Nonsteroidal Anti-Inflammatory Drugs: Confusion, Controversy and Dental Implications

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SOMMAIRE

Les anti-inflammatoires non stéroïdiens (AINS) sont utilisés pour le traitement de la douleur, y compris la douleur odontogène, depuis de nombreuses années. Bien qu'ils soient efficaces pour soulager les symptômes, ces médicaments ne sont pas sans effets secondaires, lesquels se manifestent principalement par une toxicité des voies gastro-intestinales supérieures. Pour prévenir ces effets secondaires, l'industrie pharmaceutique a mis au point des AINS qui inhibent de façon sélective l'isoenzyme cyclo-oygénase 2 (COX-2) – une enzyme inductible qui s'exprime aux sièges de l'inflammation – mais qui n'agissent pas sur l'isoenzyme COX-1 associée à la protection gastrique. Le 30 septembre 2004, la société pharmaceutique qui produisait le rofécoxib (Vioxx) – un inhibiteur de la COX-2 – a volontairement retiré ce produit du marché, sur la base des données recueillies dans le cadre d'un vaste essai clinique continu qui établissaient un lien entre ce médicament et un risque accru d'effets cardiovasculaires indésirables. Cette découverte inattendue a forcé le milieu médical à recenser la littérature existante sur ce produit et d'autres médicaments connexes et a aussi donné lieu à des recherches nouvelles visant à mieux comprendre les mécanismes par lesquels pourrait se produire ce grave effet secondaire. Cependant, plutôt que de clarifier la situation, les rapports ont semé la confusion et la controverse au sujet de l'innocuité de tous les types d'AINS, les principales préoccupations ayant trait au risque d'effets cardiovasculaires indésirables associés à l'utilisation d'un médicament en particulier et à la possibilité d'un effet de classe. Les auteurs de cet article passent en revue les derniers événements et résultats d'études et discutent de leurs répercussions en dentisterie.

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Over the past 40 years, nonsteroidal anti-inflammatory drugs (NSAIDs) have been widely used to treat various types of acute and chronic pain. Although NSAIDs relieve symptoms, they are not without significant adverse effects, the most noteworthy being upper gastrointestinal (stomach and duodenum) toxicity. Use of NSAIDs leads to hospitalization due to ulcer complications (bleeding and perforation) in about 1% of users annually and may result in thousands of deaths every year.[1]

COX-1 and COX-2 Isoenzymes

NSAIDs act by inhibiting both forms of the cyclooxygenase enzyme: COX-1 and COX-2. Cyclooxygenase catalyzes the conversion of arachidonic acid to prostaglandins, prostacyclin and thromboxane. The COX-1 isoenzyme is constitutively expressed in many tissues, including gastrointestinal mucosa, where it provides mucoprotective prostaglandins, initiates platelet aggregation and regulates renal blood flow. The COX-2 isoenzyme is induced to generate prostaglandins that mediate inflammation contributing to pain, edema and tissue destruction. COX-2 is also expressed in the brain and kidneys, where it plays an undefined physiologic role.[2] Nonselective NSAIDs can inhibit both COX-1 and COX-2 isoenzymes, producing both therapeutic and toxic effects. Therapeutic doses of nonselective NSAIDs lead to gastrointestinal bleeding and inhibition of mucoprotective prostaglandins. These potentially adverse events led to the discovery of selective COX-2 inhibitors, which spare COX-1 thus maintaining the gastroprotective effect.[3]

COX-2 Inhibitors

In 1999, rofecoxib (Vioxx, Merck & Co., Inc., Whitehouse Station, N.J.) and celecoxib (Celebrex, Pfizer, Inc., New York, N.Y.) were the first 2 drugs in this new class of COX-2 inhibitors to be approved for use. In 2001, a third medication in this class, valdecoxib (Bextra, Pfizer, Inc., New York, N.Y.) was approved. In 2003, the COX-2 inhibitors accounted for more than $5 billion in sales in the United States.[4] Dentistry also embraced the use of this class of medications for the management of acute pain in the belief that COX-2 inhibitors have therapeutic effects and are devoid of gastric toxicity.[5]

