

Prescribers and drug withdrawals

Gillian Shenfield, Clinical Professor in Clinical Pharmacology, Department of Clinical Pharmacology, Royal North Shore Hospital, Sydney

Key words: COX inhibitors, drug industry, drug regulation.

(*Aust Prescr* 2005;28:54–5)

'Disingenuous surrogate markers and misleading composite outcomes may create good advertising material, but can obscure data and hinder genuine patient-centred care.'¹

The much publicised withdrawal of rofecoxib and the subsequent queries about the safety of celecoxib evoked a huge response in both the lay and the medical press. Medical journals have thundered about the irresponsibility of the pharmaceutical industry and the lack of vigilance of government agencies.² These criticisms are generally justified, but the use of new drugs is not solely determined by industry and government.

Australia has a National Medicines Policy which is a partnership between health professionals, consumers, the government and the pharmaceutical industry. The Quality Use of Medicines (QUM) arm of the policy builds on this with advice on giving the appropriate drug, to the right patient, at the right time, by the safe and judicious use of high quality medications. Prescribers are central to this process and we must therefore bear some of the responsibility when things go wrong. We certainly share the brunt of the aftermath, as drug withdrawals create widespread panic and far more work than writing a prescription for a new drug. Could we have prevented the debacle with the cyclo-oxygenase-2 (COX-2) inhibitors before the recent trials made the importance of vascular adverse effects completely clear?

In this issue...

New drugs may be associated with new risks of harm. While Gillian Shenfield comments on the 'debacle with the cyclo-oxygenase-2 inhibitors', Daniel Worthley and Robert Fraser remind us that non-steroidal anti-inflammatory drugs are commonly associated with gastrointestinal bleeding.

New indications may also expose new risks. Gerard Byrne tells us that antipsychotic drugs may have cardiovascular adverse effects in patients with dementia.

While the risks of isotretinoin are now well-known, John Sullivan stresses the importance of ensuring patients know about the adverse effects and how to minimise them. Most smokers know about the harmful effects of tobacco, but are unable to quit. John Litt advises on new approaches to help them successfully stop.

Consider what happened in Australia. Celecoxib was first available on prescription in 1999 and numerous sample packs were given to both general practitioners and specialists. It was listed on the Pharmaceutical Benefits Scheme (PBS) in 2000 and in its first year it cost the PBS \$200 000 000. This equalled the cost of **all** cytotoxic drugs in the same period. Why did this enthusiastic prescribing occur? Both celecoxib and rofecoxib were marketed as 'safer', rather than more efficacious, but the limited extent of the benefit was not made clear to prescribers. In 1999 it was known that the major demonstrated effect of COX-2s, compared with non-steroidal anti-inflammatory drugs (NSAIDs), was a reduction in shallow 'endoscopic' ulcers which are clinically unimportant.³ The beneficial effect on serious, complicated ulcers was very much less. In patients with rheumatoid arthritis and no other risk factors, the annual risk of developing a complication related to NSAID use is only 0.4%. COX-2s could possibly reduce this to 0.2% (likely to be expressed as a 50% reduction for marketing purposes). In this group it would be necessary to treat 500 patients to prevent one complicated ulcer. In younger, healthier individuals the 'number needed to treat' would be even higher.³ Yet in Australia more than 50% of the patients prescribed COX-2s were under 65.⁴

Many doctors gained the false impression that selective drugs were also less likely than conventional NSAIDs to have adverse effects on blood pressure and the kidneys. This view was also held by some key opinion leaders – people who always have a major influence on prescribing patterns and, for this reason, are invited by pharmaceutical companies to talk to groups of prescribers. To complicate the situation, the media persuaded consumers that the new 'wonder' drugs were more efficacious than older medications. Word of mouth completed a marketer's dream situation. Certainly the drugs were heavily promoted by both industry and the media, but why did prescribers fail to follow QUM principles? The facts were all there³ and there are many independent sources of information about drugs (see box). Unfortunately, independent sources do not have the same resources as pharmaceutical companies and their information usually lags behind marketing campaigns. Independent organisations, such as the National Prescribing Service, are often perceived to be driven by cost containment when they advise cautious use of new drugs. In fact their caution usually relates to the paucity of safety data and limited experience with the drug.

