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# SAFETY AND EFFICACY OF A NOVEL XANTHINE OXIDASE/XANTHINE DEHYDROGENASE INHIBITOR IN THE TREATMENT OF GOUT

INTERNSHIP PRACTICUM REPORT

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By

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SAFETY AND EFFICACY OF A NOVEL XANTHINE OXIDASE/XANTHINE DEHYDROGENASE INHIBITOR IN THE TREATMENT OF GOUT

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## Summary

The internship report is based on the activities completed during the Internship Practicum at the Department of Internal Medicine, Division of Rheumatology, at the University of North Texas Health Science Center at Fort Worth and at the Rheumatology Clinic at John Peter Smith Hospital. This internship serves as partial training in the area of Clinical Research Management and focuses on studies involving rheumatic diseases, with specific emphasis on Gout.

## Specific Aims/Hypothesis

Ongoing clinical trials in the Department of Internal Medicine Rheumatology clinic are the bases for the project which focuses on the treatment of gout and a proprietary study on the uses of a novel xanthine oxidase/ xanthine dehydrogenase inhibitor (XOD/XDH inhibitor) to relieve the symptoms of gout. The particular research is a phase three study to assess the safety and efficacy of a novel xanthine oxidase/ xanthine dehydrogenase inhibitor compared to a placebo and an established xanthine oxidase/ xanthine dehydrogenase inhibitor, allopurinol.

The hypothesis of the study is that the new XOD/ XDH inhibitor will be more effective at lowering uric acid levels and thus will reduce the frequency of gout more effectively and with fewer side effects than traditional treatment or a placebo. Under the direction of the Department of Internal Medicine, subjects who met inclusion/exclusion

criteria of the study were randomly assigned to be treated with colchicine in addition to either allopurinol, or the novel compound, which hereafter will be referred to as the novel XOD/XDH inhibitor, or to a placebo. The safety and efficacy of the novel XOD/XDH inhibitor will be compared to the traditional drug of choice allopurinol, a uric acid lowering agent, and to a placebo. The placebo is an inactive pill that is designed to look and taste like either allopurinol or the novel XOD/XDH inhibitor.

While the period of the internship is not long enough to complete the study and thereby assess the reliability of the hypothesis, the internship and this report have two specific aims: (1) to perform a literature search of gout and related topics and (2) to understand and perform activities of a clinical research coordinator as they relate to the novel XOD/XDH inhibitor study and to other clinical trials in rheumatology. The literature search focuses on specific areas concerned with details about gout: history, epidemiology, forms, causes, signs and symptoms, clinical diagnosis, differential diagnosis, complications, therapeutics (past, present, and future), prevention, associations, cellular mechanisms involved in hyperuricemia, as well as inflammation. The project also provides a description of the activities involved in clinical research, and discusses specifically the roles of the various personnel: Clinical Trials Coordinator, Principle Investigator, Sub-investigator, Institutional Review Board, and Clinical Trials Monitor as they have been involved in the novel XOD/XDH inhibitor study and other studies in rheumatology.

## Significance

Finding a new treatment for gout is of significant importance for several reasons. In countries with a high standard of living, such as the United States, prevalence of gout has increased and is probably the second most common form of inflammatory arthritis[1]. Gout can result in significant short-term disability, occupational limitations, and increased utilization of medical services therefore making the disease a significant public health problem[1]. New treatment options could greatly improve the prognosis for patients and in addition reduce the cost of the disease by preventing loss of wages due to patient absence from work, for example. Furthermore, new treatments for gout could provide patients with safer therapeutic alternatives than the traditional treatments.

## Background

### *History*

References to gout date back to the fifth century BC. Excavations of Egyptian ruins yielded mummies described as having gouty tophi[2]. Gout which comes from the Latin word "gutta" for drop, as in a drop of one of the four humors of the body, was described as flow of body humor[3]. The flow of the body humor, when following the normal course, would deposit the gouty excess in the joints. It was not until Thomas Sydenham (1624-1689) described gout's clinical course and Sir Alfred B. Garrod (1818-1907) linked gout to excess uric acid in the blood did the etiology of the disorder become understood[4].

### *Description and Etiology of Gout*

Gout is predominantly a disease of adult men, with peak incidence in the fifth decade, but postmenopausal women are also subject to the condition[1]. Range of onset of the first attack of gout is seen between the fourth and sixth decades. Yet, there is some evidence that these peaks may differ in various populations, as discussed in a study done in Taiwan that described onset of attack closer to the third than fourth decade of life[5].

