

The road to consensus: considerations for the safe use and prescribing of COX-2-specific inhibitors

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THE ACCOMPANYING ARTICLE ("Considerations for the safe prescribing and use of COX-2-specific inhibitors" — page 328)¹ is the outcome of an attempt by a group of clinicians and other health professionals to arrive at a concise consensus statement on the safe use and prescribing of COX-2-specific inhibitors (CSIs), based on an assessment of the published literature on the CSIs currently available in Australia. The initiative arose out of concern among rheumatologists on advisory boards to pharmaceutical companies that these drugs not be perceived as "NSAIDs [non-steroidal anti-inflammatory drugs] without side-effects", but be used with appropriate care and caution. Further, there appeared to be some confusion about the merits of these drugs relative to each other and to conventional NSAIDs.

As we believe that aspects of the process undertaken by the Australian COX-2-Specific Inhibitor Prescribing Group have a bearing on evidence-based summaries and the consensus process in general, we describe that process here.

The process

As the formulation of precise indications for the use of NSAIDs rather than CSIs (or vice versa) would generate interminable controversy, we agreed to confine ourselves to the apparently simpler topic of safe CSI use. Nonetheless, the process of reaching consensus proved difficult, the more so as summary statements were simplified.

Membership of the working group

Membership of the group was the first point of debate — and dissent. It was proposed that the group would comprise the rheumatology members of the two pharmaceutical advisory boards (Pharmacia/Pfizer and Merck, Sharp & Dohm), representatives from the medical and economic departments of the pharmaceutical companies, general practitioners, gastroenterologists, nephrologists and cardiologists,

ABSTRACT

We describe a process which aimed to achieve consensus on evidence-based considerations for the safe prescribing and use of the COX-2-specific inhibitors available in Australia among a group of 31 clinicians and other health professionals, drawn from practice, academia and industry.

Difficulties were encountered at several points:

- the composition of the working group was contentious;
- the evidence, drawn from large clinical studies, was criticised by some for problems of study design, data analysis and reporting;
- interpretation of study results was influenced by the interpreter's knowledge, skills and biases; and
- the formulation of the "Considerations" became more controversial as summary statements were contracted and simplified.

Agreement on the final draft was achieved among 23 of 31 participants. Evidence-based practice guidelines are a welcome development in modern medicine, but the consensus required to produce them can mask important diversity of opinion.

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ogists, rheumatologists with expertise in clinical epidemiology and representatives of the Arthritis Foundation of Australia (AFA), the Australian Rheumatology Association (ARA), and the National Prescribing Service (NPS). This arbitrary membership initially raised no concerns. Later, some participants noted that opinions expressed in some sections of the article may have been different had there been broader representation in the non-rheumatological specialist areas. Others questioned whether a consensus process, claiming to be evidence-based, should involve people with potentially conflicting commercial interests (such as advisory board members), although, in such an event, just who would have undertaken the task is not clear. Not surprisingly, the main point of contention from the outset was the inclusion of the medical and economic representatives of the pharmaceutical companies. Indeed, some people declined the invitation to join the group, as they considered such heterogeneity would prejudice the perception, if not the conduct, of the process. The group as a whole took a contrary view. As some form of bias is the inevitable consequence of knowledge and involvement in any issue, it seemed best to include a broad range of stakeholders, but to strive for transparency by listing the group's composition and affiliations.

For editorial comment, see page 304; see also page 328

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Aim and method

Most members of the group attended the first meeting, which agreed on the task and the method. Two documents were to be produced. First, a detailed analysis and interpretation of the relevant studies as a referenced source document for a set of recommendations or “considerations” (this will be published elsewhere); and second, a succinct and practical summary of these “considerations” (see *page 328*).¹ The group decided that it would be more appropriate to offer “considerations” rather than “guidelines” for CSIs, as the latter could be seen as having some binding force.

Having defined the aim as the development of considerations for the safe prescribing and use of the CSIs currently available in Australia, certain working agreements were adopted. First, that there were four domains of interest — gastrointestinal, renal/hypertension, cardiovascular and important comorbidities, and coprescribed medications. Second, that data on each of these areas would doubtless continue to emerge, but, if our “considerations” were not to be indefinitely delayed, an arbitrary cut-off to input would be needed. Third, that the cut-off for data from papers in peer-reviewed journals (but not abstracts) should be the end of May 2001, and that we would also use as well the pertinent sections of the United States Food and Drug Administration (FDA) website, accessible in the public domain. Data sources are described in the Box.

Additional published studies included those in which endoscopy was used as an outcome measure,^{6,7} and some pooled analyses.^{8,9} The principal papers with bearing on renal effects and hypertension were from Whelton and colleagues^{10,11} and others.¹²⁻¹⁴

The group then broke up into four working subgroups, each to address one of the four domains of interest, with one or two individuals nominated as subgroup coordinators. Subgroups were asked to survey the published data relevant to their area of interest, and to synthesise the available evidence as a supporting background for recommendations on an optimal practice approach to prescribing and monitoring CSIs. Aside from the limitations already noted, the working subgroups were not limited in the use of published information they considered relevant. Given that there were real differences in the degree of difficulty between the tasks of the working subgroups, the assignments were accomplished by the target date with varying levels of efficiency and completeness.

