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UPCOMING ISSUES

Depression and Pain

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COX-2 Inhibitors and the Kidney: A Word of Caution

The selective cyclooxygenase-2 (COX-2) inhibitors celecoxib, etoricoxib, rofecoxib, and valdecoxib account for a large and growing share of the analgesics market worldwide.¹ It is widely accepted that these agents (termed *coxibs*) are superior to the classical nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin, diclofenac, ibuprofen, indomethacin, naproxen, and piroxicam with respect to gastrointestinal (GI) safety.² Coxibs appear to be more effective than acetaminophen for arthritis pain.³ Nevertheless, these drugs are not without unwanted side effects.⁴ International scientific attention has focused on the cardiovascular risks, although these are not high⁵ and are of concern only in groups at risk for cardiac infarctions and thromboembolic events. Less attention is given to renal side effects, although pharmaceutical companies are including in their promotional materials claims of reduced impairment of renal function relative to their competitors' products. Yet recent reports that coxibs cause fluid retention, increases in blood pressure, and renal damage in some patients mandate a cautious discussion of these risks.⁶⁻¹⁰

Is COX-2 Constitutively Expressed?

Selective COX-2 inhibitors were introduced into experimental and clinical research over a decade ago.¹¹ The prevailing assumption was that COX-2 is not expressed constitutively (i.e., in basal conditions) but only after tissue damage and inflammation.¹¹ In principle, therefore, GI adverse effects and renal toxicity should be absent.¹¹ However, investigation of COX-2 knockout mice (animals genetically manipulated to lack COX-2 throughout development) revealed signs of kidney dysplasia.¹² Similar effects could be induced by treating mother animals with coxibs throughout their pregnancy.¹² Human studies showed that COX-2 is expressed constitutively in many organs, particularly the central nervous system and the kidney.^{13,14} Moreover, administration of celecoxib reduces the urinary excretion of prostaglandin metabolites.⁶ Clinical investigation has shown that kidney disorders such as Bartter's syndrome (juxtaglomerular cell hyperplasia)¹⁵ are associated with enhanced expression of COX-2 in the kidneys. Indications that COX-2 byproducts exert protective effects on tubular cells¹⁶ have led to the conclusion that part of the adaptive regulation of kidney function is mediated by COX-2 products released from the juxtaglomerular cells and from epithelial cells in the renal cortex and medulla.¹⁶ These data clearly show that COX-2 is constitutively active in the human kidney, where it plays an important role in regulatory and adaptive mechanisms.^{11,17}

Table I

Pharmacokinetic characteristics of selective COX-2 inhibitors in clinical use

	t_{\max} (hours)	$t_{50\%}$ (hours)	F_{oral} (%)
Celecoxib ^{19,23}	~3	~8	20–60
Etoricoxib ²¹	~1	~22	~100
Rofecoxib ^{19,23}	~3	~17	~100
Valdecoxib ²²	~3	~8	~80

Abbreviations: t_{\max} = time to maximal plasma concentration; $t_{50\%}$ = terminal elimination half-life; F_{oral} = oral bioavailability.

Clinical Studies

Recent uncontrolled and controlled clinical studies indicate that elderly persons treated with coxibs may develop fluid retention, mild elevation of systolic blood pressure, and (very rarely) serious kidney damage.^{6-10,18} Some studies suggest that celecoxib is less likely than rofecoxib to cause these adverse effects.^{7,8} However, the relative risk of these agents appears to depend entirely on the doses given and how side effects were assessed.⁹ It is noteworthy that the four coxibs now on the market each differ in their pharmacokinetic characteristics¹⁹⁻²³ (Table I). Celecoxib has limited oral bioavailability, low potency, and relatively fast elimination in most patients, whereas rofecoxib is more potent, is almost 100% bioavailable, and is excreted more slowly.²³ Consequently, many clinical studies have found once-daily rofecoxib at a dose of 25 mg to be more effective than 200 mg celecoxib. Twenty-four hours after administration at these doses, the effect of celecoxib on blood pressure elevation and fluid retention was significantly lower than that of rofecoxib.^{7,8} However, these doses are not equianalgesic. On the other hand, healthy elderly persons monitored during chronic administration of equianalgesic doses of celecoxib and rofecoxib (200 mg b.i.d. versus 25 mg once daily, respectively) experienced no difference in side effects. Both drugs—as well as naproxen—caused mild fluid retention and modest increases in systolic blood pressure.⁹

The above studies all found that coxibs produce dose- and pharmacokinetic-dependent increases in systolic blood pressure and fluid retention, findings that dictate lower doses and briefer courses of these compounds in patients at risk. Moreover, once-daily administration appears advisable. Patients with high blood pressure or other cardiovascular risk factors should receive concurrent low-dose aspirin (up to 100 mg daily) when coxibs are prescribed, despite the slightly increased risk of GI adverse effects.^{24,25} Moreover, patients whose high blood pressure increases further during coxib therapy require careful monitoring, judicious use of antihypertensive agents, and possible drug discontinuation. For example, angiotensin-converting enzyme (ACE) inhibitors and diuretics have pharmacodynamic interactions with COX inhibitors, and beta-blockers may interact with some coxibs, as shown recently for celecoxib.^{8,26}

Conclusion

The playwright Voltaire urged practitioners to dispense new medicines quickly, before the initial rush of enthusiasm is replaced by jaded insight that they are little better than the agents they have supplanted. Coxibs have been called “super aspirins” in the popular press. There is little question that tens of thousands of premature deaths from GI toxicity annually due to NSAID use could be averted were coxibs to be used instead. But clinicians’ gratitude for these new, and in some ways superior, anti-inflammatory and analgesic agents should not blind them to the renal and cardiovascular risks that these agents share with their pharmacological predecessors.²⁷

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