Effects of Rheumatic Drugs

People of all ages, including children and young adults, can develop arthritis. Arthritis is a disease which can affect anyone at anytime. Although it is a disease which can cause severe problems, many things can be done to help those who are affected. Exercise, hot/cold treatments, and medications can aid in relieving the effects of rheumatoid arthritis. Presently there is no cure. This essay will be focused on rheumatoid arthritis, typically prescribed medications, and the problems associated with these medications.

Arthritis literally means joint inflammation. A joint is any place in the body where two bones meet. The ends of the bones are covered by cartilage. Cartilage is a tough, elastic tissue which acts as a shock absorber. It also prevents bones from rubbing against each other. The entire joint is enclosed in a capsule that is lined by an inner skin known as the synovial membrane. The synovial membrane releases drops of a fluid (synovial fluid) into the small space between the two bones. The synovial fluid nourishes the cartilage and keeps the joint lubricated, making movements smooth and easy. Outside of the joint are muscles, tendons, and ligaments. These provide support and help the bones move. The numerous forms of arthritis belong to a larger group of diseases called rheumatic diseases. Rheumatic diseases include those that affect the joints or other supportive tissues.

Rheumatoid arthritis is a "disease of articulating joints in which the cartilage and bone is slowly eroded away." It is a disease that causes inflammation and loss of

movement necessary for daily activities. It is usually chronic, meaning that it can go on and off for up to a lifetime. Rheumatoid arthritis affects between one and two percent of people worldwide. It is a painful, crippling disease in which joints become swollen and are gradually destroyed by the body's immune system. As the disease progresses, treatments become more severe. If joints become deformed, the best option is surgery and artificial joints.

A theory to explain the onset of rheumatic symptoms is that a T-lymphocyte that recognizes an antigen in the synovial membrane surrounding the joints is triggered. Whether the antigen is foreign (like a viral protein or protein from host's body) is still unclear. But this single event triggers a response that attracts a range of immune cells and potent chemicals. These chemicals (cytokines) are the messengers of the immune system and include interferons, interleukins, and TNF (tumour necrosis factor). Interleukins induce bone and cartilage destruction. In rheumatoid arthritis, these processes are turned against the joint.

Inflammation is the reaction of the body that causes swelling, redness, pain, and loss of motion in an affected area. It is the major physical problem in most forms of arthritis. Normally, inflammation is the way the body responds to an injury or to the presence of disease agents such as viruses or bacteria. During this reaction, white blood cells are rushed to the injured area to fix the problem, clean up damaged cells, and repair damaged tissues. However, in arthritis, inflammation doesn't go away. Instead, it damages healthy tissues which may lead to more inflammation and more damage. The damage that occurs can change the bones and other tissues of the joints, sometimes affecting their shape, often making movement difficult.

Pain signals are sent through a complex system of nerves in the brain and the spinal cord. The body tries to stop these signals by creating endorphins (morphine-like painkilling substances that decrease the hurting sensation). The body also produces endorphins in response to outside controls such as exercise, massage, heat/cold treatments, or most effectively, medicine.

The types of treatment an arthritic patient receives depends on several factors including the type of arthritis, how it affects the person, how severe the disease is, which joints are affected, the patient's age, occupation, and daily activities. Treatment programs are individualized, but most include some combination of rest, exercise, methods of protecting the joints, and medication. The different parts of the program complement the others and together they help reduce inflammation, minimize damage to joints, and improve joint movements. Many different drugs are used in treating arthritis. They range from the typical non-steroidal anti-inflammatory drugs (NSAIDs) to more advanced drug therapy.

Over the last two decades, NSAIDs have become an integral part of therapy for rheumatic disease. NSAIDs help inhibit the enzymes which are required to produce prostaglandins. Prostaglandins stimulate inflammation, regulate blood flow to certain organs, control ion transport across membranes, modulate synaptic transmission, and induce sleep. They are 20- carbon fatty acids containing a 5-carbon ring. They alter the activities of cells in which they are synthesized and of adjoining cells. There are two activities of Prostaglandin H Synthase: cyclooxygenase and peroxidase. The anti-inflammatory properties of this NSAIDs reside in its ability to inhibit cyclooxygenase. Cyclooxygenase is a major enzyme in the biosynthesis of prostaglandin from arachidonic

acid. By inhibiting cyclooxygenase, there will be fewer prostaglandins produced, resulting in decreased inflammation and less drowsiness.

