Digging for data from the COX-2 trials

We agree with Joel Lexchin's request for more access to the information from randomized controlled trials on new drugs.[1] To that end we felt *CMAJ* readers would find a brief synopsis of some of the findings from the latest cyclooxygenase-2 (COX-2) inhibitor trials valuable so that they could make informed decisions about the safety issues associated with these new agents compared with older NSAIDs.

Randomized controlled trials are the best way of determining whether a cause–effect relation exists between treatment and outcome.[2] They are also one of the best ways to determine if there are important clinical differences in efficacy or safety between therapies. In the last year or so, 2 trials looking at the safety of the COX-2 inhibitors have been published.[3,4] These results have been used to suggest that the COX-2 inhibitors are safer than older NSAIDs. However, the US Food and Drug Administration (FDA) has not put these agents in a class by themselves.[5] Recently, Mucklow has suggested that journal reporting of clinical trial adverse events is inadequate.[6] Since February 2001 it has been possible to review more complete trial results on the FDA Web site. Unfortunately, the data on this Web site are presented in numerous reports and it is difficult and time-consuming to get a complete picture of the overall differences in clinical end points. A synopsis of the information at this Web site follows. We chose to present primarily those end points that we felt readers would find interesting, as well as results that were statistically different. Biochemical and laboratory test differences are not reported in this synopsis. The percentages presented are the crude incidence rates. Numerous subset analyses of the information are also presented at the FDA Web site, but a discussion of these data is beyond the scope of this letter. More detailed trial reports are available at www.fda.gov/ohrms/dockets/ac/01

Table 1: Results of the CLASS trial as reported in *JAMA*[3] (6-month data)

Event	Frequency of event (%)	
	Ibuprofen plus diclofenac	Celecoxib
Gastroduodenal ulcers (uncomplicated)	0.73	0.48
Ulcer complications		
Upper gastrointestinal bleeding	0.5	0.25
Perforation or gastric outlet obstruction	0	0.03
Ulcer complications plus gastroduodenal ulcers	1.3	0.8
Serious adverse effects (hospital admissions or malignant diseases)	4.2	4.3
Other adverse effects		
Abdominal pain	13.1	9.7*
Dyspepsia	16.1	14.4*
Hypertension	2.3	1.7*
Cardiovascular	1.0	0.9
Rash, pruritus, urticaria	4.1	7.5*
Adverse effects causing withdrawal from the trial		
Gastrointestinal	10.7	8.7*
Cutaneous	1.2	2.7*

*Significant difference ($p < 0.05$) for ibuprofen plus diclofenac versus celecoxib as reported in *JAMA*.[3]

Table 2: Results of the CLASS trial as presented in FDA reports (12- and 15-month data)

	Frequency of event (%)		
	Ibuprofen	Diclofenac	Celecoxib
Gastroduodenal ulcers (uncomplicated)	1.3	0.8	0.65
Ulcer complications			
Upper gastrointestinal bleeding	0.65	0.5	0.4
Perforation or gastric outlet obstruction	0	0.05	0.08
Ulcer complications plus gastroduodenal ulcers	1.9	1.3	1.2*
Deaths	0.4	0.5	0.5
Serious adverse events	6.0	5.6	6.8
All adverse events	79.5	82.9	81.8
Adverse events causing withdrawal from the trial			
All adverse events	23	26.5	22.4†
Moderate to severe gastrointestinal	7.5	9.6	7.5†
Abdominal pain	4.9	6.5	4.3†
Dyspepsia	3.9	4.4	3.8†
Nausea	1.8	2.8	1.7†
Rash	1.3	0.7	2.1‡

*Significant difference ($p < 0.05$) for diclofenac plus ibuprofen versus celecoxib and for ibuprofen versus celecoxib as reported by the authors of the report.
†Significant difference ($p < 0.05$) for diclofenac versus celecoxib as reported by the authors of the report.
‡Significant difference ($p < 0.05$) for diclofenac and ibuprofen versus celecoxib as reported by the authors of the report.

/briefing/3677b1_03_med.doc and www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_03_med.doc.

Results of the CLASS trial as reported in *JAMA* are presented in Table 1.[3] The CLASS trial was actually a planned pooled analysis of 2 trials, one comparing ibuprofen with celecoxib and the other comparing diclofenac with celecoxib. In the *JAMA* article the CLASS trial was presented as a 6-month trial (mean duration of exposure 4 months).[3] However, the trial comparing ibuprofen with celecoxib was 15 months long (mean duration of exposure 7 months) and the trial comparing diclofenac and celecoxib trial was 12 months long (mean duration of exposure 6.5 months). A synopsis of the overall results of these 2 trials and a more complete presentation of the adverse events that occurred are presented in Table 2.

Results of the VIGOR trial are presented in Table 3. Results from the FDA Web site are virtually the same as those presented in the published version of this 9-month trial.[4] The data presented in boldface are from the FDA Web site and were not presented in the *N Engl J Med* article.[4]

The interpretation of the clinical importance of these results compared with the published data in journals is left to the reader.

James P. McCormack
Associate Professor
Faculty of Pharmaceutical Sciences
University of British Columbia
Vancouver, BC
Robert Rangno
Associate Professor
Departments of Medicine and Pharmacology
University of British Columbia
Vancouver, BC

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Table 3: Results of the VIGOR trial as published in *N Engl J Med*[4] and FDA reports

	Frequency of event (%)	
	Naproxen	Rofecoxib
Gastric or duodenal ulcers, upper gastrointestinal bleeding, perforations, obstructions	3.0	1.4*
Upper gastrointestinal bleeding, perforations, obstructions	1.0	0.4
Serious cardiovascular thrombotic events	**0.7**	**1.7***
Myocardial infarctions	0.1	0.4*
Deaths	0.4	0.5
Serious adverse events	**7.8**	**9.3**
All adverse events causing withdrawal from the trial	**15.8**	**15.9**
Specific adverse events causing withdrawal from the trial		
Cardiovascular	**0.8**	**2.7**
Congestive heart failure	**0.2**	**0.5†**
Digestive	**9.7**	**7.2**
Gastrointestinal	10.6	7.8*
Edema	**0.3**	**0.6‡**
Hypertension	**0.1**	**0.7***

Note: Data in boldface are from the FDA reports. For differences not indicated with asterisks, statistics were not reported.
*Significant difference ($p < 0.05$) as reported in the *N Engl J Med* or FDA reports.
†$p = 0.07$
‡$p = 0.06$

Safe drug prescribing

The excellent article on safe drug prescribing for patients with renal insufficiency addresses many questions that pharmacists are asked by physicians in daily practice.[1]

However, in Table 5 a statement on COX-2 selective NSAIDs would have been useful, as many physicians believe that these agents have less potential to adversely affect renal function than older nonselective agents. No evidence exists to support this belief. The new COX-2 selective agents are similar in net effects on renal prostaglandin function to the older nonselective NSAIDs.[2,3]

In addition, another nephrotoxic drug class to watch out for is radiocontrast "dyes." Exposure to intravenous radiocontrast agents for diagnostic and interventional procedures is quite common. Aside from considering non-ionic, low-osmolality agents and hydration, reasonable evidence suggests that pretreatment with oral *N*-acetylcysteine may further reduce the risk of renal damage.[4] Given its low cost and minimal toxicity, *N*-acetylcysteine should be considered in patients with renal insufficiency before they are exposed to parenteral radiocontrast agents.

Bruce Lange
Clinical Pharmacist, Nephrology
Royal Columbian Hospital
New Westminster, BC

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