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DOES KILLING PAIN KILL THE HEART? The saga of Vioxx, Celebrex & Bextra
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For years it was simple - If you had arthritis, you took aspirin (and got ulcers and bruises) or steroids (and got ulcers, bruises and osteoporosis) to reduce inflammation and pain. All other pain killers didn't hit the cause of arthritis, so they generally weren't used for it.

Then came a slew of other **Non-Steroid Anti-Inflammatory Drugs (abbreviated NSAID's), <u>all</u>** of which worked against pain, fever and inflammation. Some were very strong, such as indomethacin and ketorolac, but the drug that works well for one person may not touch another - There is huge inter-person variability of response. Unfortunately, these drugs often destroyed the stomach. People died from ulcer bleeding.

So the search was on for an NSAID that didn't hurt the stomach. Initial attempts, in the form of Lodine and Relafen, helped, but were only half good. Then came the selective **COX2 inhibitors**, Vioxx (rofecoxib), Celebrex (celecoxib) and Bextra (valdecoxib). Compared to drugs like Alleve (naproxen), they **caused less than half the ulcers and stomach erosions**, seemingly filling a niche for people who could not take the usual NSAID's. (Please remember that they still caused ulcer disease - half as often, not zero - That fact usually gets lost in the hype.)

Though COX2 inhibitors were developed for those who can't take the non-selective anti-inflammatories, that's not who has blown the COX2 market into billions of dollars. Soon after initial marketing efforts, which responsibly directed physicians to prescribe appropriately, all pretenses of selectivity dropped. As the newest kids on the block, they were presumably somehow 'better' for pain (which they are not). Between 1999 and 2002, the prescription frequency of COX2 inhibitors increased dramatically, from 35% to 61% of all NSAID prescriptions. Even people who had virtually no risk of ulcer bleeding were prescribed COX2 inhibitors 35% of the time in 2002. **Thus, the growth of COX2 inhibitor use was largely due to patients who had no reason to take them.**

The fault doesn't lie 100% with the drug companies, though they did give a lot of samples to doctor's offices. With cupboards full of samples, well meaning doctors handed them to patients to get therapy started - "Try it for the pain, and if it works, fill the prescription." They couldn't do that with the older NSAID's -With most available in generic form, drug reps no longer sample them.

Then came trouble in COX2 paradise - Studies found more heart and vascular disease in patients taking COX2's. Even the initial trial of Vioxx against naproxen showed three times the cumulative risk of heart attacks (1.8% vs. 0.6%) in 10 months. Everyone assumed that the reason was that naproxen was *preventing* attacks, rather than Vioxx *causing* them. (Compared to the average Joe on no drugs, low-dose aspirin *prevents* heart disease. So people assumed that naproxen was acting similarly to aspirin.)

But ongoing studies (to see if COX2's prevent colon cancer and Alzheimer's disease, for example) have confirmed that, regardless of what drug is used for comparison, **COX2's increase the risk of vascular/heart disease.** (With Celebrex, the least selective COX2, the risk is dose related - 100 mg/day seems to be safe, 200 mg/day is still safe, but double's the risk (from .003 to .006) and 400 mg/day triples it.)

Logical, scientific reasons explain this. COX stands for cyclooxygenase, an enzyme that makes prostaglandins in various tissues. There are two forms, COX1 and COX2, which produce different prostaglandins, with different functions, in different tissues. COX2 products cause pain and inflammation in joints. They also relax and keep open blood vessels in the heart, kidney and all over the body. Use COX2 inhibitors and lose the joint pain, at the expense of constricted blood vessels, potentially causing heart attacks and kidney failure.

COX1 products from blood platelets make them clot easily and blood vessels close. In the stomach COX1 products protect the stomach from acid and ulcers. Inhibit COX1 and your heart disease risk is less, at the expense of stomach upset.

The punch line: All the non-selective NSAIDS, like ibuprofen and naproxen block both COX1 and COX2, but not all NSAID's block the two enzymes equally. THIS IS WHY ALL THE NSAID's ARE NOW BEING QUESTIONED BUT SOME ARE BETTER THAN OTHERS. **The only heart-safe NSAID is low-dose aspirin** (81 mg/day), with relatively more opening-blood-vessels effect than closing-blood-vessels effect, so it protects against heart disease.

YOUR CHOICE depends on YOUR risks and degree of pain. If you can't move or sleep due to severe arthritis, you stand to gain more from taking any NSAID, as opposed to the weekend warrior with a twinge in the knee, who might survive with a grin and bear it.

Risks are always relative. People are different. While the studies that caused all this hoopla showed cardiovascular risk, not all people who took the drugs keeled over from a heart attack or stroke. As yet, we just don't know how to predict which people will. "Only" one in five people on long-term NSAID's suffered from ulcers in 1988, prior to the selective COX2s' appearance. While not 100"%, often stomach upset heralds the onset of ulcer and should be heeded by stopping the drug. Some, but not all people with familial colonic polyps will be protected by aspirin- with no way to predict which will. Very few patients end up on NSAID-induced dialysis from kidney failure, but people with heart failure, cirrhosis, old age, or pre-existing kidney disease are more likely to. Your decision depends on your odds of risk and benefit.

Alternatives:
1) aspirin or naproxen (which is actually more like aspirin in the effects on the heart than the others) plus a drug (ask your doctor) to block stomach acid - a recent study showed as little ulcer disease with this as with a COX2 drug;.
2) acetaminophen (Tylenol) or glucosamine for pure pain relief;
3) specific medications for rheumatoid arthritis, if appropriate;
4) low dose COX2 inhibitor plus a baby aspirin (the blood vessels still tend to constrict, but at least something is blocking the platelets), if OK with the stomach