To reach the active site of prostaglandin synthesis within inflammatory cells, NSAIDs must be distributed to the extravascular compartment. Passage across the vascular endothelium can be through gaps between the endothelial cells or by diffusion through them. Normally the gaps between endothelial cells are small. They allow only a limited amount of solutes in and out and they restict the loss of protein. The presence of inflammation weakens the endothelial barrier, and the wider gaps allow the extraction of water, molecules, and proteins. Diffussion of NSAIDs into the cell is dependent on the concentration gradient across the plasma membrane. For acidic NSAIDs, decreasing the pH enhances transport across the lipid membrane. Where pH gradients exist across lipid membranes, ionizable molecules are subject to ion trapping. The non-ionized form will equilibrate across the membrane and will move down its concentration gradient into the high pH compartment where it will be ionized. More non-ionized drug is then pulled across the membrane and this process continues until equilibrium is reached. Ion trapping of NSAIDs within cells occurs in situations where the pH of the extracellular fluid is lower than the intracellular fluid. For example, the gastric mucosa has the largest pH gradient in the body and is therefore a prime site for NSAID trapping. These drugs accumulate in the cells of this tissue and produce a prolonged reduction in prostaglandins.[5] These findings suggest a possible explanation for gastric toxicity.

There are four main types of NSAIDs: salicylates, acetic acid derivatives (indomethacin, tolmentin sodium, sulindac), propionic acids (naproxen, ibuprofen), and others that do not fit into a single group.

The first type of NSAID is salicylate. Salicylic acid is used chiefly in the preparation of several important esters and salts. One medicinal salicylic compound used as analgesics is acetyl salicylic acid--which is also known as aspirin. Aspirin is the prototype NSAID and is still in common use. It has been used for centuries to decrease inflammation, pain, and fever. Aspirin irreversibly inhibits the cyclooxygenase activity of this enzyme by acetylating a specific serine hydroxyl group.[1]

The second type of NSAID is any acetic acid derivative. These include indomethacin, tolmetin sodium, and sulindac. Indomethacin reduces stiffness, and inflammation. However, it has several serious side effects. These include gastrointestinal disorders, severe headaches and dizziness, and it may mask the symptoms of infections. Tolmetin sodium does not help cure the disease but helps with pain and inflammation. It may be given in conjunction with the slow acting drugs (which will be discussed later) to reduce symptoms while the slow acting drugs take effect. Adverse effects of tolmetin sodium, occur less frequently and are rarely serious. However, it can cause fluid retention leading to the swelling of ankles, and is used with caution on the elderly. (Caution is taken with the elderly due to the fact that advanced age is a factor associated with the risk for NSAID induced gastro-intestinal bleeding.) A third acetic acid derivative is sulindac. Sulindac may be preferred to other NSAIDs for long-term use because it requires only two doses per day. Common side effects are indigestion, nausea, diarrhea, and constipation. There is also a risk of stomach bleeding or peptic ulcer.

The third type of NSAID is propionic acid derivatives including naproxen, ibuprofen and fenoprofen. Naproxen is used to relieve symptoms of rheumatoid arthritis. It is also taken with other anti-rheumatic drugs to relieve inflammation while the other

drugs take effect. Gastrointestinal side effects are fairly common, and there is an increased risk of bleeding. It is safer than aspirin and only needs to be taken twice a day. Ibuprofen is a more widely used drug. It is similar to aspirin in the way it works and in the way it can be used. Because it acts as an analgesic as well as an works only as an analgesic because it can only aid in producing anti-inflammatory, it is an effective treatment for the symptoms of rheumatoid arthritis. Ibuprofen has fewer side effects than other NSAIDs and unlike aspirin, it rarely causes bleeding in the stomach. Fenoprofen is one of the newest NSAIDs. It has similar side effects of other NSAIDs including a risk of a peptic ulcer.

