Pharmacology 203

Windward Community College

Non-opioid Analgesics

NSAIDs, Acetaminophen, Biologics

This lecture covers an assortment of drugs

In the opioid lecture, we looked primarily at the treatment of severe visceral pain. The drugs covered here are used to treat most kinds of musculoskeletal pain.

NSAIDs work by inhibiting cyclooxygenase (COX)

The NSAIDs all inhibit an enzyme called COX. COX transforms Arachidonic acid into a variety of prostaglandins and thromboxane. Arachidonic acid is just one of many fatty acids that combine with a phosphate to make a phospholipid, part of the phospholipid bilayer that makes up all membranes in our bodies. This Arachidonic acid is a precursor, a substrate, used to make chemicals the cell uses in cell signaling. Most of the prostaglandins are “pro-inflammatory” meaning they promote the processes of inflammation, but some are anti-inflammatory. The mixture of pro- versus anti-inflammatory chemicals is determined in large part by our diet. The more omega-3 fatty acids in the diet, the more anti-inflammatory prostaglandins are synthesized.

Rheumatoid arthritis is an autoimmune condition typically treated with disease-modifying drugs, biologics or something like methotrexate, an anticancer drug we will cover with cancer.

Osteoarthritis is due to the wearing down of the cartilage cushion at the ends of bones in a joint. This leads to inflammation and pain. Osteoarthritis is typically treated with the NSAIDs we will cover in this lecture.

Corticosteroid anti-inflammatories may also be part of the treatment package for either condition. We will cover corticosteroids with autoimoids, cancer, and the lung drugs.

Migraine pain is a challenge therapeutically due to the diverse nature of migraine causes. The triptans, β blockers, NSAIDs, Ergot alkaloids, caffeine, opioids, corticosteroids, antidepressants, antiepileptic drugs, antihistamines, and botox all have applications in the treatment of migraine.
NSAIDs are…

**Antipyretic**
- They block PGE synthesis in CNS

**Analgesic**
- They are mild analgesics that work best before inflammation begins
- They are best for musculoskeletal pain

**Anticoagulant**
- They are antiplatelet anticoagulants, they block the synthesis of thromboxane by platelets. TXA is critical for platelet aggregation.

**Anti-inflammatory**
- They inhibit COX the enzyme responsible for PG synthesis. Many prostaglandins are mediators of inflammation (pro-inflammatory).

**Non-steroidal**

**Non-opioid**

**Not Acetaminophen!**

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**Reyes Syndrome**

In sub-adults, aspirin can cause a syndrome of severe liver damage and encephalopathy when given during a viral infection, especially influenza or chickenpox (Varicella zoster virus). While unclear, what may occur is that the virus alters the sensitivity of mitochondria to aspirin.

Kids with any viral infection, especially influenza or chickenpox should not receive aspirin.

This warning is on ALL aspirin products!
NSAIDs

Aspirin as we know it has only been around for just over 100 years, but salicylates, especially from willow tree bark, have been used for millennia to treat fever and pain. Bayer was the 1st company to commercialize acetylsalicylate, which they named Aspirin, in 1899. Acetaminophen came on the market in 1956, Ibuprofen in 1969 (in the UK), both of which revolutionized the treatment of arthritis and fever.

Aspirin is the most widely used analgesic in the world, accounting for more than 20 tons/year in the US alone! It betters the opioids in that it does not lead to tolerance or addiction, and the risk of toxicity is lower, but it is ineffective against severe pain or pain affecting the viscera (other than menstrual cramps).

About 10% of people taking aspirin will develop Aspirin-Exacerbated Respiratory Disease (AERD), which is a type of asthma characterized by wheezing and nasal congestion. The onset is 30 minutes to 3 hours after taking aspirin. Continued use of aspirin in aspirin-intolerant patients will lead to the growth of nasal polyps.

Such patients will typically cross-react with other COX-1 inhibiting NSAIDs such as ibuprofen. It appears to be caused by an increase in leukotriene synthesis due to the inhibition of COX (which results in more Arachidonic acid available to make leukotrienes). These patients have higher levels of leukotrienes than non-reacting patients even without taking NSAIDs. AERD is also known as Samter’s Triad¹.


http://www.hindawi.com/journals/ja/2012/473863/

“Neuralgine” actually toxic acetanilide

Originally used in the dye industry, acetanilide was accidentally discovered in the 1880’s to be antipyretic and analgesic (because of workplace exposures).

Acetanilide is metabolized to acetaminophen in the body. It is actually the acetaminophen that is antipyretic and analgesic.

However, acetanilide is also metabolized to another compound known to cause cyanosis secondary to methemoglobinemia. Above a certain ratio of Methemoglobin to normal hemoglobin, the affected red blood cell (RBC) is removed, resulting in hemolytic anemia.

Methemoglobin is the oxidized (ferric) form of hemoglobin and does not carry oxygen (well). It is normally reduced to the ferrous state by enzymes in the RBC. Methylene Blue can be used to reduce methemoglobin back to the ferrous state.
**Ibuprofen (Advil).** Unlike aspirin, reversibly inhibits COX-1, but is just as effective as an analgesic, antipyretic, anti-inflammatory agent. It can cause toxic amblyopia or other ocular disturbances, and patients should be instructed to discontinue using ibuprofen if they experience any vision abnormalities.

**Celecoxib (Celebrex)** is a COX-2 inhibitor. COX-2 is only expressed during inflammation, so the COX-2 inhibitors are ineffective antiplatelet anticoagulants. Celecoxib is very effective at reducing colorectal polyps in familial adenomatous polyposis as well as providing relief from the pain and inflammation associated with arthritic conditions.

