



THERAPEUTICS INITIATIVE

Evidence Based Drug Therapy

CELECOXIB (CELEBREX[®]) Is it a Breakthrough Drug?

Health professionals need rapid access to unbiased information about new drugs. We try to provide it at the Therapeutics Initiative (TI) but it's not always possible. A case in point is the latest NSAID licenced for sale in Canada; celecoxib has recently become available on prescription without full publication of a single clinical trial report. How are physicians, pharmacists - and researchers like ourselves - to evaluate such a drug without any means of validating efficacy and safety claims? This Letter looks at the issues.

• Case

A 53-year-old logger with long-standing painful osteoarthritis requests the new "wonder drug" he's heard about, celecoxib. A variety of painkillers taken over the years have given him some benefit with no significant adverse effects. Celecoxib is a new arrival, and you've never prescribed it before. You've seen the promotional material, but have become sceptical of the superior efficacy and safety claims that regularly accompany this class of drugs. There's no description in the CPS, so you phone your community pharmacist for advice. She has the same dose and contraindication information available to you. You both agree to do some homework and talk again. But where to start?

• Does this drug provide a therapeutic advantage for osteoarthritis?

This is the key question to which you need an answer. While it's essential to know that any drug is safe and effective, a more important issue for a new NSAID within a class of 18 existing drugs (See Letter #5) is its relative safety and effectiveness either within the class or compared with the drug of choice for osteoarthritis, acetaminophen.

• Is relative efficacy and safety information available?

You head for the standard database, and a Medline search for celecoxib produces some promising citations, including several "randomized trials" comparing celecoxib with commonly prescribed NSAIDs, naproxen, ibuprofen and



diclofenac.¹⁻⁴ **The retrieved material proves of no help, however, amounting to no more than single-page abstracts of conference presentations (see inset) and a published report containing four abstracts.**⁵ Fortunately, you know the TI often reviews the evidence for new drugs, so you give us a call.

• Is relative efficacy and safety information available to the TI ?

The TI has conducted its own literature search in relation to this drug, following a rigorous protocol, which included searches of Medline, Current Contents, and Embase (the European version of Medline). But to our surprise, this revealed no published trial reports comparing celecoxib with placebo, other NSAIDs, or acetaminophen. In our experience, this is not typical of new drug submissions. While manufacturers commonly obtain a licence for sale of a drug in Canada without head-to-head comparisons with competing drugs, it is impossible to obtain a licence without providing efficacy and safety data versus placebo.

• How did celecoxib obtain a licence for sale in Canada?

Health Canada's Therapeutic Products Programme (TPP) regulates drug licencing in Canada. In deciding to licence celecoxib, scientists at the TPP presumably had access to full reports of trials establishing at the least that celecoxib is more effective than placebo and reasonably safe.



• Is independent verification of the TPP decision possible?

Unfortunately, not without access to the full trial reports. While abstracts provide an outline of the research design and a summary of major findings, they don't provide sufficient details to determine the validity and quality of the study or its findings. The latter requires analysis of how the trial was conducted and how the results were analyzed.

• Why were trial reports not published?

This is unknown. Publication can sometimes be delayed as journals conduct peer review and editing. In the present case, however, the abstracts were published more than a year ago and several of the trials were completed at least a year prior to that. A second common explanation is "publication bias", whereby small trials not showing a significant treatment effect go unpublished either because they're not submitted or are rejected by the journals. Neither of these possibilities seem likely, as several of the published abstracts report a positive treatment effect. One abstract for example, reports on 14 randomized trials involving a total of 11,007 patients (placebo 1864, celecoxib 6378, and other NSAIDs 2768)⁴.

• Why insist on published data?

Because it is fundamental to scientific inquiry. Without publication of trial reports, an essential feature of the scientific method is lost. Full disclosure of experimental methods and analysis is needed so that the research can be replicated, critically appraised, and accepted or refuted. **When the TI draws conclusions about drugs we want others to be able to review the same data and independently verify or refute our interpretation of the evidence.**

This Letter contains an assessment and synthesis of published (and whenever possible peer-reviewed) publications up to September 30, 1999. We attempt to maintain the accuracy of the information in the Therapeutics Letter by extensive literature searches and verification by both the authors and the editorial board. In addition this Therapeutics Letter was submitted for review to 65 experts and primary care physicians in order to correct any identified shortcomings or inaccuracies and to ensure that the information is concise and relevant to clinicians.



Please mark this in your calendar:

The 11th annual

DRUG THERAPY

DECISION MAKING COURSE

March 10 & 11, 2000

• Future TI assessment

The TI will review celecoxib as soon as publication of trial reports makes it possible. Under this process, a written synopsis of the review outlining the clinical evidence and the method of assessment is circulated to local clinical and research experts. The review and expert reports are then presented to the Scientific Information and Education Committee of the TI for modification or verification. The final review is used by the Education Working Group to aid in the development of clinically relevant messages, and by the Editorial Board for a future Letter. The review is also sent to Pharmacare, who use it in conjunction with an economic analysis by the Pharmacoeconomics Initiative, to assist their decision whether or not to include the compound on the Drug Benefit Plan.

• Conclusion

In this case, the only information available to help you decide whether to prescribe celecoxib for your patient are the summary data contained in the abstracts and the promotional material supplied by the manufacturer. **Since almost all clinical data about celecoxib remains unpublished and is therefore unavailable for critical appraisal and assessment, it is impossible for the TI to provide timely unbiased information to you and other health professionals.** If and when that information becomes available, we will include it in a future Therapeutics Letter.

Abstracts and partially reported clinical trials

1. Geis GS, Stead H, Morant S, et al. *Efficacy and Safety of Celecoxib, a Specific COX-2 Inhibitor, in Patients with Rheumatoid Arthritis.* Arthritis and Rheumatism, 1998;41: S316, **Abstract** 1699.
2. Geis GS, Hubbard R, Callison D, et al. *Safety and Efficacy of Celecoxib, a Specific COX-2 Inhibitor, in Patients with Rheumatoid Arthritis.* Arthritis and Rheumatism, 1998;41: S364, **Abstract** 1990.
3. Hubbard R, Geis GS, Woods E, et al. *Efficacy, Tolerability, and Safety of Celecoxib, a Specific COX-2 Inhibitor, in Osteoarthritis.* Arthritis and Rheumatism. 1998;41: S196, **Abstract** 982.
4. Goldstein JL, Agrawal NM, Silverstein F, et al. *Celecoxib is Associated with a Significantly Lower Incidence of Clinically Significant Upper Gastrointestinal (UGI) Events in Osteoarthritis (OA) and Rheumatoid Arthritis (RA) patients as Compared to NSAIDs.* Gastroenterology, 1999. 116 (4): Part 2, A174. **Abstract** G0758.
5. Simon LS, Lanza FL, Lipsky PE et al. *Preliminary Study of the Safety and Efficacy of SC-58635, a Novel Cyclooxygenase 2 Inhibitor.* Arthritis and Rheumatism, 1998.41:1591-1602.