The fourth type of NSAID is actually a category of the other drugs that do not fit in the above three groups. This group also includes some of the newest medications. The newest anti-inflammatory and analgesic agent to be introduced in the U.S. is Piroxicam. Piroxicam appears to be the equivalent of apirin, indomethacin, propionic acid derivatives, or naproxen for long term treatment. It is tolerated better than aspirin or indomethcin. Its mechanism of action is also through prostaglandin synthesis inhibition. Piroxicam is completely absorbed after being ingested. Its mean value of plasma half-life is 45 hours. This is the principal advantage of piroxicam. Its long half-life allows the patient to take it only once a day. It is shown to be the most effective drug in prolonged treatment of rheumatic disorders.[6]

Nitric oxide has been implicated as a mediator of the inflammation in rheumatic and autoimmune diseases. It is synthesized by inducible nitric oxide synthase (iNOS). The generation of nitric oxide by inducible NOS plays an important role in inflammation,

host-defense responses, and tissue repair. Nitric oxide formation is increased during inflammation. Several classic inflammatory symptoms are reversed by NOS inhibitors.

Overall, NSAID therapy carries a low incidence of significant complications. Gastrointestinal toxicity is by far the most common adverse effect and is generally of a mild degree. Less frequent, but potentially serious, is renal toxicity. Renal complications make up six categories. They are acute renal failure, interstitial nephritis and naphrotic syndrome, papillary necrosis, water retention, sodium retention, and hyperkalemia.

Acute renal failure is the most common renal complication described with NSAID therapy. It occurs most often in salt-depleted individuals and in patients with intrinsic renal disease. The renal insufficiency that occurs is generally reversible within 24 to 72 hours. Indomethacin is the most common drug associated with this syndrome. Patients with interstitial nephritis/nephrotic syndrome did not necessarily have antecedent renal disease. By discontinuing the intake of NSAIDs, clinical manifestations are usually resolved. This syndrome is usually associated with propionic acid derivatives. Papillary necrosis is a chronic renal injury that is most commonly thought to result from analgesic abuse, particularly from those preparations containing phenacetin. It has also been reported in adults on multiple-drug therapy. Substantial evidence indicates that renal prostaglandins may impact water balance and regulation. When renal prostaglandin synthesis is decreased by NSAID therapy, excretion of water may be limited and can result in severe hyponatremia. The hyponatrmia is usually resolved with discontinuation of the drug. Sodium retention represents a much more universal side effect of NSAID therapy and essentially all NSAIDs have been implicated. The promotion of sodium uptake by the renal tubules as a result of prostaglandin synthesis inhibition is the major

influence. Sodium retention has been described in normal humans treated with aspirin and indomethacin. Hyperkalemia has been found in patients who received indomethacin. A defect in the cellular uptake of potassium may also contribute to the development of this particular syndrome. In order to try to prevent all of these complications of NSAID therapy, physicians must monitor clinical parameters such as blood pressure, weight gain, hydration level, laboratory tests (such as urinalysis and electrolyte and BUN-creatinine levels). If these complications develop, discontinuation of NSAID therapy should be considered. NSAID therapy should not be resumed as long as renal abnormalities persist.

Researchers are presently in search of improving NSAID effects. They say that we can anticipate a trend toward the use of less toxic NSAIDs with proven clinical efficacy.[4] The ideal NSAID would have a lower incidence of gastrointestinal and renal side effects, a superior antiinflammatory effect, and would be safe for the elderly to ingest. Also, agents with a lower degree of cyclooxygenase inhibitor activity may have the potential for fewer side effects.

Although rapidly acting therapy in the form of salicylates or NSAIDS may adequately subdue arthritis activity, some patient's disease may still progress. They may need drugs which require more aggressive intervention, especially if remission, and not just disease control is the ultimate goal. Clear guidelines indicating when advanced therapy should be introduced after failure of first-line therapy have not been established. In general, advanced therapy should be considered if arthritis progresses despite sequential trials of three rapidly acting NSAIDs during a six to nine month period. Often, first-line treatment is continued together with advanced drugs. "Disease-modifying anti-rheumatic drug" is a term that refers to any medication that is known to retard or halt the

progression of a rheumatic disease.[1] The term refers to more advanced drugs that are used to alter substantially and favorably the natural course of rheumatoid arthritis and aid in inducing remission. These advanced (or slow acting) drugs include sulfasalazine, antimalarial agents, gold, penicillamine, methotrexate, and corticosteroids. These drugs work by impeding or interrupting the progression of rheumatoid arthritis.

