronic use compared with placebo in studies [15]. Such data only exist for naproxen (at lower dose), celecoxib and rofecoxib. This has led the FDA to issue a requirement that all nonselective NSAIDs and all selective NSAIDs should have a 'box warning' within their product label identifying cardiovascular events of stroke, acute myocardial infarction, sudden cardiac-related death and congestive heart failure as a risk of use for these drugs, in addition to the potential for gastrointestinal adverse events.

NSAIDs will continue to be an important drug class in the treatment of arthritis and other causes of pain for the foreseeable future. The past decades have witnessed multiple changes in the public's risk perception of these drugs: a low risk of nonselective NSAIDs compared with aspirin in the 1970s to early 1980s; a growing understanding of gastrointestinal toxicity in nonselective NSAIDs in the 1980s and 1990s; a high-risk perception for nonselective NSAIDS and a low-risk perception for coxibs in the late 1990s to 2001; and a high-risk perception for coxibs and an unclear risk perception for nonselective NSAIDs from 2001 to the present.

Competing risks of gastrointestinal and cardiovascular conditions have added further confusion regarding the understanding of the overall relative risk to benefit of these therapies. This 'yo-yo' reflects evolving science, diminished public tolerance of uncertainty and risk, and changing risk–benefit perceptions influenced by physicians, pharmaceutical companies and the media

Hopefully, the NSAID experience will yield a better permanent sophistication on the part of physicians and the public in understanding the inevitable competing risks and benefits of medical therapy and the inherent uncertainties in the current paradigm of drug development.

For the practicing clinician confronted by a patient who needs an analgesic for osteoarthritis, the choices for therapy appeared quite simple until several years ago [15]. Physical measures such as exercise, support devices, modified activities of daily living along with cognitive therapies, and thermal modalities are suggested. The pharmacologic therapies are titrated upward based on perceived potency/risk. These therapies include acetaminophen, NSAIDs (coxibs if the patient was at risk of upper gastrointestinal complications, such as prior peptic ulcer disease, gastrointestinal bleed, anticoagulant therapy, cardiovascular disease and

advanced age that would increase the morbidity of an acute upper gastrointestinal bleed) and opioids.

The medical literature estimated that over 15,000 deaths per year and over 100,000 hospitalizations per year were attributed to nonselective NSAIDs. With the evidence of lower rates of upper gastrointestinal ulcers associated with coxib use compared with nonselective NSAID use, the major reason for continued use of nonselective NSAIDs after initial approval of celecoxib and rofecoxib was cost. After publication of the results of the VIGOR trial, comparative safety became less clear between nonselective NSAIDs and coxibs.

Results of the placebo-controlled polyp prevention studies with rofecoxib, celecoxib and naproxen became public in late 2004. These studies showed an increased risk of cardiovascular disease with chronic use of coxibs and naproxen. The entire field of relative NSAID safety entered a period of upheaval that continues to this day. The previously established risk of gastrointestinal adverse events with nonselective NSAIDs must still be considered, but now the cardiovascular risk including hypertension as well as ischemic events is added to the mix. Will intermittent use or on-demand use of NSAIDs/coxibs minimize the risk of serious adverse events? Will the co-use of low-dose aspirin and coxibs minimize cardiovascular toxicity but preserve some coxib gastrointestinal safety advantage? Will proton pump inhibitor co-use with nonselective NSAIDs adequately protect against gastrointestinal toxicity even in high-risk patients? The absence of robust comparative studies of these alternative strategies prevents quantitative comparative assessment of the risk of serious gastrointestinal and cardiovascular disease. Once again we are reminded that risk–benefit assessment is not a simple task, and that individual physician and patient risk perception must guide choices in analgesic NSAID therapy.

Competing interests

The authors declare that they have no competing interests.

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