

COX-2 inhibitors: exemplars of the drug-safety conundrum

Using clinical trials to assess long-term drug safety is problematic; in Australia, simple data linkage based on Medicare numbers may provide useful monitoring information

The era of pharmaceutical medicines began with the synthesis of acetylsalicylic acid (ASA) in the late 19th century. The reason for its synthesis was that natural salicylic acid was irritating to gastric mucosa, and the synthesised product less so. Subsequently, more potent non-steroidal anti-inflammatory drugs (NSAIDs) were introduced and, more recently, cyclooxygenase-2 (COX-2) inhibitors, also with a lesser risk of gastric irritation and bleeding.¹ The rapidly widespread and often prolonged use of these agents meant that even a small increase in the risk of a serious adverse event could be very significant in population health terms.

This theoretical concern became a reality when rofecoxib (a COX-2 inhibitor) was found to confer an increased risk of cardiovascular disease — a risk uncovered in a trial to determine whether rofecoxib could prevent the recurrence of colorectal polyps.² Subsequently, the United States Food and Drug Administration has issued warnings on the cardiovascular safety of celecoxib and naproxen.^{3,4} More recent information links long-term use of celecoxib and short-term use of parecoxib and valdecoxib (though non-significantly for the latter two) with adverse cardiovascular events.^{5,6} This is consistent with a class effect.

Although the mechanism underlying the increased cardiovascular risk with COX-2 inhibitors is unknown, there is a biological rationale that might have predicted it and which, in retrospect, should have led to intense postmarketing surveillance of these inhibitors. The non-selective COX inhibitors (ASA and NSAIDs) inhibit platelet aggregation, whereas selective COX-2 inhibitors do not.⁷ Selective COX-2 inhibitors may also be prothrombotic through prostacyclin, which has a markedly enhanced action in atherosclerosis.⁸

The widespread use of COX-2 inhibitors has been part of the historic trend from short-term use of drugs to treat acute conditions to prolonged use of drugs to treat symptoms and prevent disease. This change has brought to light shortcomings in the current methods of drug safety monitoring. In the past, the linchpin of postmarketing surveillance has been the spontaneous reporting system in which doctors, pharmacists and others report recognised adverse reactions to drugs. However, this mode of reporting is useful only for detecting narrow spectrums of adverse events, particularly those occurring soon after drug administration or those that have overt effects (eg, rash, hepatic inflammation or blood dyscrasia). This spontaneous reporting is particularly unsuitable for long-term monitoring of drug safety.

These realities are poorly appreciated by healthcare professionals, who often assume that, in comparison with older drugs, a newly registered drug has superior short-term and long-term safety.⁹ However, the events with the COX-2 inhibitors, which follow on the heels of similar, unsuspected concerns about anti-arrhythmic therapy and hormone replacement therapy, has again highlighted the need for a more systematic approach to long-term safety monitoring of long-term drug therapy.^{10,11}

The accepted gold standard for establishing the balance of long-term drug safety and efficacy is the controlled clinical trial. In 2005, it should not be possible for any long-term medicine to be approved without the security of a large-scale morbidity–mortality trial, or the

commitment of the pharmaceutical industry to perform one as soon as practicable. Licensing should be conditional on these requirements being met, and the onus should be on regulators to make these changes in the interests of both the end-users and the pharmaceutical industry.

However, even large-scale morbidity–mortality trials have their limitations. They are very costly to establish, and ethical considerations may preclude the use of placebos. Comparisons with other active drugs may be difficult to interpret, as illustrated by the comparison of rofecoxib and naproxen.¹ Study inclusion criteria may lead to the exclusion of patients with comorbidity or polypharmacy, and yet these individuals are both more likely to be prescribed drugs and be at higher risk of adverse reactions. In addition, it has proven difficult to continue large-scale trials beyond 5–6 years, so adverse events with prolonged latency, such as malignancy, may not be identified.

A solution to long-term drug safety monitoring might include observational epidemiology. Methods must be developed for early identification of users of new drugs and their subsequent disease history determined by data-linkage to various mortality and morbidity databases (such as hospital admissions, cancer and death registries). The inclusion of Medicare numbers on prescriptions in Australia provides a simple means for participation in these studies. An ongoing hurdle is the issue of confidentiality.

We do not claim that data-linkage will provide a foolproof answer to drug safety issues. The future mortality and morbidity experiences of any cohort of drug recipients may be influenced by the underlying disease for which the drug has been prescribed. This makes it desirable to have one or more control groups (typically individuals receiving a different drug for the same disease) for comparison. Even if there are control groups, there may still be confounding by differences in indications or contraindications. Therefore, the gathering of linkage data is often relatively low grade, retrospective and useful mainly as a screen for further study if an unexpected finding arises. Such linkages were used in the US to bring into question the cardiovascular safety of rofecoxib before the VIGOR trial.¹² Large linked databases are increasingly seen as the only reliable means of gaining the information necessary for monitoring long-term drug safety.¹³ Our unified healthcare system in Australia, with its standardised Medicare numbers and national databases, has the potential for providing Australia with a strategically important role in this crucial area of drug research.

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