Rheumatoid arthritis was once thought to be caused by an infectious agent. Due to the fact that salicylates provided anti-inflammatory effects, a compound was made that combined the antibacterial properties of sulfonamides with the anti-inflammatory properties of salicylates. Sulfapyridine and 5-aminosalicylic acid were linked by an azo bond to create sulfasalazine. In the colon, the azo bond is broken in the presence of bacteria. This process releases sulfapyridine and 5-aminosalicylic acid. Sulfapyridine is almost completely absorbed and either excreted by the kidneys or metabolized by the liver. Only a small amount of 5-aminosalicylic acid is absorbed and is therefore unable to contribute any useful effects toward relieving rheumatic symptoms. The sulfapyridine is the part of the compound which is responsible for the therapeutic effectiveness. Its mechanism of action is unknown but antibacterial and antiinflammatory effects may have been suggested. At first, it seemed as if sulfasalazine was quite effective in adult rheumatoid arthritis. But a later study showed that there was no difference between its effects and those of a placebo.[2] Therefore, this drug became disfavored as a treatment for arthritis. Recently, this drug has been studied and has been shown to have beneficial results similar to the original results. Sulfasalazine may be safer than other advanced agents, but it does exhibit serious adverse effects. These include gastrointestinal

disturbances (hepatotoxicity) and neurologic abnormalities (mood changes, depression, or irritability).

After success in treating lupus patients with antimalarial agents, studies began on treating rheumatic diseases with antimalarial agents. It was found that antimalarial therapy helped to reduce cartilage destruction by inhibiting enzymes (including collagenases). "In general, the studies of antimalarial efficacy in adults with rheumatoid arthritis suggest that these agents favorable alter the course of the disease. However, the effect is slow, taking anywhere from three to six months for results. The most serious adverse effects are ocular. "Dose-related corneal deposition of the drug, which is usually reversible, can occur."[2] Eye examinations should be performed at three month intervals.

A third type of advanced drug therapy is gold. "The usefulness of gold for the treatment of rheumatoid arthritis was a serendipitous discovery and followed [findings] that gold inhibited the growth of *Mycobacterium tuberculosis*."[2] The belief that rheumatoid arthritis was related to tuberculosis promoted treatment with gold. Reports of improvement in the symptoms and signs of arthritis were followed by suggestions that gold salts change the path of the disease and impede joint destruction.[2] Indications for discontinuing gold include a decrease in the leukocyte count, a 50% fall in the absolute neutrophil count, or allergic reactions to the injections of gold.

Penicillamine is also an advanced drug which is used to treat rheumatoid arthritis. It was found that it can dissociate the rheumatoid factor. However, serious toxic effects can occur with penicillamine therapy. It must be discontinued if dermatitis, nausea, or vomiting appear.

A fifth type of advanced therapy is done with methotrexate. "Clinical responses to low doses of methotrexate suggest an anti-inflammatory response." During initial studies of the drug, improvement was found in all adults that were tested. However, it is only effective while the patient is taking the drug. Gastrointestinal manifestations, including stomatitis, abdominal pain, diarrhea, and melena have been reported.

Physicians must be careful when starting a patient on corticosteroid therapy. They must carefully monitor the risks of osteoporosis and muscle wasting that occur with the disease which may occur during the used of corticosteroids. But, there are always certain situations where the benefits of steroids outweigh the risks. However, "despite potent anti-inflammatory and immunosuppressive effects, steroid therapy does not favorably influence the duration or eventual prognosis of arthritis.

Rheumatoid arthritis is frequently chronic, painful, and potentially debilitating. Living with arthritis is definitely not easy. But, there are several types of medications available for the patient to use to help alleviate some of the pain and stress accompanied by having arthritis. However, all of the medications that were discussed have had serious potential side effects. The patient may have to evaluate the pros and cons of their prescribed medication to see if it is worth taking. Due to the fact that there is no available cure, ongoing studies are being performed to try to find one.

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