New restrictions on celecoxib (Celebrex) use and the withdrawal of valdecoxib (Bextra)

PRACTICE

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Reason for posting: Coxibs, the class of NSAIDs that selectively inhibit cyclooxygenase 2 (COX-2), were designed to reduce joint pain and inflammation without causing the gastric epithelial adverse effects typical of nonselective NSAIDs. Rofecoxib (Vioxx) was withdrawn from the market in September 2004 over concerns about cardiovascular adverse effects, and key safety trials involving celecoxib (Celebrex)[1] and valdecoxib (Bextra)[2] have recently been published. Health Canada now recommends new restrictions on celecoxib use, and valdecoxib has been taken off the market. The US Food and Drug Administration has gone further, directing that all prescription and over-the-counter NSAIDs include specific information regarding potential cardiovascular, gastrointestinal and other risks.

The drugs: The results of recent trials have raised concerns that coxib use increases the risk of cardiovascular adverse events. In the APC study, a trial on colorectal adenoma prevention, 2035 patients were randomly assigned to celecoxib 200 mg twice daily or 400 mg twice daily or placebo. After about 3 years, cardiovascular events (death from cardiovascular causes, myocardial infarction, stroke, heart failure) had occurred in 1% of patients receiving placebo, 2.3% of the group taking 200 mg celecoxib (hazard ratio [HR] 2.3, 95% confidence interval [CI] 0.9–5.5), and 3.4% (HR 3.4, 95% CI 1.4–7.8) of the group taking 400 mg.[1]

In a trial involving 1671 patients who underwent coronary artery bypass grafting, cardiovascular events were more frequent among those taking valdecoxib and parecoxib for pain than among those taking placebo (2% v. 0.5%; risk ratio 3.7, 95% CI 1.0–13.5).[2] Amid concerns about reports of severe cutaneous reactions (Stevens–Johnson syndrome, erythema multiforme, toxic epidermal necrolysis) among patients taking valdecoxib,[3] the drug was removed from the market.

What to do: COX-2 inhibitors appear to increase the risk of cardiovascular adverse events in a dose-related fashion, and all patients should be informed of this. Calculating the patient's baseline risk of cardiovascular disease (e.g., with Framingham risk calculators) may be wise, and celecoxib should not be prescribed to patients with cardiovascular disease or diabetes or those at increased risk of cardiovascular events. Celecoxib should be used in the lowest effective doses for short periods (weeks) only. A risk–benefit discussion is necessary for those requiring the drug for a longer period. Of note, patients in the APC study[1] who used celecoxib for 3 years at a dose double that recommended for osteoarthritis had an increase in absolute risk of cardiovascular events of about 1.3% (number needed to harm of 77).

The only NSAID known to reduce primary and secondary cardiovascular events is ASA. The absolute risk of other NSAIDs is unclear. Appreciating the relative degree of COX-2 selectivity of some commonly used NSAIDs (Table 1) may be useful. Alternative pharmacologic and nonpharmacologic approaches to pain management should be reviewed and strongly considered.

Table 1: The degree of inhibition of COX-2 relative to COX-1 for various NSAIDs

NSAID type	COX-2 selectivity*
COX-2 selective inhibitors	
Rofecoxib	80
Etodolac	23
Meloxicam	11
Celecoxib	9
Nonselective NSAIDs	
Diclofenac	4
Sulindac	3
Piroxicam	2
Ibuprofen	0.4
Naproxen	0.3
Indomethacin	0.2
Ketorolac	0.003

Note: COX = cyclooxygenase.
*The 80% inhibitory concentration ratios of COX-2 relative to COX-1 in human whole blood assays.[6]

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References

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