Gout is an inflammatory response to deposition of monosodium urate (MSU) crystals in and around the joints[6]. Using light microscopy, examination of synovial fluid reveals MSU crystals within polymorphonuclear leukocytes (PMN), also known as neutrophils, as well as in fine needle aspirations of gouty tophi[7]. Tophi are macro accumulations, frequently subcutaneous deposits, of MSU crystals and can be found anywhere over the body, but occur most commonly in the helix of the ear, fingers, wrists, knees, olecranon bursa (elbow), and pressure points, such as the forearm and Achilles tendon[8]. But, MSU crystals have also been found in the fluid of asymptomatic joints, and this has led to the supposition that MSU crystals provoke inflammation.

Inflammation of the synovium of a joint, called synovitis, provoked by MSU, involves several mediatory factors. Crystals in the synovial fluid are taken up by phagocytosis by circulating PMNs that have entered the synovium from the surrounding vasculature. PMNs then release chemotactic factors, such as the activated fifth complement (C5a), leukotriene $B_4$ ($LTB_4$), kinins, latent collagenases, kallikrein, prostaglandin $E_2$ ($PGE_2$), and interleukin-1 (IL-1). Other cells which mediate the release of these factors include platelets and basophils in the vasculature, and mast cells located within tissues. Release of chemotactic factors acts to recruit other leukocytes from the vasculature compartment into

the tissue, a process called chemotaxis. PMNs phagocytize crystals and enclose them into phagosomes that merge with lysosomes. The crystals perforate the lysosomal cell membrane causing release of hydrolytic enzymes. As a consequence, the cell undergoes necrosis or rupturing. Cell lysis releases additional mediators which cause local inflammation. Monocytes, macrophages, platelets, and synovial phagocytic cells also contribute to inflammation by releasing mediators such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-8 (IL-8)[9, 10].

Inflammatory mediators, such as interleukins and TNF-α, interact with specific receptors to undergo G-protein coupled receptor (GPCR) activation. The GPCR complex then activates phospholipase $A_2$ ($PLA_2$) which in turn cleaves arachidonic acid-containing membrane phospholipids, such as phosphotidyl choline. A cyclo-oxygenase (COX) enzyme then catalyzes the conversion of arachidonic acid to prostaglandins and thromboxanes through a two step reaction. A lipoxygenase enzyme converts arachidonic acid to leukotrienes (Figure 1)[11]. Prostaglandins are one of the key vasodilators that lead to increased blood flow and the subsequent redness of the skin or joint seen in inflammation. Prostaglandin $E_1$ is a potent pyrogen or fever producer in animals and edema, erythema, and histologic changes of inflammation have been associated with prostaglandin administration in animals[12]. Clinically, the cardinal signs of inflammation in humans are swelling, warmth, redness, pain, and to a lesser extent stiffness and functional incapacity[12].

