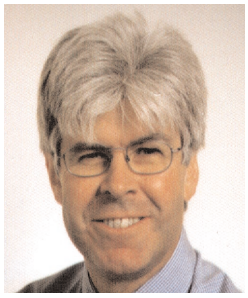
Editorial



NSAID Toxicity: Where Are We and How Do We Go Forward?

Nonsteroidal antiinflammatory drugs (NSAID) are the best recognized cause of iatrogenic pathology. They have been estimated to cause as many as 16,500 deaths per annum in the United States of America[1]. That estimate is based upon an analysis of patients in the Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS) database, which may not be representative of all patients using NSAID, and is much higher than other estimates[2].

Attempts to metaanalyze data on NSAID and ulcer complications, to produce as objective a quantitation as possible of the relationship between NSAID use and severe gastrointestinal (GI) complications, are therefore always welcome. The most recent of these, by Ofman and colleagues, is published in this issue of *The Journal*[3]. In their review of 2177 papers, they identified 55 published and 37 unpublished NSAID versus placebo randomized clinical trials (RCT), 57 case control studies, and 24 cohort studies. These yielded overall estimates of the odds/risk ratio for NSAID use that varied between 2.7 (cohort studies) and 5.36 (RCT). Interestingly, later epidemiological studies showed higher estimates of risk than earlier ones. This is probably because the definition of NSAID exposure became more tightly controlled as time progressed, whereas for RCT, exposure is controlled by trial protocol.

This suggests that epidemiological estimates of NSAID associated risk based on older studies may be conservative. Moreover, there may be other reasons why the direct effect of NSAID may be greater than previously estimated. This would occur if unmeasured factors causing ulcers were present in cases and controls but their confounding effects are not allowed for. Thus, the metaanalysis did not attempt to identify the interaction with other risk factors such as past history or *Helicobacter pylori*. Because risks associated with *H. pylori* would be present in both cases and controls, one would expect that an underestimate of the "pure" effects of NSAID would result. Recent publications suggest that this is the case. Stack, *et al* report an odds ratio associated with NSAID use of 11.3 (95% CI, 3.8–33.6) for ulcer bleeding in *H. pylori* negative patients[4]. In a metaanalysis of studies investigating the interaction between *H. pylori* and NSAID, Huang and colleagues reported an odds ratio of 18.1 (2.64–124) for endoscopic ulcers for NSAID use in the absence of *H. pylori* infection[5] (although their estimates of risk for ulcer complications were very much lower). The 2 publications differ in their assessments of whether combinations of NSAID and *H. pylori* lead to further enhancement of risk [reduction to 7.8 (2.3–26.3) for ulcer complications in the study by Stack, *et al* and an increase to 61.1 (9.98–373) for endoscopy ulcers in the study of Huang and colleagues). Such wide discrepancies between studies suggest that the interaction between *H. pylori* and NSAID varies according to the population studied[6].

Other combined analyses suggest that risk is dose dependent and may vary between individual drugs[7]. Non-dose dependent differences may occur to some extent because of differences in selectivity between the constitutive cyclooxygenase (COX)-1 and inducible COX-2 enzymes. The increased GI safety of COX-2 inhibitors compared to non-selective NSAID has been sufficiently striking for COX-2 inhibitors to be evaluated recently as a group by the United Kingdom National Institute for Clinical Excellence (NICE)[8]. NICE concluded that COX-2 inhibitors as a group were associated with fewer adverse events than non-selective NSAID, sufficient for their use to be recommended at least in high risk groups. Unfortunately NICE's evaluation did not define what a COX-2 inhibitor was. Drugs such as etodolac and meloxicam, which have a selectivity ratio of between 5 and 10 in whole blood assays, were included, but diclofenac, which consistently is COX-2 selective although to a somewhat lesser extent[9], was not.

In their guidance, NICE did not draw distinctions between the safety of the individual drugs they analyzed. Nevertheless there are differences in the amount and robustness of data available (Table 1). The COX-2 hypothesis

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Table 1. Comparison of effect on the GI system of 4 studied COX inhibitor.

	Rofecoxib		Celecoxib		Meloxicam		Etodolac	
	Dose, mg	Result	Dose, mg	Result	Dose, mg	Result	Dose, mg	Result
Daily dose range	12.5–25		200–400		7.5–15		600	
Gastric prostaglandins	50	= P.lacebo[10]	800	= Placebo[17]	7.5	= NSAID[14,18]	600–800	= Placebo[11,19]
Endoscopy: ≤ 1 month: acute injury	250	= Placebo[20]	800	= Placebo[21]	7.5	Reduced[22,23]	400–800	= Placebo[12,24-27]
Endoscopy > 1 month: endoscopic ulcers	50	= Placebo[28]	800	= Placebo		ND		ND
Prospective outcomes study: ulcers + complications	50	Reduced[15]	800	NS[16]	7.5	+/–*[29,30]	300 mg–1 g	Reduced#[31]
Prospective outcomes study: GI symptoms	50	Reduced[15]	800	Reduced[16]	7.5	Reduced*	300 mg–1 g	Reduced#[27,31]

* One month study. + *Ad hoc* analysis. # Unblinded study. ND: not done. NS: not significant.

states that COX-2 inhibitors spare gastric mucosal prostaglandin synthesis and consequently cause no gastroduodenal injury. Until recently, data on gastric prostaglandin synthesis were available only for rofecoxib[10] and etodolac[11,12], although the data on etodolac differ because they were not obtained using supratherapeutic doses (Table 1). Recently, an abstract has suggested that supratherapeutic doses of celecoxib also spare gastric mucosal prostaglandin synthesis[13]. A recent study of meloxicam 7.5 mg daily has shown reductions in prostaglandin synthesis that are similar to those seen with piroxicam 20 mg daily[14].

As with biochemical mechanisms, so too the hypothesis of reduced injury has been tested robustly only with supratherapeutic doses and not been made in all cases (Table 1) with rofecoxib[15] and celecoxib[16]. Both drugs have shown placebo levels of acute injury and chronic ulceration. Both have been subject to outcomes studies. These were positive in the case of rofecoxib but not significant in the case of celecoxib (almost certainly because of deficiencies in trial design rather than a failure of the COX-2 hypothesis). Shorter, less direct, uncontrolled or descriptive data with meloxicam and etodolac are consistent with reduced gastroduodenal damage, but the evidence is sketchier and a systematic evaluation of supratherapeutic doses has not been made.

One consequence of the attention COX-2 inhibitors have generated has been to draw attention to the non-GI toxicities of NSAID. In particular, both COX-2 inhibitors and NSAID result in fluid retention, edema, and hypertension. Where truly equivalent doses have been compared, the effects of different COX-2 inhibitors and NSAID have been similar. Where lower effective doses of one drug have been compared with another, not surprisingly there have been smaller changes in blood pressure. These considerations, along with evidence that GI toxicity is dose dependent[7], emphasize the importance of using the lowest effective dose, whether a selective or non-selective NSAID is used. Perversely, much more attention has focused on coronary disease as a result of studies of high doses, with resulting inconsistency with other studies or with inappropriate choice of controls. Overall, studies of both selective and non-selective COX-2 inhibitors do not strongly suggest that these drugs have a direct effect on coronary thrombosis. Nevertheless, in due course evaluations of both selective and non-selective COX inhibitors, similar to those presented in this issue by Ofman and colleagues[3], should be done. The challenge of such studies will be to assess the effect of drugs on overall health, morbidity, and mortality.

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