



PHARMACY Update

SANTA BARBARA REGIONAL HEALTH AUTHORITY



Update from the Pharmacy and Therapeutics Committee October 2004

More on the Removal of Vioxx from the Market:

The jury is still out on the cardiovascular safety of selective COX-2 inhibitors. Two studies raise big questions, as well as highlights how we may use these agents. In the Vioxx GI Outcomes Research (VIGOR) study, RA patients who received rofecoxib had significantly fewer GI events and more MI's than patients who received naproxen. It is unclear if this result was attributable to more harmful effects of Rofecoxib, cardio protective effects of naproxen, or other factors. In the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), patients with OA were randomly assigned to groups that received lumiracoxib (available in the UK), naproxen, or ibuprofen for 52 weeks. Several important findings were found among the groups. Patients not taking low-dose aspirin in the lumiracoxib group had fewer GI events than did the naproxen and ibuprofen groups. Among patients taking low-dose aspirin in all three groups, there weren't any significant differences in GI events. Patients in the ibuprofen and lumiracoxib groups had a similar incidence of combined cardiovascular events (MI, stroke, and cardiovascular death). Compared to patients in the naproxen group, the patients in the lumiracoxib group had a trend (not statistically significant) toward more MIs that was more noticeable in the patients that did not receive the low-dose aspirin.

Two important conclusions can be made from these large studies:

1. The GI protective effects of selective COX-2 inhibitors is lost in patients taking low-dose aspirin and there is little reason to prescribe these expensive agents over less expensive NSAIDs in patients that are taking low-dose aspirin
2. Similar trends towards higher MI rates in the lumiracoxib versus naproxen and rofecoxib versus naproxen study cause concern for some of the selective COX-2 drugs.

We want to clarify that both Celecoxib (Celebrex) and Valdecoxib (Bextra) have sulfonamide side chains on their ring structures and therefore both should not be used in patients with a history of sulfur allergy.

Therapeutic Issue: Impact of NSAIDs on Aspirin Cardio protective Effects

There is a need to clarify some of the issues surrounding the use of NSAIDs in patients who are also taking low-dose aspirin. What are the effects of NSAIDs on platelets: 1) Nonselective NSAIDs inhibit platelet function and prolong bleeding time; 2) The effect of individual NSAIDs on platelet function is reversible and determined by the specific NSAID clearance and half-life; 3) Ibuprofen appears to have the greatest effect on inhibiting the effect of aspirin on platelets and is dose schedule related (400mg given concurrently with aspirin will negate the effect of aspirin on platelets, no impact if given 2 hours before the dose of aspirin whether once daily for three times daily); and 4) acetaminophen, diclofenac (generic Voltaren) and Celebrex appear not to impact the effect of aspirin on platelet function. The data is summarized in 4 studies in the table below.

Citation	Methods	Results
TM McDonald Lancet 2003;361:573	Prescription database	Increased cardiovascular mortality in the group that took ibuprofen with aspirin
SE Kimmel J AM Coll Cardio 2004;34:985	Case control study	Twice the incidence of first non-fatal MIs in the ibuprofen aspirin group versus aspirin alone
TN Patel Arch Inter Med 2004;164:852	Record based study	No increase in incidence of MIs
T Kurth Circulation 2003;108:1191	Physicians Health Study	Higher incidence of the first MI amongst patients on aspirin and regular NSAIDs

Conclusions:

1. Regular use of ibuprofen appears to interfere with the antiplatelet effects of aspirin
2. Ibuprofen should be avoided in patients taking aspirin
3. Alternative agents include: acetaminophen, diclofenac, and Celebrex
4. There is insufficient data on other NSAIDs and the impact on aspirin effect on platelets

New Drugs

The Pharmacy and Therapeutic (P and T) Committee recently reviewed tiotropium (Spiriva – Boehringer Ingelheim). Spiriva is a long-acting anticholinergic drug and is approved for the daily maintenance treatment of bronchospasm associated with COPD. Tiotropium has several advantages over ipratropium (Atrovent) and long-acting beta agonists e.g. salmeterol. Tiotropium dissociates slowly from the M1 and M3 muscarinic receptors. Of these, M3 is the most important as it blocks the final association between acetylcholine and its receptor thus resulting in prolonged bronchodilation. A more extensive review of tiotropium will be coming in the next months. Therefore, we will summarize the findings of the P and T Committee below:

1. Tiotropium as an inhaled powder reaches peak in about 3 hours and lasts for more than 24 hours
2. The bronchodilator effect reaches maximum in about 8 days
3. Clinical trials demonstrate that tiotropium increases trough FEV1, just prior to the next dose and after the first dose, which persisted for the duration of the one year study period. This increase was not demonstrated by ipratropium or salmeterol.
4. Tiotropium decreases the number of COPD exacerbations per patient year, number of hospital admissions, and dyspnea; improved QOL scores; and produced greater improvement in FEV1 than placebo. This is contrast to salmeterol, which was superior to the placebo only in decreasing FEV1 and decreasing dyspnea.
5. The most common adverse effect is dry mouth. Patients should be instructed to rinse their mouth with water after administration to reduce this effect.
6. The dosage is one inhalation per day.
7. Medical Letter “Consultants consider this an important advance in the treatment of this disease”
8. Cost is about \$100 per month versus Advair at about \$140 per month

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