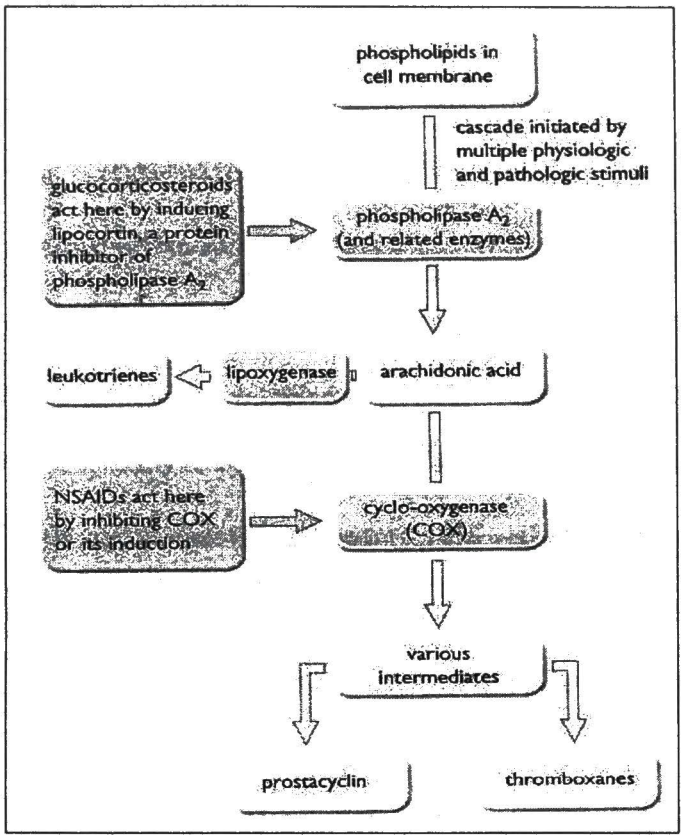


**Figure 1 Arachidonic acid and its metabolites.** Arachidonic acid is released from phospholipids in the cell membrane through the enzyme phospholipase A2. Arachidonic acid is then converted to precursor molecules of prostaglandins called prostacyclins via the catalytic activities of cyclo-oxygenase. Arachidonic acid is also converted into leukotrienes via catalytic properties of lipoxygenase.[15]

Gouty attacks usually occur in patients with hyperuricemia, where hyperuricemia is defined as serum uric acid level above 7mg/dl in men and above 6mg/dl in women. Patients with symptoms of gout, who have normouricemia, were found to be in the minority (12%) in a retrospective study of newly diagnosed gout patients in a Korean Hospital[13]. Normal uric acid levels in patients with gout can be attributed to one of two explanations, either the patient does not have gout and has therefore been misdiagnosed or the uric acid level is normal when measured, but the patient is actually chronically hyperuricemic. In another study of Taiwanese patients, uric acid was found to be the only predictor of onset of gout[14].

The culprit of hyperuricemia, uric acid, is a byproduct of the catabolic steps that break down nucleic acids and adenylic and guanylic acids (Figure 2)[15]. This metabolic pathway involves degradation of guanine monophosphate (GMP) to guanosine, and then to guanine, which undergoes removal of its amino group to yield xanthine. The xanthine is converted to uric acid by xanthine oxidase. Degradation of adenine monophosphate (AMP) involves degradation to adenylic acid, which is then degraded to adenosine. Adenosine is converted to inosine which in turn is hydrolyzed to hypoxanthine, and finally oxidized to xanthine and then uric acid. Hypoxanthine and xanthine are ultimately oxidized to uric acid by sequential reactions catalyzed by the enzyme xanthine oxidase[16]. XOD inhibitors, such as allopurinol and the novel XOD inhibitor employed in this study block the conversion of xanthine and hypoxanthine to uric acid, thus lowering uric acid production.

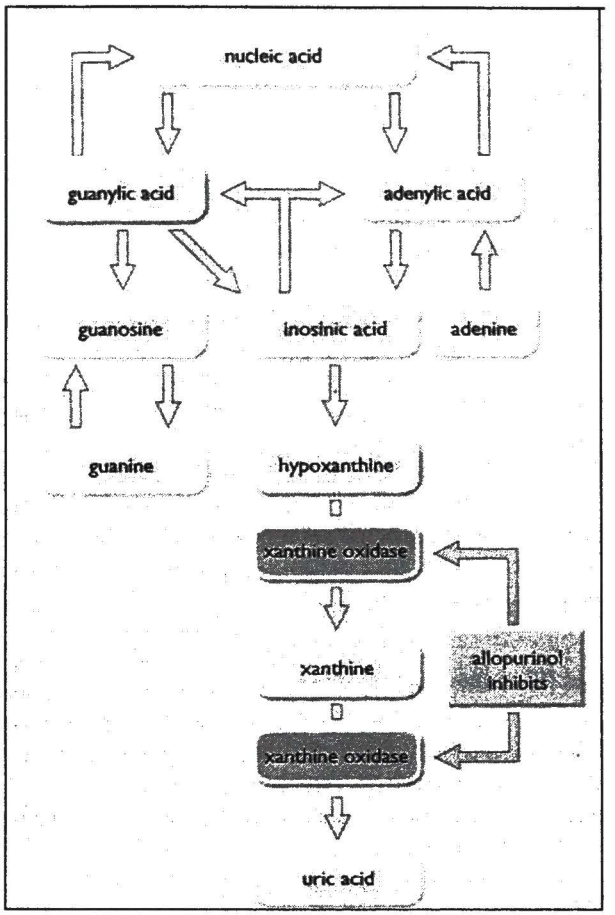


**Figure 2. Overview of purine metabolism.** Guanylic acid and adenylic acid are broken down through a series of steps to inosinic acid and ultimately to uric acid.[15]

Hyperuricemia either results from under excretion of the uric acid or overproduction of uric acid. Under excretion is thought to be the most frequent mechanism to explain hyperuricemia and is seen in about 85% of patients with gout[17]. About 10% of patients with hyperuricemia are overproducers of uric acid and, consequently, excrete greater than 800 mg of uric acid into the urine over a 24-hour period[8]. A small percentage of patients are a combination of both over producers and under excretors.

