# EDITORIAL



## Are we being COaXed-2 much?

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit 3 different cyclooxygenase (COX) isoenzymes, known as COX-1, COX-2, and COX-3. COX-1 and COX-2 isoforms of the enzyme are responsible for the first step in the conversion of arachidonic acid into a variety of prostaglandins, thromboxanes, and leukotrienes. Less is known about COX-3, which is found in the cerebral cortex and cardiac tissue and appears to be involved in centrally mediated pain. In addition to effective analgesia and anti-inflammatory effects, COX-1 and COX-2 blockade underlies the unwanted gastrointestinal (GI), renal, and antiplatelet effects. Patients currently using NSAIDs are at 4 times more risk of dying from GI complications than nonusers. Current users of NSAIDs are estimated to be twice more likely to be hospitalized for congestive heart failure, and 2 to 4 times more at risk for acute renal failure. These risks are dose dependent and highest during the first month of therapy—important considerations for dental practice.

The simplistic hypothesis that the anti-inflammatory and analgesic effects of NSAIDs result solely from COX-2 inhibition at the site of tissue injury propelled the creation of selective COX-2 inhibitors (COX-2i). Additionally GI complications were considered a result of inhibition of prostaglandin synthesis mediated by COX-1 in the gastrointestinal mucosa. However, it became obvious that COX-1 has an important role in the inflammatory response whilst COX-2 has fundamental constitutive roles. COX-2 is important for the normal function of many systems, including the renal, nervous, cardiovascular, and reproductive systems.

The promised combination of effective analgesia with no significant GI toxicity fueled the attractiveness of COX-2i. Indeed, studies clearly showed the superiority of COX-2i in GI adverse events. However, COX-2 is important in healing, and concerns have been raised that COX-2i use in the presence of GI ulcers may delay healing. Moreover, in the background was the concern that selective COX-2i would suppress endothelial prostacyclin, and leave COX-1 mediated thromboxane A2 in platelets relatively unchecked. With loss of the antiplatelet and vasodilatory effects of prostacyclin, a relative excess of thromboxane A2 would favor vasoconstriction, platelet aggregation, and thrombosis. The beauty could easily become the beast. Analgesic efficacy of COX-2i and nonspecific NSAIDs has consistently been shown to be similar; the success of the COX-2i is totally reliant on an unequivocally safer side-effect profile. As we have experienced, this is not consistently the reality we face in clinical practice.

The first approved COX-2–specific drugs on the market were rofecoxib and celecoxib, appearing in the late 1990s, and these were rapidly incorporated into standard medical and dental care for inflammatory conditions. Concomitantly, early studies showed significantly more frequent thromboembolic events in patients receiving rofecoxib, even in short-term studies. These events included acute myocardial infarctions and cerebrovascular accidents. Rofecoxib was only voluntarily withdrawn by the manufacturer in 2004. Valdecoxib was withdrawn shortly after. I inadvertently caused the hospitalization of one of my patients in 1999 due to cardiovascular complications within 48 hours of rofecoxib use; I saw the beast in COX-2 inhibitors and have been wary ever since. The marketing of these drugs is, however, persistent and effective, and we are constantly "coaxed" to incorporate them into our routine care for pain. Newer COX-2 inhibitors, such as lumiracoxib and etoricoxib, have appeared but it is unclear if they are any safer than their predecessors or nonselective NSAIDs. Early data suggest that etoricoxib is associated with thromboembolic events and an increased cardiovascular risk. Data on lumiracoxib are sparse but suggest no increased cardiovascular risk. In Europe the use of COX-2 inhibitors has been contraindicated in patients with established coronary heart disease, cerebrovascular disease, and peripheral arterial disease, and a number of compulsory warning statements have been included in the packaging. In my view, caution is in order until further data accumulate.

The data may leave us confused, and rightly so. Choosing the appropriate analgesic may be tricky. Luckily, dental practitioners are rarely in the situation of managing long-term NSAID use; but some of the risks occur early in therapy. Of all NSAIDs (other than aspirin), naproxen has consistently demonstrated marginal or nonsignificant changes in cardiovascular risk. The data suggest that the use of naproxen, with a proton pump inhibitor, is the safest NSAID when cardiovascular risks are considered. Ibuprofen has a good GI profile but increases cardiovascular risks in long-term use, particularly at high doses. However, both these drugs are probably safe for short-term therapy (days).

We often forget the efficacy and safety of simple analgesics. Acetaminophen (1 g) is modestly inferior to ibuprofen or diclofenac, but combined with 60 mg codeine its efficacy is improved to that of NSAIDs (eg, 400 mg ibuprofen). Moreover, recent data suggest no significant differences in pain scores or swelling between ibuprofen and acetaminophen following third-molar extraction. Acetaminophen is therefore a viable alternative to the NSAIDs, especially because of the low incidence of adverse effects. It should be the preferred choice in patients who have cardiovascular disease, take anticoagulants, or have renal problems. All drugs taken in large doses or for prolonged periods are associated with adverse events. Acetaminophen is no exception; long-term ingestion of large doses may be associated with increased cardiovascular risk, hepatic enzyme induction (contraindicated in alcohol abusers), and moderate renal dysfunction. Simple analgesics may be uglier than COX-2i, but they are definitely friendlier.

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