VIGOR and CLASS Studies

The emergence of rofecoxib and celecoxib was based on 2 large prospective, randomized, double-blinded controlled trials. The primary outcome measure was a lower incidence of gastrointestinal toxicity. The Vioxx Gastrointestinal Outcomes Research (VIGOR) study[6] involved over 8,000 patients with rheumatoid arthritis, who were assigned to receive either rofecoxib, 50 mg daily, or naproxen (a nonselective NSAID), 500 mg twice daily, for approximately 10 months. The results of this study showed that rofecoxib and naproxen had similar efficacy against rheumatoid arthritis; however, rofecoxib resulted in half the number of clinically relevant adverse upper gastrointestinal events. An unexpected finding was a higher incidence of myocardial infarction (MI) in the rofecoxib group (0.4% vs 0.1%). Because this trial did not have a placebo group, the findings generated several possible hypotheses to account for the results: that this may have been a chance finding, that "coxibs" produce adverse events, that naproxen has cardioprotective effects or that rofecoxib promotes adverse cardiovascular events.

The Celecoxib Long term Arthritis Safety Study (CLASS)[7] involved over 8,000 patients with either osteoarthritis or rheumatoid arthritis with a total of 4,573 patients receiving treatment for 6 months. Patients were randomly assigned to receive either celecoxib, 400 mg twice daily (2 and 4 times the maximum doses for rheumatoid or osteoarthritis), ibuprofen, 800 mg 3 times daily, or diclofenac, 75 mg twice daily. Acetylsalicylic acid (ASA; Aspirin, Bayer Inc, Toronto, Ont.) use for cardiovascular prophylaxis (≤ 325 mg/day) was permitted. The study revealed that celecoxib, at doses greater than those indicated clinically for pain management, was associated with a lower incidence of gastrointestinal toxicity compared with nonselective NSAIDs. Importantly, there were no differences in the incidence of cardiovascular events between celecoxib and NSAIDs users irrespective of ASA use.

Re-evaluation of Studies

These diverging results prompted researchers to re-evaluate the studies. Weir and others[8] and Konstam and others[9] conducted a pooled analysis from 23 studies (including VIGOR) representing more than 14,000 patient-years. They demonstrated that rofecoxib was not associated with excess cardiovascular events compared with either placebo or nonnaproxen NSAIDs. In addition, they concluded that naproxen was the outlier, suggesting a possible cardioprotective benefit. Another observational study[10] reported that although high-dose rofecoxib (> 25 mg/day) was associated with a greater risk of cardiovascular events, at lower doses (≤ 25 mg/day) there was no evidence of increased risk. In a large population-based retrospective cohort study, there was no increase in the short-term risk of acute MI among users of rofecoxib or celecoxib.[11]

Studies investigating the effect of naproxen on cardiovascular risk have also yielded conflicting results. In 2 observational cohort studies, no reduction in risk was reported with naproxen use,[11,12] whereas a cardioprotective effect was noted in several other studies.[13–16] It appears from these studies that rofecoxib was not involved in producing a higher rate of adverse cardiovascular events, with uncertainty surrounding the cardioprotective effects of naproxen.

In September 2004, the medical community was shocked to hear that Vioxx was being voluntarily withdrawn from the market. The decision was based on the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial, which studied 2,600 patients with no history of cardiovascular disease before enrolment for the prevention of recurrence of colorectal polyps. The study was to be 3 years in duration, but was halted early due to the increased risk of MI or stroke among the group that was taking 25 mg/day rofecoxib, which was twice that of the group taking placebo. The results of this study were contrary to previously reported data (other than the VIGOR study) and prompted investigation as to whether cardiovascular events are a result of all "coxibs" or only the individual drug.

