

COX-2 DRUGS

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I. BACKGROUND

The modern pharmaceutical era was born in 1897 when the German chemist Felix Hoffman, an employee of Bayer Industries, synthesized acetylsalicylic acid, or aspirin, in the laboratory. For decades aspirin was one of the few non-narcotic analgesic choices that physicians and patients possessed for the relief of fever, pain and inflammation. While not perfectly safe, aspirin was practically devoid of the much more serious side effects associated with the use of narcotic analgesics.

In the 1950's more potent anti-inflammatories, such as corticosteroids, were developed. However, corticosteroids had serious side effects that limited their long-term usage. In the 1960's and 70's a new class of compounds was born which came to be known as non-steroidal anti-inflammatory drugs or NSAIDs. The NSAIDs offered significant fever, pain and inflammation relief with less serious side effects than the corticosteroid family of drugs. By the early 1990's, these drugs were used by millions of persons in the United States on a daily basis. The usage of these drugs was especially prevalent in individuals age 65 and older.

While relatively safe, NSAIDs did prove to increase levels of gastrointestinal toxicity in long term, or chronic users. By the 1980's, data from

several epidemiological studies demonstrated conclusively that chronic NSAID use increased the risk of gastrointestinal toxicity by 4-6 times. These studies also showed that the risk of gastrointestinal problems such as perforations, ulcerations and bleeds (i.e., PUBs) was increased relative to the dose of the drug. The risk was especially pronounced for elderly users of the drug (i.e., the predominant population of NSAID users).

II. THE THEORY BEHIND COX-2 INHIBITION

Research into the cause of the gastrointestinal toxicity associated with chronic NSAID use led to the discovery that NSAIDs were significant inhibitors of the production of prostaglandins. It was discovered that particular prostaglandins are involved in the defense of the stomach from the adverse effects of gastric acid. Thus, the resulting decrease of the production of prostaglandin within the body that is inherent in the usage of NSAIDs ultimately leads to a decrease of the effectiveness of the gastrointestinal mucosa, as well as other necessary gastro-protective aspects, resulting in a loss of integrity of the stomach lining.

The turning point or “birth” of the entire class of medications known as Cox-2 inhibitors arose upon the discovery that all prostaglandin production in the body relies upon the enzyme cyclooxygenase (i.e., COX). Moreover, in 1991 it was discovered that there were at least two types of COX enzymes, which were described as COX-1 and COX-2. Researchers theorized that the COX-1 isoenzyme is involved in the protection of the gastrointestinal mucosa or stomach

lining. Alternatively, it was hypothesized that the COX-2 isoenzyme was produced as a part of the body's response to pain or inflammation.

The theory was then developed that if a medication could be created that would inhibit the production of the COX-2 isoenzyme within the body, while maintaining the body's production of the COX-1 isoenzyme, that pain and inflammation could be eliminated while still maintaining gastrointestinal integrity. The "race" was then on as the world's largest pharmaceutical companies clambered over each other to discover drugs that would inhibit production of the COX-2 isoenzyme while leaving untouched, to a relative degree, the body's production of the COX-1 isoenzyme.

This new class of compounds was known as the "coxibs". They were distinguished from the older NSAIDs in that NSAIDs as a class would inhibit both the COX-1 and the COX-2 isoenzymes. The coxibs, however, would theoretically only inhibit the COX-2 isoenzyme.

The first coxibs to reach the market in the US were celecoxib (Celebrex), followed by rofecoxib (Vioxx) and valdecoxib (Bextra). Vioxx was by far the strongest inhibitor of the COX-2 isoenzyme. Merck documents indicate that Vioxx is at least 5 times more selective an inhibitor of the COX-2 isoenzyme than Celebrex. Research into this issue has determined that Vioxx has a nine times stronger inhibitor of the COX-2 isoenzyme than does Celebrex. This difference in selectivity is the most likely explanation for the difference in clinical findings concerning Celebrex and Vioxx.

