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COX-2 inhibitors: a story of greed, deception and death

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Abstract—In 1999, drug manufacturers introduced a class of NSAIDs called COX-2 inhibitors or coxibs. The drugs were avidly promoted directly to the consumers and became bestsellers from the start. Arthritis sufferers were eager to take medications that eased joint pain with less risk of causing gastrointestinal pain, bleeding and other side-effects. In the year after their introduction, doctors wrote over 100 million prescriptions for celecoxib (Celebrex) and rofecoxib (Vioxx). Celebrex is the sixth best-selling drug, with sales of more than US$ 4 billion since its debut in 1999. Vioxx had sales of US$ 2.6 billion in 2001. However, the coxibs increase the risk of heart attacks and strokes, and their price, in the USA, is obscene. The manufacturers faced a possibly complicit, toothless and bloodless FDA, and used every maneuvering to fleece the patients. We must now reflect on attitudes that we thought only belong to the tobacco industry. Fortunately, safe and active alternatives exist.

Key words: Coxibs; NSAIDs; risk; gastro-intestinal bleeding; greed; Lyprinol.

1. BACKGROUND: SOME RECENT HISTORY (HALPERN, 2004)

In 1999, drug manufacturers introduced a class of NSAIDs called COX-2 inhibitors (sometimes called COX-2-selective inhibitors). The drugs were bestsellers from the start. Arthritis sufferers were eager to take medications that eased joint pain without causing gastrointestinal pain, bleeding, and other side-effects from NSAIDs. In the year after their introduction, doctors wrote over 100 million prescriptions for celecoxib (Celebrex) and rofecoxib (Vioxx). Celebrex is now the sixth bestselling drug, with sales of more than US$ 4 billion since its debut in 1999. Vioxx had sales amounting to US$ 2.6 billion in 2001.

In theory these new drugs only inhibit COX-2 enzymes, but in practice, the jury is still deliberating. COX-2 inhibitors may erode the stomach's mucus protection, although the drugs are not as harmful to the gastrointestinal tract as other NSAIDs.

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Like other NSAIDs, the drugs may damage the kidneys. Some physicians believe that COX-2 inhibitors increase the risk of heart attacks and strokes. Others have called into question the drugs' benefits given how expensive they are compared to other NSAIDs. COX-2 inhibitors cost roughly US$ 2.75 per tablet, significantly more than naproxen, for example, which costs US$ 0.18.

Much to the displeasure of Pharmacia (now Pfizer) and Merck (the makers of Celebrex and Vioxx, respectively), the Federal Drug Administration (FDA) requires COX-2 inhibitor drugs to carry the same gastrointestinal risk warning as other NSAIDs. In February 2000, on the strength of new studies they had commissioned, Pharmacia and Merck asked the Arthritis Advisory Committee to the FDA to review whether these warnings were necessary. The Committee concluded that the studies did not show that COX-2 inhibitors have a "clinically meaningful" safety advantage over standard NSAIDs, nor did the studies show an overall reduction in gastrointestinal complications. The gastrointestinal health warnings remain on the labels of COX-2 inhibitors.

Other problems with COX-2 inhibitors, namely renal, cardiovascular, questionable cost-effectiveness and marketing, are outlined below (items 1–4).

(1) NSAIDs decrease blood flow to the kidneys, and for that reason they have been linked to kidney failure, especially in elderly patients and patients with preexisting kidney damage. COX-2 inhibitors, it appears, are no different from other NSAIDs in their effect on the kidneys. In a study published five years ago (Swan *et al*., 2000), researchers had 75 patients aged 60 to 80 years with normally functioning kidneys take the COX-2 inhibitor rofecoxib (Vioxx), the NSAID indomethacin (Apo-Indomethacin, Indocid, Novo-Methacin), or a placebo. Subjects in all three groups were placed on a low-sodium diet because salt intake can affect test results in renal studies. To gauge the subjects' kidney health, researchers examined sodium levels and potassium levels in the subject's urine and blood. In groups taking the COX-2 inhibitor and the NSAID, the subjects' ability to filter waste products declined to the same degree. The authors of the study concluded, "the renal effects observed... are likely to be reproduced throughout this class of medications". In other words, COX-2 inhibitors are as likely as standard NSAIDs to cause problems for the kidneys.