Mukherjee and others[16] conducted a meta-analysis of clinical trials to compare cardiovascular events associated with rofecoxib and celecoxib. Their results revealed an increased risk with both COX-2 inhibitors. Juni and others[17] did a standard and cumulative random-effects meta-analysis of 18 randomized trials from bibliographic databases and United States Food and Drug Administration (FDA) files. They reported that by the end of 2000, patients assigned to rofecoxib had a relative risk of MI of 2.24 (1.24–4.02) compared with the control group (placebo, non-naproxen NSAID or naproxen). Solomon and others[18] conducted a matched case–control study of 54,475 patients 65 years of age or older and concluded that rofecoxib was associated with an elevated risk of acute MI compared with celecoxib and no NSAID use. They also found that doses of rofecoxib > 25 mg/day were associated with a higher risk than doses ≤ 25 mg/day with the risk elevated in the first 90 days but not thereafter.

Additional controversy and confusion occurred in December 2004 when the FDA halted the Adenoma Prevention with Celecoxib (APC) trial in which 2,000 patients were being studied over 33 months to determine

whether celecoxib could prevent colon cancer. Patients taking 400 mg celecoxib twice daily had a 3.4 times greater risk of a cardiovascular event than those taking placebo. Patients taking 200 mg celecoxib twice daily also had a risk that was 2.5 times that of patients taking placebo.[19]

This was contrary to 2 other long-term studies involving celecoxib. In the Prevention of Spontaneous Adenomatous Polyps (PreSAP) study, 2,400 patients were followed for 2 years to determine whether 400 mg celecoxib daily could prevent polyps from progressing to colon cancer. The results of this ongoing study have not revealed any increased risk of cardiovascular events compared with placebo.[20] In a second study, the Alzheimer's Disease and Prevention Study (ADAPT), 2,500 patients at high risk of Alzheimer's disease and aged ≥ 70 years were being studied to determine whether 400 mg celecoxib daily or 220 mg naproxen sodium (Aleve, Bayer, Morristown, N.J.) twice daily could prevent Alzheimer's disease. This study was halted by the National Institutes of Health after 70 of the 2,500 patients had a stroke or heart attack resulting in 23 deaths. Interestingly, the rate of cardiovascular events associated with the use of celecoxib was similar to that with placebo but there was a 50% increase in the rate of heart attacks or strokes with naproxen sodium

Table 1. Summary of findings of COX-2 inhibitor trials related to cardiovascular events

Trial	Drug (dose)	Disease treated	Findings related to cardiovascular events
ADAPT (2,500 patients aged ≥ 70 years at high risk for Alzheimer's disease; to determine whether the drugs could prevent Alzheimer's disease)	Celecoxib (400 mg qd) Naproxen (200 mg bid)	Alzheimer's disease	Compared with placebo, no difference with celecoxib; 50% increase in risk of MI/stroke with naproxen
APC (about 2,000 patients; to study whether celebrex could prevent colon cancer)	Celecoxib (400 mg or 800 mg qd)	Colorectal cancer	Compared with placebo (6 CV events), at 400 mg qd, celecoxib increased risk of major adverse cardiac event 2.5-fold (15 CV events); at 800 mg qd, risk increased 3.4-fold (20 CV events)
APPROVe (2,600 patients; to investigate the prevention of recurrence of colorectal polyps)	Rofecoxib (25 mg qd)	Colorectal cancer	At 18 months, rate of MI/stroke for rofecoxib vs. placebo: 3.5% vs. 1.9% ($p < 0.001$)
CLASS (over 8,000 patients with OA and RA)	Celecoxib (400 mg bid) Diclofenac (75 mg bid) Ibuprofen (800 mg tid)	Arthritis	No differences between groups
PreSAP (about 2,400 patients; to determine whether celebrex could prevent polyps from progressing to colon cancer)	Celecoxib (400 mg qd)	Colorectal cancer	Compared with placebo, preliminary reports suggest use of celecoxib not associated with increased risk of CV events
VIGOR (over 8,000 patients with RA)	Rofecoxib (50 mg qd) Naproxen (500 mg bid)	Arthritis	For any thrombotic CV event, rofecoxib (45 events) vs. naproxen (19 events); $p < 0.002$

ADAPT = Alzheimer's Disease Anti-inflammatory Prevention Trial; APC = Adenoma Prevention with Celecoxib; APPROVe = Adenomatous Polyp Prevention on Vioxx; bid = twice a day; CLASS = Celecoxib Long-term Arthritis Safety Study; CV = cardiovascular; MI = myocardial infarction; OA = osteoarthritis; PreSAP = Prevention of Spontaneous Adenomatous Polyps; qd = daily; RA = rheumatoid arthritis; tid = 3 times a day; VIGOR: Vioxx Gastrointestinal Outcomes Research.

compared with placebo.[21] A summary of these studies is presented in **Table 1**.

