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Rofecoxib

A Viewpoint by Richard H. Hunt

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Conventional nonspecific nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with a panoply of adverse gastrointestinal (GI) events. These range in severity from dyspepsia to endoscopic lesions, which in turn can range from mucosal haemorrhage and erosions to frank ulceration complicated by bleeding, perforation and death.

Newer NSAIDs include nabumetone, meloxicam, etodolac and nimesulide, all of which are associated with a lower rate of GI adverse events than their predecessors. However, it is the introduction of the cyclo-oxygenase-2 (COX-2)–specific inhibitors, celecoxib and rofecoxib, that promises to have the greatest impact on improving GI tolerability.

A prediction of improved GI tolerability is based on the hypothesis that two of the COX isoforms are found in the GI tract; COX-1 is primarily constitutive and essential for maintaining mucosal integrity, whereas COX-2 is associated with the inflammatory response. The high incidence of adverse GI events evident with nonspecific NSAIDs is primarily a consequence of inhibition of both COX-1 and COX-2. The development and introduction of rofecoxib and celecoxib has essentially provided proof for this concept.

Proof has come from several key studies. First, rofecoxib does not inhibit prostaglandin E_2 synthesis, a product of COX-1, in human gastric mucosal biopsies, whereas the nonspecific NSAID, naproxen, clearly does. Secondly, faecal blood loss of ^{51}CR-labelled red blood cells and studies of small bowel macromolecular permeability show no significant differences between placebo and rofecoxib [at 2 to 4 times the therapeutic dose required for osteoarthritis (OA)] in contrast with increased blood loss and bowel permeability observed with ibuprofen and indometacin, respectively. Thirdly, short term endoscopy studies performed over 7 days revealed erosions/ulcers in 12% of healthy volunteers receiving rofecoxib (at 10 to 20 times the therapeutic dose) compared with rates of 8, 94 and 71% with placebo, aspirin (acetylsalicylic acid) and ibuprofen, respectively.

The relevance of such short term studies to clinical outcomes has been much debated. Thus, two 6-month endoscopy studies were conducted in high-risk patients with OA (15% had a history of previous ulcer complicated by bleeding and perforation and 12% had erosions at baseline endoscopy). Rofecoxib 25 and 50mg (2 to 4 times the therapeutic dose) was associated with ulcers in 5 and 8% of patients, respectively, and was not significantly different from placebo (7%) over the first 12 weeks, whereas significantly more ulcers were seen with ibuprofen (2400 mg/day) at 28%. The incidence of ulcers observed at 24 weeks did not increase significantly with rofecoxib (10 and 13%, respectively) over that seen at 12 weeks, whereas the incidence of ulcers with ibuprofen increased to 46%.

Thus, on all counts the COX-2–specific inhibitor, rofecoxib, is superior to nonspecific NSAIDs, including ibuprofen, considered to be one of the most tolerable of the existing drugs. The true impact of the development of the COX-2–specific inhibitors will come from clinical experience and from long term studies such as the Misoprostol Ulcer Complications Outcomes Safety Assessment (MUCOSA) trial undertaken with misoprostol. It is wise to bear in mind that the COX-2–specific inhibitors cannot be expected to be associated with a zero incidence of GI adverse events, since these will occur with placebo within the community. It is probable that the new COX-2–specific inhibitors, such as rofecoxib, will contribute dramatically to reducing the life-threatening complications of the current nonspecific NSAIDs. ▲