COX-2 Specific Inhibitors

Early, short-term data promising; but some caution warranted

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Cyclooxygenase-2 specific inhibitors (**CSIs**) have hit the market with promises of an improved side effect profile over previous NSAIDs. Rather than provide another review of the theory behind COX-2 inhibition, this newsletter will focus on specific questions regarding the optimal utilization of these agents.

CURRENTLY AVAILABLE CSIs (Canada)

- **Celecoxib** (***CELEBREX***®) since April, 1999
- **Rofecoxib** (***VIOXX***®) since November, 1999

ARE COX-2 INHIBITORS MORE EFFECTIVE THAN PREVIOUSLY AVAILABLE NSAIDS?

- **No. The efficacy of CSIs is similar to, but not greater then that of other NSAIDs**.[1,2,3,4,5,6] Information from the manufacturer suggests that celecoxib's efficacy in treating osteoarthritis (OA) and rheumatoid arthritis (RA) is similar to diclofenac (75mg bid), ibuprofen (800mg tid), and naproxen (500mg bid).[7] Likewise, information from the manufacturer suggests that rofecoxib's efficacy in treating OA is similar to diclofenac (50mg tid) and ibuprofen (800mg tid).[8]

- There is considerable variation in individual response to NSAIDs. Efficacy rates in OA and RA are about 70%. It is not possible to predict which NSAID will work best in any given patient. If one NSAID does not work after a ≥2 week trial of maximum doses, an alternate NSAID may be tried.

HOW GI-SAFE ARE CSIs ?

- **Theoretical evidence and preliminary clinical data from manufacturers suggest that the GI toxicity profile is much safer than nonspecific NSAIDs.** In over 5000 patients who have received celecoxib in unpublished controlled clinical trials of one to six months duration, there were only two reports (0.04%) of significant upper GI bleeding. This contrasts with a recently published meta-analysis which suggested a ~1% incidence of significant upper GI bleeding in patients treated with NSAIDs for three to six months.[9]

- Early experience in the U.S. appears to confirm a safer GI profile. A study based on the FDA MedWatch program suggested that for the period of Jan-June, 1999, the number of serious GI events (adjusted for estimates of underreporting), was 1560 (including 140 deaths).[10] This was similar to the expected background rate (1483 events;148 deaths), and less than would be expected for non-specific NSAIDs (4,654 events;465 deaths). {Total Rx's for celecoxib: 6,663,676}

- Whether CSIs actually cause less dyspepsia is inconclusive.

- Concerns regarding the GI-safety profiles of CSIs have been raised. In cases where there is existing inflammation or ulceration, some evidence suggests that inhibition of COX-2 may exacerbate inflammation and delay ulcer healing.[11] Caution is warranted given the lack of published trials and long-term data.

ARE CSIs SAFER TO USE IN PATIENTS WITH PREVIOUS HISTORY OF PEPTIC ULCERS (PU)?

- CSIs have not actually been studied specifically in this patient group although some trials have included patients at higher risk. Clinical studies have generally excluded patients with current or recent history of GI bleeds. In patients at highest risk of PU (3 or more risk factors), it is not known if CSIs can be administered safely alone or whether co-therapy with misoprostol or a PPI is required. Long-term, well designed clinical trials are needed.

WHAT ABOUT THEIR RENAL EFFECTS?

- **CSIs have shown renal effects similar to other NSAIDs.** COX-2 is constitutively expressed throughout the kidney and adverse renal effects have been reported.[12,13] Adverse renal effects may be mediated by non-COX related mechanisms. Sodium and potassium retention can occur especially in dehydrated or salt-depleted patients. [14] Due to this potential for **fluid retention**, caution is warranted in impaired renal/hepatic function, CHF, the elderly, and in patients on diuretics or ACEIs.

WHAT'S THEIR CURRENT ROLE?

- **Due to both the cost and lack of long-term/published studies, a degree of caution is still warranted.**
- CSIs may have a role in the treatment of OA and RA in patients at high risk of GI ulcers: (e.g. elderly - age 65 and over, past history of peptic ulcers, concurrent prednisone or warfarin therapy). They may be a good alternative in patients intolerant to the GI side effects of other NSAIDs. Long-term effects, such as potential beneficial or detrimental effects on cartilage, are yet to be studied.
- Potential roles in preventing colon cancer and slowing down the progression of Alzheimer's disease look promising but require further investigation.[15,16]
- They are not first choice agents for treatment of acute pain, or in uncomplicated patients where acetaminophen or other well studied, less-costly NSAIDs (e.g. ibuprofen) are preferred.
- The optimal role of CSIs is likely to evolve as more data from independent, well designed clinical trials becomes available.
- Comparative advantages: ***celecoxib*** -1yr of extensive post-marketing experience, EDS on SK formulary; ***rofecoxib*** -quicker analgesic effect, longer duration of action with OD dosing.

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References available on request

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The Rx Files
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