**Acetaminophen (Tylenol) is not an NSAID!** It is not particularly anti-inflammatory and is not antiplatelet at all. It is effective as an analgesic to replace aspirin and as an antipyretic.

Acetaminophen is also known by the acronym APAP (N-acetyl-para-aminophenol), and overseas, by the name Paracetamol. You should know all these names.

APAP is metabolized to a toxic metabolite that destroys the liver. It is the number 1 cause of acute liver failure in the US and Europe and is a common cause of accidental death due to overdose. In normal adults, no more than 1 gram (1,000 mg) per dose should be administered, and no more than 4 gm/day. In alcoholics and other sensitive populations, no more than 2 gm/day should be given to avoid toxicity.

The Institute for Safe Medication Practices (ISMP) reports at least one hospitalized patient/day is poisoned with APAP.

The drug **N-acetylcysteine (Mucomyst, Acetadote)** is used in cases of overdose in an attempt to save the liver, though timing is critical. We will cover this drug in the Respiratory pharmacology section.

John Nicholson, one of the discoverers of ibuprofen

2011 marks the 50th anniversary of the discovery of ibuprofen.

Dr Stewart Adams OBE was the scientist whose research lead to the discovery of the cyclooxygenase inhibitor. When Dr Adams discovered ibuprofen, he was working as a pharmacologist in the Research Department for the Boots Pure Drug Company Ltd.

Dr Adams was assigned to work on rheumatoid arthritis (RA) and chose in 1953 to search for a drug that would be effective in RA but would not be a corticosteroid. He was one of the first researchers of drugs that later became known as NSAIDs (Non-Steroidal Anti-Inflammatory Drugs).

In 1961, Dr Adams with John Nicholson, an organic chemist, filed a patent for the compound 2-(4-isobutylphenyl) propionic acid, later to become one of the most successful NSAIDs in the world, ibuprofen.
The next type of anti-inflammatory we will cover is a biologic. Biologics are drugs (or vaccines or antitoxins) that are synthesized in a living organism. You should also be aware of the term “biosimilar,” which is a “generic” version of a biologic. As well as “biobetter,” which is a recombinant protein drug in the same class as an existing biologic, but is not identical and has improved performance characteristics.

Biologics are often “disease-modifying” drugs.

The biologic, “Remicade” (infliximab) is a tissue necrosis factor alpha (TNF α) inhibitor and was the number 2 best selling drug in the US in 2011.

TNF α is a cytokine produced mainly by activated macrophages to regulate the activity of other WBCs involved in acute phase inflammation. It promotes the synthesis of PGE to induce fever, interleukins involved in the production of sepsis, and other cytokines involved in triggering apoptosis, cachexia and other processes related to systemic inflammation. An interesting effect of TNF α is its role in the anti-tumoral and anti-viral responses of the immune system as it is used by WBCs to trigger apoptosis of these affected cells.

Etanercept (Enbrel), like infliximab, is also a TNF α inhibitor and a monoclonal antibody (note, however, the stem: “mab” is not present). Etanercept is an isotype of IgG that acts as the plasma receptor for TNF α and inactivates the factor. It is immunosuppressant and causes increased susceptibility to infectious disease and malignancies, however, it has wide usage in rheumatology and may have indications to treat other diseases including Alzheimer’s.

Hyaluronic acid (Hyalgan) is a glucosaminoglycan normally found in connective tissue (as collagen). It is also in synovial fluid as a lubricant. Hyaluronic acid has been obtained at slaughterhouses as well as a biologic produced by recombinant DNA technology in bacteria. It is used in osteoarthritis as an injection into the joint to improve lubrication and it is formulated into a variety of skin treatments (including wound dressings) that are available as topicals or subcutaneous injections.

http://www.drugs.com/pro/hylase-wound-gel.html

http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=0d68f35d-75c8-45fe-9d3dc4a2c41b

GOUT

Colchicine is a natural product used for centuries to treat gout.

Allopurinol (Zyloprim) is used to treat chemotherapy-induced hyperuricemia (CIH), gout, recurrent renal calculi and other hyperuricemic conditions.

Rasburicase (Elitek) is only used for CIH, but is a very important drug in cancer therapeutics.

Probenecid (Benuryl) is a gout drug used perhaps more frequently to increase the half-life of other drugs, most notably many penicillin antibiotics.
Using Probenecid to slow renal secretion of drugs

Probenecid is uricosuric, which means it decreases the serum uric acid levels which become elevated due to gout. It does this by blocking renal tubular transport and thus, the reabsorption of urate, leading to increased urinary excretion of uric acid.

It may also be useful to manage hyperuricemia secondary to other conditions, for instance following thiazide or loop diuretic use. But it is not useful to treat CIH, or elevated uric acid levels following radiation therapy or due to cancer.

It inhibits the tubular secretion of penicillin and will increase penicillin plasma levels by any route the antibiotic is given. This is true for a number of other drugs as well.

Aspirin also inhibits renal tubular secretion, but does so by a different mechanism that will cancel out the effect of Probenecid. The two should not be given together.

Homework and Exercises

1. Read the “START HERE” announcement in Laulima for updates and instructions.
2. Read about non-Opioid analgesics in Chapter 44 Pharmacology of Inflammation and Fever. Adams & Urban, PHARMACOLOGY Connections to Nursing Practice.
3. Review the Powerpoints and listen to the audio from the face-to-face lecture. You may opt to watch the appropriate videos for this lecture. Review any handouts available for this lecture in the Course Index.
5. Use “Chat,” “Discussions and Private Messages” or the lecture “Forum” to ask questions and find answers or to seek assistance.
6. Complete the online quiz in Laulima, Tasks, Tests and Surveys.

If you have any questions, email me at abeale@hawaii.edu