

Lessons on prescribing and drug safety from the withdrawal of rofecoxib



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Merck Sharp and Dohme (Australia)'s recent recall of rofecoxib not only shook the company's financial foundations, but also the faith that doctors and patients had in the safety of modern pharmaceutical medicines.¹ What followed was a scramble by rival companies to reassure consumers and doctors that their related products were safe. This was done to prevent consumers stopping their current selective or nonselective nonsteroidal anti-inflammatory drug (NSAID), and to capture the market share previously held by rofecoxib.

Selective cyclooxygenase-2 (COX-2) inhibitors were developed to circumvent the gastric irritation and bleeding associated with aspirin and other nonselective NSAIDs. However, we clinicians are still left with a dilemma as there is an absence of long term safety data for all COX-2 inhibitors. An absence of data, as we have seen with rofecoxib, does not mean that a drug is safe. The unfortunate sequence of events that occurred with rofecoxib should provide us with a timely opportunity to re-think our use of new drugs both from a clinical point of view and in terms of how drug safety is assessed postmarketing.

Utilisation of COX-2 inhibitors

Current Therapeutic Goods Administration (TGA) approved uses for COX-2 inhibitors are:

- symptomatic treatment of osteoarthritis (celecoxib, rofecoxib, meloxicam) and rheumatoid arthritis (celecoxib, rofecoxib)
- the treatment of primary dysmenorrhoea in adults, and
- familial adenomatous polyposis (celecoxib).

The Pharmaceutical Benefits Scheme (PBS) restricts subsidisation of their use to symptomatic treatment of osteoarthritis (celecoxib, rofecoxib, and meloxicam) and rheumatoid arthritis (celecoxib).²

Figure 1 shows the recommended place of COX-2 inhibitors in the management of osteoarthritis of the knee and hip; a common condition encountered in general practice.³ It can be seen that COX-2 inhibitors are suggested to be used by a specific subgroup of patients in an intermittent fashion. Furthermore, there is no evidence that COX-2 inhibitors are more effective than the nonselective NSAIDs for which long term safety data are available. Kerr et al⁴ found evidence that COX-2 inhibitors were prescribed for conditions that did not comply with PBS restrictions, and that approximately half the patients studied had not received a prescription for analgesics in the year before their prescription. Pharmaceutical Benefits Scheme expenditure data demonstrates the community cost of this prescribing pattern (Figure 2).²

Such widespread, long term and 'off-label' use has significant safety implications.

Postmarketing drug safety surveillance

The most reliable method to assess the overall risks and benefits of a drug is a prospective randomised controlled trial (RCT). However, even RCTs have limitations. They are expensive, there are ethical problems with the use of placebos, they often have restrictive participation criteria and therefore rarely include the majority of end-users, and they rarely extend beyond 5 years. It is therefore possible that adverse events with a long lead time such as cancer may not be identified by RCTs.

Another method to check safety is through the use of large databases such as those held by the Health Insurance Commission. By cross linking these databases to disease registries such as a cancer register, it may be possible to identify safety issues during routine use of the drug in the community.

Finally, there is the current and least reliable method: that of spontaneous reports of adverse events. This method is good at identifying the 'point of the needle', and classic well recognised adverse events such as aplastic anaemia. It is not good, however, at identifying delayed events or increased incidence of common, seemingly unrelated conditions, eg. cholelithia-