A draft paper was compiled and circulated before a meeting of the working group. It quickly became clear that, because of disagreement over the adequacy of study designs, data interpretation and other points (discussed below), a number of areas would prove difficult to resolve (cardiovascular risk, gastrointestinal adverse event reduction). Despite this difficulty, we decided to finalise a summary document, as, with these drugs already in widespread use, advice on best use needed to be circulated promptly if it was to assist in addressing the problems posed by clinical practice. However, agreement within such a large group became no easier with the reduction process. In fact, as those drafting the document tried to make clear, concise statements, without resort to subordinate explanations and caveats, the intensity of discussion and dissent increased, the consulta-

Data sources

Data used by the group were derived principally from the powerful datasets generated by the CLASS² and VIGOR³ studies, which together compared conventional NSAIDs with specific COX-2 inhibitors in more than 16 000 patients.

- **The CLASS study** was a double-blind randomised controlled trial (RCT) in patients with either rheumatoid or osteoarthritis, compared celecoxib (400 mg twice daily in 3987 patients) with ibuprofen (800 mg three times daily in 1985 patients) and with diclofenac (75 mg twice daily in 1996 patients) and allowed the use of aspirin at doses up to 325 mg daily, if needed for cardiovascular prophylaxis. (The report of this study² covered just the first six months of the trial, but an analysis of results for the entire study was available from the FDA Arthritis Advisory Committee website.⁴)
- **The VIGOR study³** was a double-blind RCT in patients with rheumatoid arthritis, and compared rofecoxib (50 mg daily in 4047 patients) with naproxen (500 mg twice daily in 4029 patients), which disallowed the use of aspirin and aimed to exclude patients with a history of myocardial infarct or coronary bypass surgery within the past year. An FDA analysis of the data was also available on the web.⁵
- **Additional published studies** included those in which endoscopy was used as an outcome measure,^{6,7} and some pooled analyses.^{8,9} The principal papers with bearing on renal effects and hypertension were from Whelton and colleagues^{10,11} and others.¹²⁻¹⁴

tion process moving largely to email correspondence of striking volume and rapidity. Almost 250 email messages record the vigorous exchange of strong points of view, many from among those who were unable to provide assent for the final document, and many from the pharmaceutical company participants.

Disagreement despite the evidence

The point of documenting these details relates to the basis for disagreement among stakeholders. There is an assumption that medical controversy can largely be solved by evidence, given that evidence is of appropriately high quality. The problem that remains, however, is the interpretation of evidence and the extent to which that is influenced by bias, whether subtle or bold. The CSI working group members were using evidence that, on face value, was of high quality (Level 2 or better), based on results from large, double-blind RCTs reported in prestigious journals. However, close examination of trial design, exclusions and inclusions, the fact that the CLASS report provides a six-month interim analysis, the relative weight that should be assigned to the FDA analysis of the major studies, the degree to which an endoscopic endpoint infers major clinical outcomes, the validity of pooled analysis results, and many other factors, combined to pose different problems for participants with different points of view.

After the struggle with data interpretation came conflicts over the expression of conclusions. Should an idea be conveyed with a descriptive adjective or by a number, a mean or a median, a range or a confidence interval? Should each statement be qualified to reflect the spectrum of opinion among participants or would that simply obscure the message?

After some weeks of vigorous viewpoint interchange and multiple redrafts, the working group felt the need to terminate further debate, finalise the document and offer participants four options: (i) to sign off on the final draft; (ii) to decline to sign off and remain anonymous; (iii) to decline to sign off and add their names without expressing a reason; and (iv) to decline to sign off and add both their names and reasons. In the event, all participants chose option (i) or (iv).

Twenty-three of the 31 participants agreed that the document was a reasonable statement. Those who declined authorship of the final document — the four representatives of one pharmaceutical group (Pfizer/Pharmacia), two rheumatologists with epidemiological expertise and two other rheumatologist members of advisory boards — represent a diverse range of views, listed on page 331.¹

Conclusions

The important lesson of this exercise is that evidence, even of high quality, requires interpretation, and interpretation then requires a form of expression. Within any large group, a proportion of individuals, for reasons of their biases, whether owing to knowledge, expertise, affiliations or commercial interests, and despite genuine willingness to make reasonable concessions and seriously consider alternative points of view, will be unable to assent to statements which others find well founded on the evidence before them. Clearly, the size and composition of the group working towards consensus is a critical element: the more alike in view, the easier and more complete the agreement, but the less likely to represent the prevalent range of views. And where there is a real polarisation of views, this should not be concealed under cover of a facile consensus. In the current era of “evidence based medicine” we need to be aware of the vagaries of the interpretive part of the exercise and, where possible, bring the inevitable dissent to the fore so that those struggling with an abundance of evidence-based guidelines and summary statements are alert to their faults and fallacies.

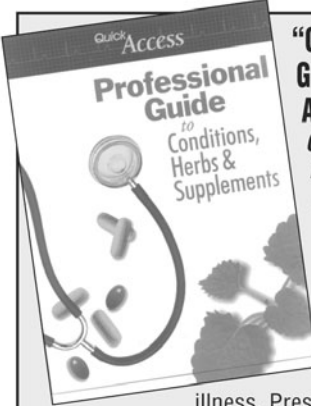
Competing interests

JPE is a member of the Celebrex Australian Advisory Board; ROD and JVB are members of both the Celebrex Australian Advisory Board and the Rofecoxib Australian Advisory Board

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