(2) Another troubling aspect of COX-2 inhibitors is the drugs' potential to increase the risk of heart attacks and strokes. As early as 1999, the National Academy of Sciences warned that COX-2 inhibitors increase the risk of strokes, heart attacks and blood-clotting disorders. One theory is that COX-2 inhibitors suppress the production of prostacyclin in the walls of blood vessels that acts to dilate the vessels and inhibit blood clots. So concerned is the FDA that COX-2 inhibitors increase the risk of heart attacks, the agency's Health and Human Services Department cited Merck (the maker of Vioxx) in a September 21, 2001 warning letter. Merck, the agency wrote, has "engaged in a promotional campaign for Vioxx that minimizes the potentially serious cardiovascular findings that were observed... and thus, misrepresents the safety profile for Vioxx".

(3) The high cost of COX-2 inhibitors, relative to other NSAIDs, has caused many people to question whether the drugs are cost-effective. In some studies, the absolute risk reduction of taking COX-2 inhibitors is only 1 or 2%, compared to other NSAIDs. If the risk reduction is this low, is spending an extra US$ 500 to 700 a year for COX-2 inhibitors worthwhile? To measure the cost-effectiveness of COX-2 inhibitors, researchers at UCLA and the V.A. Greater Los Angeles Healthcare System devised a QALY (quality-adjusted life-year) measurement scale for a hypothetical 60-year-old patient with mild to severe arthritic pain. This study found that COX-2 inhibitors cost US$ 275 809 more than naproxen to produce each additional QALY. For patients with heart disease, COX-2 inhibitors cost US$ 395 324 more. The authors concluded: "The risk reduction seen with coxibs (COX-2 inhibitors) does not offset their increased costs compared with nonselective NSAIDs in the management of average-risk patients with chronic arthritis. However, coxibs may provide an acceptable incremental cost-effectiveness ratio in the subgroup of patients with a history of bleeding ulcers."

(4) Some have suggested that COX-2 inhibitors were placed on the market before sufficient studies were done as to their effectiveness, and that the drugs were pushed too hard, too fast by pharmaceutical companies. Larry Sasich, a pharmacist for the Public Citizen Health Research Group, put it this way: "The question prescribers have to ask is how did Celebrex reach US$ 1 billion in sales at a time when there was not a single controlled trial published that looked at the effectiveness in treating arthritis and pain compared to similar drugs, What sources of information do prescribers use to choose drugs? In the case of Celebrex, because there was no science, the decision had to be based on promotional materials".

2. COMMENTARY

Within three years, all the dangers, the side-effects, the killing potentials of these new drugs were known, published and available to those (few) who wanted to know. Jüni *et al*. (2004) stated: "Our findings [a cumulative meta-analysis] indicate that rofecoxib should have been withdrawn several years earlier. The reasons why manufacturer and drug licensing authorities did not continuously monitor and summarise the accumulating evidence need to be clarified". However, the billions of promotional dollars, the bribes, the intimidation, the "neutralization" of opinion leaders were stronger, much more efficient than the scientific evidence. And the story is not over. Even in February 2005, the manufacturers try to mask the evidence and deny the truth; deception is well anchored as a strategy. Greed is such that morals, ethics and even the law are being trampled on. Who cares about the cost of innocent lives, when Pfizer and Merck have as hired guns some of the best and brightest lawyers, and when Celebrex had sales of US$ 3.3 billion last year?

Pfizer CEO Hank McKinnel, interviewed by CNN's Aaron Brown on December 20, 2004 offered the following disclaimer, "But remember, we do not actually sell our products. All the resources we put into "sales and marketing" is really to make sure that physicians and patients are fully aware of all the information around the risks and benefits of the medicines we are offering. And then we leave it to the doctor and the patient to decide what is the best option for them" (Gallagher and Oransky, 2005).

Pfizer was caught red-handed on February 1, 2005 (Berenson and Harris, 2005) when it was revealed that it never published, nor submitted to the FDA until June 2001 (4 months after a review by the FDA of the safety of Vioxx and Celebrex) a 1999 clinical trial that found that elderly patients taking Celebrex were far more likely to suffer heart problems than patients taking a placebo. "The 1999 study is further evidence that Celebrex is dangerous" said Sidney M. Wolfe, a director of Public Citizen, who found it on a new website where Pfizer and other drug companies have begun to post some clinical trials results. This 1999 Alzheimer's study found that 22 out of 285 patients taking Celebrex suffered heart attacks, strokes and other heart problems. Only 3 of 140 patients taking a placebo had similar problems. Even accounting for the difference in the sizes of the two groups, Celebrex users were almost four times as likely to suffer heart problems. In the study, patients took 400 mg of Celebrex daily, a dose commonly used by arthritis patients. A statistically significant difference favoring placebo in adverse events was observed.