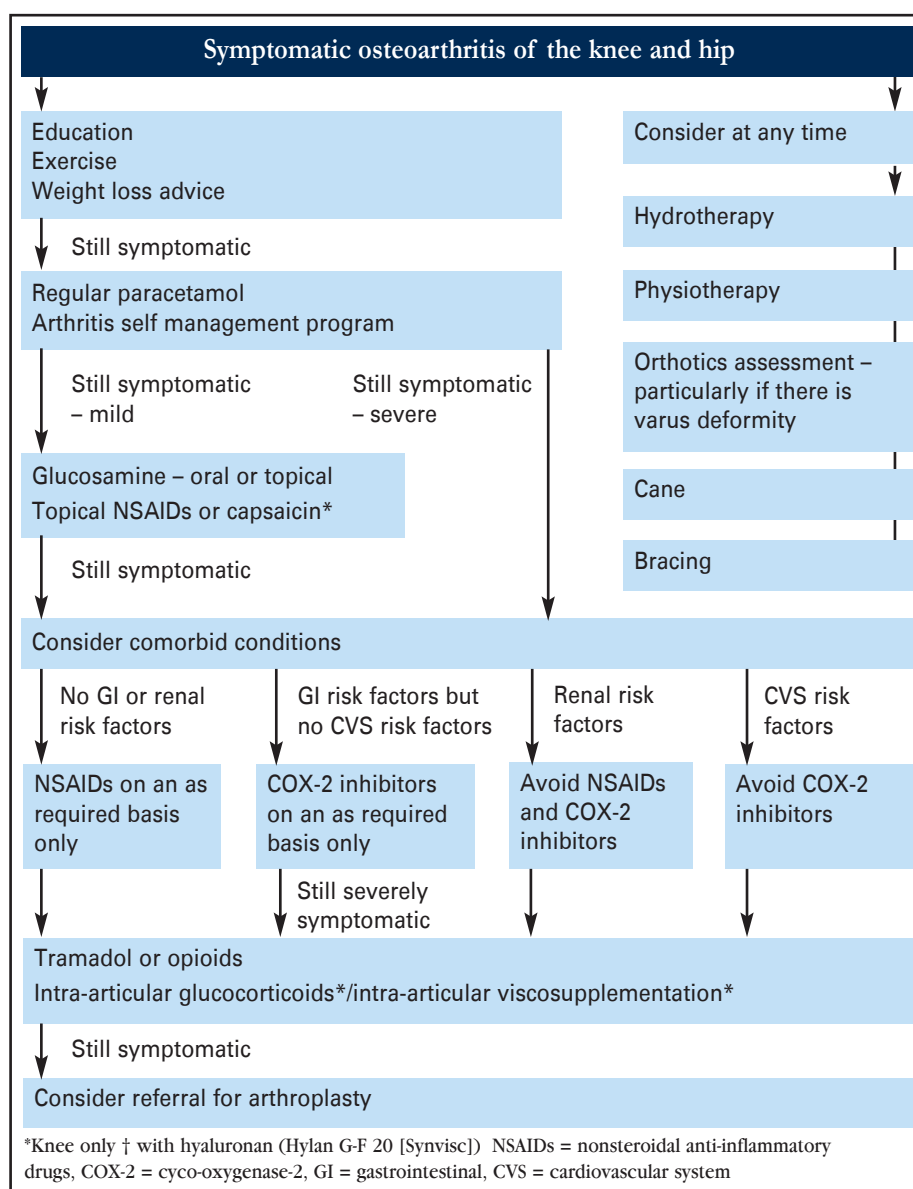


Figure 1. Management algorithm for osteoarthritis of the knee and hip. Reproduced with permission: *Medical Journal of Australia*¹

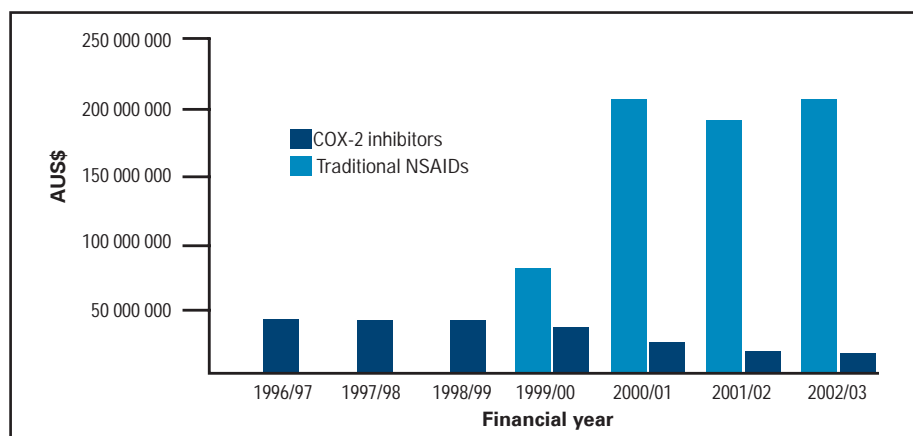


Figure 2. Comparison of costs for selective and nonselective NSAIDs²

sis. It is also very likely to grossly underestimate the incidence of adverse events.

So what are the lessons?

The following are a few pointers to both reduce the risk of adverse drug reactions and contain costs:

- keep a healthy scepticism of claims of 'breakthrough' drugs
- where possible, prescribe according to evidence based guidelines
- read the drug reviews in independent sources such as publications of the National Prescribing Service and Australian Prescriber
- use pharmacopoeias such as the Australian Medicines Handbook
- avoid being an 'early adopter' of newly marketed drugs. If you are, then you have an obligation to provide early safety monitoring data by reporting all suspected adverse events to the Adverse Drug Evaluation Committee, and
- prescribe drugs according to their TGA approval and PBS restrictions.

Finally, we must change our attitude that newer drugs may be more expensive but are preferable because they always have superior efficacy and short and long term safety.⁵

References

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