There have also been reports of increased risk of cardiovascular events in patients administered valdecoxib (intravenous and oral) following coronary artery bypass graft surgery.[22]

In light of these recent controversial findings, Graham and others[23] completed a nested case–control study with data from Kaiser Permanente in California on a cohort of patients treated with NSAIDs. They compared current exposure to COX-2 inhibitors and nonselective NSAIDs with remote exposure to any NSAID, and rofecoxib was compared with celecoxib. They found that during 2,302,029 person-years follow-up, there were 8,143 cases of serious coronary disease of which 2,210 (27.1%) were fatal. They concluded that rofecoxib use (all doses) increased the risk of serious coronary disease compared with celecoxib use. Celecoxib was not associated with any increased risk of cardiac events compared with remote NSAID use, while naproxen use appeared to confer a slightly increased risk. They further estimated that between 88,000 and 140,000 excess cases of serious coronary disease might have resulted from the use of rofecoxib rather than other NSAIDs in the United States alone since the introduction of rofecoxib in 1999.

In a population-based, retrospective cohort study of 113,927 elderly people without previous MI and newly treated with an NSAID over a 3.5-year period, Levesque and others[24] assessed the influence of various NSAIDs on the risk of a first MI. Their results provided evidence for increased risk of acute MI in current users of rofecoxib among elderly patients with no history of MI. There was a further increase in risk at higher doses. No increased risk was observed with celecoxib or other NSAIDs under study.

The results of these studies seem to support the hypothesis that adverse cardiovascular events are more related to a particular drug, rofecoxib, than to the entire class of COX-2 inhibitors. Kimmel and others[25] addressed this situation using a case–control design to study patients presenting with a first non-fatal MI. After discharge from a hospital, patients and those in the control group were interviewed by telephone regarding their use of nonselective non-aspirin NSAIDs as well as COX-2 inhibitors (excluding valdecoxib). No evidence of a class effect of COX-2 inhibitors on cardiovascular toxicity was found. However, rofecoxib use was associated with a statistically significant (2.72) increase in the odds of MI compared with celecoxib use. Nonselective NSAIDs were associated with reduced odds of a non-fatal MI relative to non-users.

Dental Practitioner Choices

Amid the conflicting information, the dental practitioner must assess the usefulness of COX-2 inhibitors in the practice of dentistry. An appraisal of the drug interaction profile of NSAIDs and COX-2 inhibitors must be made and the practitioner must determine whether COX-2 inhibitors are more advantageous than and equally efficacious as NSAIDs as a therapeutic agent in dentistry. Contraindications for the use of either class of drug are patients with a history of impaired renal or hepatic function; hypersensitivity to ASA, the specific drug, or the class of drugs; and precaution for those with a history of congestive heart failure, hypertension or asthma. The risk of gastrointestinal toxicity associated with COX-2 inhibitors is less than that with nonselective NSAIDs. Also, nonselective NSAIDs inhibit platelet aggregation, thus prolonging bleeding times, whereas COX-2 inhibitors do not. Celecoxib should not be prescribed to those who are allergic to sulfonamides.