Of the growth in the use of coxibs in the USA, 63% was in patients who were at low risk of gastrointestinal side-effects, who should not have been prescribed the drugs in the first place (Dai *et al*., 2005). "A higher number of patients were exposed to potential harms than if [the drugs] were limited to the particular group of the population where it is most proven", said Randall Stafford (Stanford University School of Medicine). "We found a nationwide shift away from older, inexpensive drugs with better established safety and efficacy to newer, costly drugs with no real history", adds G. Caleb Alexander (University of Chicago). This "therapeutic creep" (R. Stafford) may be due to aggressive marketing and also the misconception amongst doctors and patients that because a drug is new, it must be better than older drugs. The FDA's criterion for a drug's entry into the market is that it performs better than... a placebo, rather than showing superior efficacy when compared to existing drugs (Bhattacharya, 2005).

3. ALTERNATIVES TO COXIBS

What were, and still are the options *vs*. NSAIDs, including the coxibs? Since the majority of patients consuming coxibs do so to control the pain of osteoarthritis, they still have many options:

– Non-pharmacologic ones include patient education, self-management programs, weight loss, exercise programs, physical therapy, occupational therapy and

the use of assistive devices for activities of daily living (ADL). Patients who participated in self-management programs noticed decrease in joint pain and frequency of arthritis-related physician visits, increased physical activity and overall improvement of quality of life (QOL). Swimming is the best therapy for patients with arthritic pain (DeAngelo and Gordin, 2004). Eight weeks of simple aerobic training improved both physical ability and functional status (Kovar *et al*., 1992).

– Natural compounds:

  - Glucosamine sulfate short-term clinical trials demonstrated effective symptomatic relief in patients with osteoarthritis (OA) of the knee (Kovar *et al*., 1992).
  - Topical capsaicin (from Cayenne) cream is available OTC in 0.025% and 0.075% concentrations, and can be applied to the painful joint four times daily (DeAngelo and Gordin, 2004).
  - Willow bark, ginger, cat's claw, celery seed, extra-virgin olive oil (data not shown) or some of their specific components claim successes (Butters and Whitehouse, 2003).
  - Lyprinol, the oil of *Perna canaliculus* (green-lipped mussel of New Zealand), is an effective and safe alternative at an initial dose of 4 capsules daily (Halpern, 2000, 2001; Cho *et al.*, 2003; Gruenwald *et al.*, 2004; Lau *et al.*, 2004).

– Paracetamol (acetaminophen) was first used clinically by von Mering in 1893 (Prescott, 2000). Bradley *et al.* (1991) in a randomized double-blind parallel-group study in 184 patients with knee OA, concluded that paracetamol 4 g/day showed similar efficacy to that of ibuprofen in analgesic (0.3 g q.i.d.) and anti-inflammatory (0.6 g q.i.d.) dosages for the short-term (4 weeks) treatment of pain due to OA. Paracetamol is safe: gastrointestinal safety was comparable with the placebo and far better than aspirin (Muller *et al.*, 1990). Paracetamol is an analgesic of choice among patients with cardiovascular disease (Hillis, 2002), contrasting with NSAIDs and coxibs, and is considered for prevention of atherosclerosis *via* a potential antioxidant activity (Prescott, 2000). It is of particular value in patients with aspirin/NSAID-sensitive asthma (Prescott, 2000). It is the first-line or reference analgesic in the treatment of pain from OA for many international, national or regional medical societies (Bertin *et al.*, 2004): British Society for Rheumatology and Royal College of Physicians (1993), Royal College of General Practitioners (1998), American Geriatric Society (1998), North England NSAID Guideline Development Group (1998), European League Against Rheumatism (2000), American College of Rheumatology (1995, confirmed in 2000), National Kidney Foundation (1996), American Pain Society (2002), etc. The liver toxicity may occur at doses higher than 4 g/day, and/or when associated with large alcohol consumption, but is preventable or controlled

with N-acetyl-cysteine (Prescott, 2000); paracetamol may increase the half-life of warfarin (Kwan *et al*., 1999) (but less than NSAIDs and coxibs).

However, paracetamol is inexpensive, and mass production in China, India or Eastern European countries will not help generate obscene bonuses for the directors and executives of phRMA. But it will not damage the cardiovascular system (or stomachs) of patients in pain, and kill thousands of them as coxibs (and NSAIDs) do.

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