Some sources of independent information

Australian Prescriber – www.australianprescriber.com

National Prescribing Service publications: Newsletter, RADAR – www.nps.org.au

Therapeutic Guidelines – www.tg.com.au

Australian Medicines Handbook – www.amh.net.au

There seems to be a glamour about anything new, despite the absence of long-term safety information when a drug is first approved. Of course the industry designs and interprets trials to maximise favourable outcomes. Of course it puts the best possible spin on its marketing messages, but doctors should be smart enough to see through the hype. They need to know that when a drug first appears on the market only limited safety data are available and long-term outcomes, both good and bad, can only emerge with time and appropriately designed, prospective safety studies. It is well established that most prescribers obtain the majority of their information from the pharmaceutical industry and they therefore need more training in how to evaluate the information and what questions to ask drug representatives.⁵

The National Prescribing Service in a recent publication suggests that we should think about what is not known rather than what is known about new drugs.⁶ Medical schools and postgraduate colleges must take more responsibility for training students and young doctors about assessing new drugs. This involves more than just an extrapolation of evidence-based medicine. We cannot complacently offload all blame onto government regulators and industry.

Rofecoxib is by no means the first drug to be summarily removed from the market. Cerivastatin and mibefradil suffered a similar fate, in both cases because of fatal toxicity due to interactions with other drugs. There are also many examples of

new drugs which have had significant safety warnings added to their product information within a few years of marketing.

There is no merit in being among the first to prescribe a new drug whatever the pressures from patients and drug companies. It has been well said that 'For all newly-licensed drugs, confidence about safety can only be provisional'.¹ It is essential that both prescribers and consumers grasp this fundamental fact.

References

1. Summerskill W. Evidence-based practice and the individual. *Lancet* 2005;365:13-14.
2. Vioxx: an unequal partnership between safety and efficacy. *Lancet* 2004;364:1287-8.
3. Peterson WL, Cryer B. COX-1-sparing NSAIDs – is the enthusiasm justified? *JAMA* 1999;282:1961-3.
4. Kerr SJ, Mant A, Horn FE, McGeechan K, Sayer GP. Lessons from early large-scale adoption of celecoxib and rofecoxib by Australian general practitioners. *Med J Aust* 2003;179:403-7.
5. Day R. How to make the most of a visit from a pharmaceutical company representative. *Aust Prescr* 2000;23:97-9.
6. NPS News. Mind the gaps: how much do we really know about new drugs? *NPS News* 2004;37. <http://www.nps.org.au/healthpro> Go to Quick Links, Newsletter Index, No. 37.

Further reading

Lasser KE, Allen PD, Woolhandler SJ, Himmelstein DU, Wolfe SM, Bor DH. Timing of new black box warnings and withdrawals for prescription medications. *JAMA* 2002;287:2215-20.

Lexchin J. Drug withdrawals from the Canadian market for safety reasons, 1963–2004. *CMAJ* 2005;172:765-7.

Professor Shenfield is on a number of National Prescribing Service committees, has chaired a writing group for Therapeutic Guidelines, and conducts reviews for the Australian Medicines Handbook.

Letters

Letters, which may not necessarily be published in full, should be restricted to not more than 250 words. When relevant, comment on the letter is sought from the author. Due to production schedules, it is normally not possible to publish letters received in response to material appearing in a particular issue earlier than the second or third subsequent issue.

Expensive new drugs – do we really need them?

Editor, – Professor Moulds' editorial (*Aust Prescr* 2004;27:136–7) suggests that in the last 20 years, new prescription medicines have failed to provide the same therapeutic advances as in the previous 20 years, but are costing significantly more. Furthermore, Professor Moulds believes that patent protection for profiteering pharmaceutical manufacturers is denying the community access to cheaper generic medicines. I would like to dispute the professor on a number of issues.

First, data from the Australian Institute of Health and Welfare show that in the last 20 years, mortality rates have decreased for cardiovascular disease (48%), respiratory disease (33%), and digestive disorders (35%). Medicines have saved more lives in the last 20 years, however morbidity rates have inversely increased.

Secondly, it now costs over \$1 billion for a pharmaceutical company to develop a single new medicine.¹ This is quadruple the cost of 20 years ago. If an innovator cannot recoup these development costs, they have less discretionary