Acute Versus Chronic Use

Most pain emanating from the dental setting is acute pain arising from preoperative conditions (infection, inflammation) or procedure-based (surgical, inflammatory). An accepted model for assessing the efficacy of analgesics to treat acute pain is extraction of third molars.[26,27] In general, studies of this acute pain model have found that COX-2 inhibitors are no more efficacious than older, nonselective NSAIDs.[5,28–33] Reported benefits of COX-2 inhibitors are reduced incidence of gastric ulceration, minimal effect on platelet aggregation and apparently longer duration of action than conventional analgesics (ASA, acetaminophen and ibuprofen). However, COX-2 inhibitors are more expensive than nonselective NSAIDs (especially those available in generic forms), they are not available over the counter and have similar contraindications and drug interactions to the equally effective and less-expensive nonselective NSAIDs.[2,5,34]

Nevertheless, any patient experiencing acute dental pain who is at high risk of gastrointestinal bleeding, ulceration or perforation would benefit from COX-2 inhibitors. Generally, elderly patients may also benefit because of their higher risk of adverse reactions. The practitioner must weigh the benefits of reduced risk of gastrointestinal toxicity against the increased risk of a cardiovascular event in this acute setting. It is important for the practitioner to understand that in the studies involving COX-2 inhibitors (discussed above), no adverse cardiovascular events occurred in the short term. Therefore, the use of COX-2 inhibitors for acute pain in selected medically compromised patients with or without cardiovascular disease may be indicated.

Chronic pain, including musculoskeletal pain, arthritic pain, cancer pain and neurologic or neuropathic pain may be treated by some dental providers, but does not represent common pain seen by dental practitioners.

FDA and Health Canada Decisions

From February 16 to 18, 2005, FDA convened an advisory panel to review the overall safety of COX-2 inhibitors. Panellists voted 31–1 to keep celecoxib on the market. Voting on valdecoxib was much closer: 17–13 in favour of keeping it on the market. In spite of this favourable vote, valdecoxib was

removed from the market in April 2005, with FDA citing risks as outweighing the benefits. For the controversial drug rofecoxib, voting was 17–15 in favour of allowing it to be sold even though it was previously withdrawn. Recently, FDA announced changes in the marketing of NSAIDs (prescription and over the counter) including COX-2 inhibitors.[35] Manufacturers will have to highlight the potential increased risk of cardiovascular events and the potential for gastrointestinal bleeding in their package inserts. This announcement did not apply to ASA due to its cardioprotective effects in certain populations. Simultaneously, Health Canada developed new restrictions on the use of celecoxib.[36]

Conclusion

Until more definitive studies are carried out, dentists should assess the risks and benefits of each medication, taking into account the medical history and analgesic requirements of each individual patient (see **Appendix 1, FDA interim recommendations (23 Dec. 2004)** at www.cda-adc.ca/jcda/vol-71/issue-8/575.html). The practitioner must realize that the risk–benefit balance for the use of pharmaceuticals in the usual dental acute setting is quite different from a chronic situation. With this knowledge, the practitioner must decide which therapeutic agent is appropriate for his or her patient.

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Appendix 1

FDA interim recommendations (23 Dec. 2004)[37]

While the results of these studies are preliminary and conflict with other study data on the same drugs, FDA is providing this advisory as an interim measure, pending further review of data that continue to be collected. Specifically:

- Physicians prescribing celecoxib (Celebrex) or valdecoxib (Bextra), should consider this emerging information when weighing the benefits against risks for individual patients. Patients who are at a high risk of gastrointestinal bleeding, have a history of intolerance to nonselective NSAIDs, or are not doing well on nonselective NSAIDs may be appropriate candidates for COX-2 selective agents.
- Individual patient risk for cardiovascular events and other risks commonly associated with NSAIDs should be taken into account for each prescribing situation.
- Consumers are advised that all over-the-counter (OTC) pain medications, including NSAIDs, should be used in strict accordance with the label directions. If use of an OTC NSAID is needed for longer than 10 days, a physician should be consulted.

Nonselective NSAIDs are widely used in both OTC and prescription settings. As prescription drugs, many are approved for short-term use in the treatment of pain and primary dysmenorrhea (menstrual discomfort), and for longer-term use to treat the signs and symptoms of osteoarthritis and rheumatoid arthritis. FDA has previously posted extensive NSAID medication information at http://www.fda.gov/cder/drug/analgesics/default.htm.