III. THE PROBLEM WITH COX-2 INHIBITION: PROSTACYCLIN VS. THROMBOXANE

Cox-2 inhibitors are inherently prothrombotic. They can cause blood clots. Thromboxane (TXA₂) is a substance produced by platelets within the body that is associated with the COX-1 isoenzyme. Thromboxane is a potent platelet aggregator and vasoconstrictor. What this means in layman's terms is that the substance thromboxane will cause platelets to aggregate or to form substances such as blood clots or scabs. This is a necessary process within the body to prevent excess bleeding and to aid in wound healing. Thromboxane is also associated with the narrowing of the vasculature. The presence of this substance will cause blood vessels to narrow or constrict.

Conversely, prostacyclin (PGI₂) is a substance produced by the endothelium (the thin, flat layer of cells that line the interior surface of blood vessels) that is associated with the COX-2 isoenzyme. Prostacyclin acts in a way essentially opposite to thromboxane. Prostacyclin helps keep the blood "thin" such that it flows without forming clots or otherwise aggregating. Prostacyclin keeps the vasculature expanded and thereby aids in blood flow. Obviously then prostacyclin and thromboxane are offsetting and competing compounds that result in a homeostatic balance.

The theory behind the coxibs is that they would inhibit the body's production of the COX-2 isoenzyme while allowing the body to produce the gastro-protective COX-1 isoenzyme. A problem arises, however, when the body's ability to produce prostacyclin (a platelet inhibitor and vasoconstrictor) is

eliminated while the body's production of thromboxane (a platelet aggregator and vasoconstrictor) is not inhibited. The body's natural homeostatic balance is thereafter destroyed and the clotting agent thromboxane has no offsetting mechanism.

Accordingly then, a prothrombotic state is created within the body wherein a person's potential for developing a blood clot increases significantly. Blood clots are alleged to be the cause of the myocardial infarctions (heart attacks) and cerebrovascular events (strokes) associated with the use of the Cox-2 inhibitors Vioxx, Bextra and Celebrex.

IV. THE VULNERABLE USERS OF COX-2 DRUGS

The marketing of Cox-2 drugs was and is (in the case of Celebrex) focused on individuals suffering from osteoarthritis and rheumatoid arthritis. The vast majority of the populations with these ailments are elderly individuals. This same population also constitutes the vast majority of individuals suffering from atherosclerotic plaquing. Indeed, the majority of our elderly population, especially men, suffers from some degree of atherosclerosis.

Atherosclerosis can be viewed as the build up of lipids within the endothelial layer protecting the internal vasculature. These areas of atherosclerotic plaquing build up and over time can result in severe vascular blockages. Plaque build-up combined with the prothrombotic nature of the cox-2 inhibitors is a recipe for disaster. Thus, the very people most likely to take Cox-2 drugs are the ones most vulnerable to their inherent adverse effects.

V. THE RESULT

On September 30, 2004, one of the largest drug manufacturers in the world, Merck & Co., removed the blockbuster drug Vioxx from the market worldwide because data from a clinical trial found a significantly increased risk of heart attack and stroke associated with use of the drug. Following the Vioxx recall, questions arose about the other Cox-2 drugs on the market, Celebrex and Bextra, manufactured by Pfizer. On April 7, 2005, the FDA and European regulators formally asked Pfizer to suspend sales of Bextra in the United States and Europe. The FDA stated that the risks posed by Bextra outweighed its benefits. These include significant risks of heart attacks, strokes and a skin hypersensitivity disorder, Stevens-Johnsons Syndrome. Pfizer complied. Celebrex is the only Cox-2 inhibitor still on the market in the United States. However, at the same time Bextra sales were suspended, the FDA issued an alert indicating that Celebrex had been linked to an increased risk of serious cardiovascular events such as heart attack or stroke and required that Pfizer place the most serious warning available (a “black box” warning) on the drug and submit it to a long term study.

V. CONCLUSION

When commercial decisions get ahead of science, bad outcomes are not far behind. While evidence from clinical trials of the danger posed by Cox-2 inhibitors was mounting and becoming the subject of intense debate in the research community, intense marketing efforts were making these drugs the darlings of Wall Street. Sales climbed into the billions of dollars in the United States alone. When the alarm was finally heard, the resulting impact on public health was substantial.