The cause of under excretion is due to either reduced urate filtration in the glomerulus, enhanced urate reabsorption, or decreased urate secretion. Due to a variety of factors, including renal insufficiency, arterial hypertension, overweight, hyperparathyroidism, hypothyroidism, toxemia of pregnancy, Down syndrome, organic acid accumulation that competes with renal tubular secretion of urate (such as seen in alcohol intoxication), lead intoxication, lactic acidosis, diabetic ketoacidosis, ketosis, and starvation. Alcohol decreases the renal tubule ability to excrete uric acid and hence plays a role in hyperuricemia. Lead intoxication can develop from occupational exposure to lead which can result in renal underexcretion[18]; however, renal excretion does not change in everyday environmental exposure to lead[19]. Pharmacologic agents such as diuretics, cyclosporines, levodopa and low-dose salicylates (less than two grams a day) alter renal tubular function and can contribute to uric acid under excretion[8, 20].

Overproduction of uric acid is seen in a variety of acquired and genetic disorders that are characterized by excessive rates of cell turnover and hence nucleic acid turnover. These disorders constitute examples of secondary hyperuricemia and include: myeloproliferative disease, hemolytic and lymphoproliferative disorders, psoriasis, Paget's disease, and inborn

errors of metabolism, such as hypoxanthine-guanine phosphoriboxyyltransferase (HG-PRT-ase) deficiency, increased phosphoribosyl pyrophosphate (PRPP) synthetase activity, glucose-6-phosphatase deficiency, myogenic hyperuricemia from a glycogen storage disease (type III, V, or VII), or fructose-1-phosphate aldolase deficiency[21]. Overproducers also tend to develop renal calculi (kidney stones) as a result of excessive urate production more frequently than underexcretors do.

Combination of overproduction and underexcretion is attributed to being overweight and excessive alcohol use which leads to overproduction of uric acid and decreased excretion with lactic acidosis[20].

The only way to clearly define a patient as an overproducer is by a urine collection in which the entire volume of urine from a patient is collected over a 24-hour period and the total uric acid excretion is measured. Several methods such as one time urine uric acid to creatine ratio have been studied and found not to indicate accurately uric acid levels[22].

Determining whether a patient is an underexcretor or an overproducer will allow the clinician to determine what kind of therapeutic agent such as a uricosuric or xanthine oxidase inhibitor can be used to lower uric acid levels. Patients who can take a uricosuric such as probenecid have 800 mg or less of uric acid in a 24 hour urine. Also, there may be some utility derived from determining if a patient is an over producer or underexcretor of uric acid in that the underlying cause of hyperuricemia can be elucidated further and treated with prevention where weight, diet, alcohol consumption, and drug-use come into effect. Determining that a patient is an overproducer of uric acid may also lead the clinician to look for disorders such as myeloproliferative disease, lymphoma, or one of the genetic disorders[20].

Allopurinol is utilized and effectual in both overproducers and underexcretors and thus is most often used[21].

**Diagnosis**

Clinically, gout passes through three distinct stages: asymptomatic hyperuricemia, acute intermittent gout, and chronic tophaceous gout. The initial gout attack usually occurs after many years of asymptomatic hyperuricemia and is characterized by rapid onset (over 8-12 hours) of redness, warmth, swelling, and extreme pain in the affected joint. Initial onset is usually monoarticular and in one half of patients involves the first metatarsophalangeal (MTP) joint. The attack can last from several hours to 1-2 weeks depending on severity. The pain is said to be exquisite and patients cannot stand the weight of a bed sheet on the affected joint, let alone walking. Early in the acute intermittent stage, attacks are infrequent and there may be years between attacks. This period is known as intercritical gout. Gradually, over time, the attacks become more frequent, more severe, last longer, and involve more joints. When the time periods between acute attacks cease in being pain free, then the patient has transitioned into the next stage, called chronic tophaceous gout. Gout attacks can now occur every few weeks without therapy, and the background pain intensifies. Tophi may or may not be present during this period. It is unusual for a patient to present for the first time with tophi as the initial clinical manifestation since tophi tend to form after about ten years of hyperuricemia and diagnosed gout. Tophi tend to develop in patients with the following characteristics: an onset of gout early in life, a period of active untreated gout,

an average of four gout attacks per year, and/or a tendency toward upper extremity polyarticular episodes[8].

