September 2015
Issue 10

RPCC Pharmacy Forum

Special Interest Articles:

- NSAID Cardiovascular Risk
- Enestro
- Methylene Blue

Did you know?

The hypothyroid drug levothyroxine (Synthroid) was the most prescribed drug in the United States, and adalimumab (Humira) was the highest grossing drug through March of 2015. Levothyroxine had about 21.6 million prescriptions, while Humira had $8.3 billion in sales.

Laura Read RPh, CSPI
(laura.read@childrensal.org)

FDA Stiffens Warning on NSAID Cardiovascular Risk

After a comprehensive review of new safety information, the FDA is requiring updates to the labels of all prescription NSAIDs to reflect recent information on risk of heart attack and stroke. Over-the-counter non-aspirin NSAIDs already contain some safety information, but the labels on these drugs will also require an update, said the FDA in its announcement posted online. Labels will now state that NSAID-associated cardiovascular risk can occur in the first weeks of use, the risk may increase with duration of use, and higher doses appear to confer greater risk. In addition to hypertension and heart failure—concerns with all NSAIDs—these agents seem to increase the risk of cardiovascular events (myocardial infarction, stroke, death) to varying degrees, even in healthy people. Adverse cardiovascular events associated with NSAIDs are thought to be caused by NSAIDs upsetting the balance between vasoconstricting, platelet aggregating thromboxane A2 (produced by COX-1) and opposing vasodilating prostacyclin (produced by COX-2). This may lead to vasoconstriction, platelet aggregation, and thrombosis. NSAIDs that are more COX-2 selective could therefore be assumed to have more cardiovascular risk. NSAIDs that provide sustained COX-1 inhibition (e.g., naproxen) may pose less cardiovascular risk. Ibuprofen (up to 1200 mg/day-OTC) is the recommended NSAID in individuals with a low risk of CV events with a low gastrointestinal risk. In patients with a high risk for CV events and a need for an oral NSAID, naproxen would be recommended. Results from a large study that should shed more light on the risks involved are expected in 2016.

New Heart Failure Drug- Entresto

Entresto is a new drug indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure. It's the first "angiotensin receptor neprilysin inhibitor" (ARNI) and combines valsartan (angiotensin receptor blocker or ARB aka ACE II) with sacubitril (sah-KYOO-bih-tril). Sacubitril works by inhibiting the enzyme neprilysin. This increases sodium loss and vasodilation and enhances ARB efficacy. In one large trial called PARADIGM that involved 8,442 patients, researchers gave half the patients Entresto and half enalapril. They found those on Entresto had a 20 percent reduction in risk of death or hospitalization. The results were so promising that the FDA granted it fast-track designation.

The FDA said that the main side effects were hypotension, high blood potassium levels and kidney impairment. FDA also said there were cases of angioedema.

"When MetHgb levels increase, the blood is less efficient in circulating oxygen."

."

What is Methylene Blue?

Methemoglobin is a form of hemoglobin. Hemoglobin's function is to carry oxygen and distribute it to tissues and organs. However, methemoglobin (MetHgb) is not useful in carrying oxygen. MetHgb normally exists in small amounts in the blood. When MetHgb levels increase, the blood is less efficient in circulating oxygen. The resulting lack of oxygen throughout the body can cause symptoms such as pale or blue-colored skin. Methemoglobinemia is a condition in which MetHgb is present in high levels in the blood. Methylene blue is a thiazine dye that increases the conversion of MetHgb to hemoglobin. The enzymes cytochrome B5 reductase (or methemoglobin reductase) and nicotinamide adenosine dinucleotide phosphate (NADPH) convert methylene blue to leukomethylene blue, which then reduces MetHgb. Glucose-6-phospate dehydrogenase (G6PD) is essential for the generation of NADPH and is therefore essential for methylene blue as an antidote. Treatment with methylene blue is ineffective and may cause hemolysis in G6PD deficient patients. Methylene blue is a monoamine oxidase inhibitor-A (MAO-A inhibitor), so therefore should not be given with other MAO inhibitors (e.g.Marplan, Nardil). Many other drugs also interact with methylene blue- meperidine, ADHD medication, migraine medication, Requip, SSRI's and TCA's. Serotonin syndrome is a potential risk when methylene blue is administered with other serotoninergic drugs. Drugs that are capable of inducing methemoglobinemia include local anesthetics, antimicrobials (dapsone, sulfonamides), analgesics (phenazopyridine), nitrites and nitrates (nitroglycerin) and other miscellaneous drugs, such as, metoclopramide.