Review: Rofecoxib increases renal events and arrhythmia, but a COX-2-inhibitor class effect does not exist

Zhang J, Ding EL, Song Y. **Adverse effects of cyclooxygenase 2 inhibitors on renal and arrhythmia events: meta-analysis of randomized trials.** JAMA. 2006;296:1619-32.

Clinical impact ratings: GIM/FP/GP ★★★★★★☆ Cardiology ★★★★★★☆ Geriatrics ★★★★★★☆ Nephrology ★★★★★★☆ Rheumatology ★★★★★★☆

QUESTIONS

What are the risks for renal and arrhythmia events in patients using cyclooxygenase-2 (COX-2) inhibitors? Does a class effect exist?

METHODS

Data sources: MEDLINE and EMBASE/Excerpta Medica (to June 2006), Cochrane Controlled Trials Register, Computer Retrieval of Information of Scientific Projects, U.S. Food and Drug Administration reports, online clinical trial information centers and repositories, references of retrieved articles, and investigators in the field.

Study selection and assessment: Double-blind randomized controlled trials (RCTs) of the COX-2 inhibitors rofecoxib, celecoxib, valdecoxib, parecoxib, etoricoxib, and lumiracoxib that assessed renal endpoints (peripheral edema, hypertension, and renal dysfunction) and arrhythmia. Trials with no control group, no relevant events in either group, abnormal baseline renal function, or simultaneous intervention of > 1 COX-2 inhibitor were excluded. 114 RCTs with 127 trial populations (n = 116 094) met the selection criteria. Comparators included placebo; nonsteroidal antiinflammatory drugs; and aspirin, acetaminophen, rizatriptan, dolotefin, morphine, or salicin.

Outcomes: Composite renal endpoint (peripheral edema, hypertension, and renal dysfunction) and arrhythmia (atrial fibrillation, ventricular fibrillation, tachycardia, cardiac arrest, sudden cardiac death, or unspecified arrhythmia).

MAIN RESULTS

Substantial heterogeneity existed among trials. Inclusion of different COX-2 inhibitors was a major contributing factor to heterogeneity, indicating no class effect. Meta-analysis using random effects showed that rofecoxib increased the risk for the composite renal endpoint, each of the specific renal outcomes, and arrhythmia (Table). Valdecoxib plus parecoxib showed a borderline increase in composite renal events and no effect on arrhythmia (Table). Celecoxib was associated with decreased hypertension and renal dysfunction, and did not increase arrhythmia (Table). Etoricoxib and lumiracoxib had no effect on renal events and were studied in an insufficient number of trials to show increased risk for arrhythmia. Meta-regression showed that the increased risk for renal events with rofecoxib was evident regardless of comparator, higher dose and longer trial duration further increased risk, and adverse effects were strongest among patients with rheumatoid arthritis.

CONCLUSIONS

Use of rofecoxib increases risks for renal events and arrhythmia. Evidence of increased risk associated with other cyclooxygenase-2 inhibitors is not supported, indicating no overall class effect.

Source of funding: National Institutes of Health.

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Risk for renal and arrhythmia events from cyclooxygenase-2 inhibitors vs placebo, NSAID, or mixed agents with median trial duration 6 to 12 weeks*

Outcomes	Relative risk (95% CI) Rofecoxib	Relative risk (95% CI) Valdecoxib + parecoxib	Relative risk (95% CI) Celecoxib
Composite renal endpoint	1.53 (1.33 to 1.76)	1.24 (1.00 to 1.55)	0.97 (0.84 to 1.12)†
Peripheral edema	1.43 (1.23 to 1.66)	1.13 (0.88 to 1.46)†	1.09 (0.91 to 1.31)†
Hypertension	1.55 (1.29 to 1.85)	1.28 (0.88 to 1.84)†	0.83 (0.71 to 0.97)
Renal dysfunction	2.31 (1.05 to 5.07)	1.68 (1.00 to 2.85)	0.61 (0.40 to 0.94)
Arrhythmia	2.90 (1.07 to 7.88)	0.78 (0.62 to 1.01)†	0.84 (0.45 to 1.57)†

*NSAID = nonsteroidal antiinflammatory drug. CI defined in Glossary. A random-effects model was used.
†Not significant.

COMMENTARY

The general concern regarding the delay in uncovering the cardiac toxicities of the COX-2? inhibiting NSAIDs has prompted a reexamination of their specific drug and class effects on other adverse outcomes. Two findings stand out in the meta-analysis by Zhang and colleagues: First, only rofecoxib seemed to cause measurable renal injury in patients with normal renal function, although data may be incomplete for the newer agents. Second, a cumulative meta-analysis of all adverse events reported in placebo-controlled RCTs would probably be superior to reliance on published trial reports.

Renal toxicities have probably been underreported in the literature, in part because clinical trials have not consistently collected or reported reliable clinical indices of acute or chronic renal injury. This may change with the recent recognition that even mild renal injury is associated with increased overall and cardiovascular mortality (1, 2). The trials in which older NSAIDs formed the control group may confound the results since older NSAIDs also increase the risks for both renal failure and proteinuria, with the latter independently increasing cardiovascular risk (2). Finally, the risk for renal failure with long-term use of COX-2? inhibiting NSAIDs might be expected to be greatest for patients with underlying renal disease. The meta-analysis excluded these patients. Thus the notion of "renally safe" COX-2? inhibiting NSAIDs, already tenuous in patients without baseline kidney disease, cannot be extrapolated to patients with underlying renal insufficiency or proteinuria, or perhaps to the elderly or those with diabetes.

With respect to the arrhythmia outcomes, the meta-analysis similarly shows a significant risk with rofecoxib and not with COX-2? inhibiting agents as a class. These findings taken together support the view that not all adverse effects are shared by all COX-2? inhibiting NSAIDs.

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References

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