Gout is diagnosed by a triad of symptoms including monoarticular arthritis, hyperuricemia, and a dramatic improvement of articular symptoms in response to colchicine. A gout diagnosis is confirmed through inspection of synovial fluid or tophaceous material and the demonstration of MSU crystals by light microscopy[8].

The differential diagnosis, or alternative diagnosis for a clinician to consider, for an acute gout attack should include bacterial cellulitis, or septic arthritis as synovial fluid findings would be consistent with moderate to severe inflammation with an increased number of leukocytes seen in the synovial fluid. Gouty tophi must be distinguished from osteoarthritis and chondrocalcinosis (pseudogout), conditions which result in the depositions of calcium pyrophosphate crystals[23], as well as tophi due to the deposition of cholesterol crystals[24].

***Treatment***

***A. Diet***

In the 5th century BC, Hippocrates attributed gout to excessive intake of food and wine[25]. This association with excess has long linked gout as the wealthy man's disease and hence the "disease of kings". More recently, gout has been associated with obesity, hyperlipidemia, and insulin resistance[26]. While hyperuricemia is not caused by obesity, hyperlipidemia, and insulin resistance, these disorders are associated with each other.

Studies have shown that the genetic allele Apo $E_2$, an isotype of apolipoprotein E, is more prevalent both in patients with hyperlipidemia and in patients with hyperuricemia due to lower renal excretion rates[27].

Diet is a modifying factor in the treatment and prevention of hyperuricemia. A diet rich in the purines, such as sardines, anchovies, broths, gravies, brains, kidneys, liver and sweetbreads can raise the uric acid level 1-2mg/dl and, conversely, a diet low in purines can lower the uric acid level in an equivalent fashion[25]. Still others suggest that a weight-reducing, calorie restricted diet, with moderate carbohydrate restriction and paradoxical increased proportional intake of protein and unsaturated fats can lower uric acid levels from 0.57 mmol/l to 0.47 mmol/l [8](9.5 mg/dl to 7.8 mg/dl.)[26], the mechanism to explain lowering of uric acid despite increased intake of protein is under investigation. Alcohol, as discussed earlier, can increase uric acid levels and when it is eliminated from the diet, uric acid levels decrease and patients experience fewer gouty attacks[25].

***B. Drug Therapy***

Gout has been a disease of interest since primordial times with ancient therapeutics based on humoral reasoning of disease. The humoral reasoning of disease was a belief that excess of one of the four humours, blood, phlegm, choler, and melancholy[2], which in equilibrium were thought to maintain the body in health, would flow into a previously weakened joint causing pain and distention. Thus, the prescribed treatment was to eliminate the offending matter from the system by all available routes including bleeding, blistering, sweating, purging with scammony (an herbal root ingested to produce vomiting and

diarrhea), white hellebore, or other herbal cathartics, and the administration of emetics and diuretics. Colchicum, an herbal treatment for the podagre, or pain in the foot, was described by Alexander of Tralles (AD 525-605) who noted the side effects of emesis and diarrhea once the maximum dosage had been obtained[3].

Present day drug treatment for gout includes three general objectives. The first is to treat pain with analgesics and inflammatory reducing agents. The second objective is to reduce inflammation and hence the frequency of attacks by prescribing colchicine which inhibits PMN microtubule polymerization thus preventing chemotaxis and phagocytosis. The last objective is to reduce hyperuricemia with either a uricosuric agent or XOD inhibitor.

Acute attacks of gout may be treated with analgesic medicines, such as propoxyphene or hydrocodone, to decrease pain. Pain can also be treated by decreasing inflammation by inhibiting the inflammatory process. Non-steroidal anti-inflammatory drugs (NSAIDs) work to decrease the amount of prostaglandins formed in the arachidonic acid pathway (Figure 1). Prostaglandin synthesis starts with isomerization of arachidonic acid by prostaglandin $H_2$ ($PGH_2$) synthase, also known as the cyclo-oxygenase enzyme (COX), to an intermediate product called prostaglandin $G_2$ ($PGG_2$). The COX enzyme has two activities, cyclo-oxygenase activity and peroxidase activity. The peroxidase activity of COX is at a different enzymatic site and reduces $PGG_2$ to $PGH_2$. Then distinct synthases and reductases convert $PGH_2$ to one of several prostaglandins (Figure 3)[28, 29].

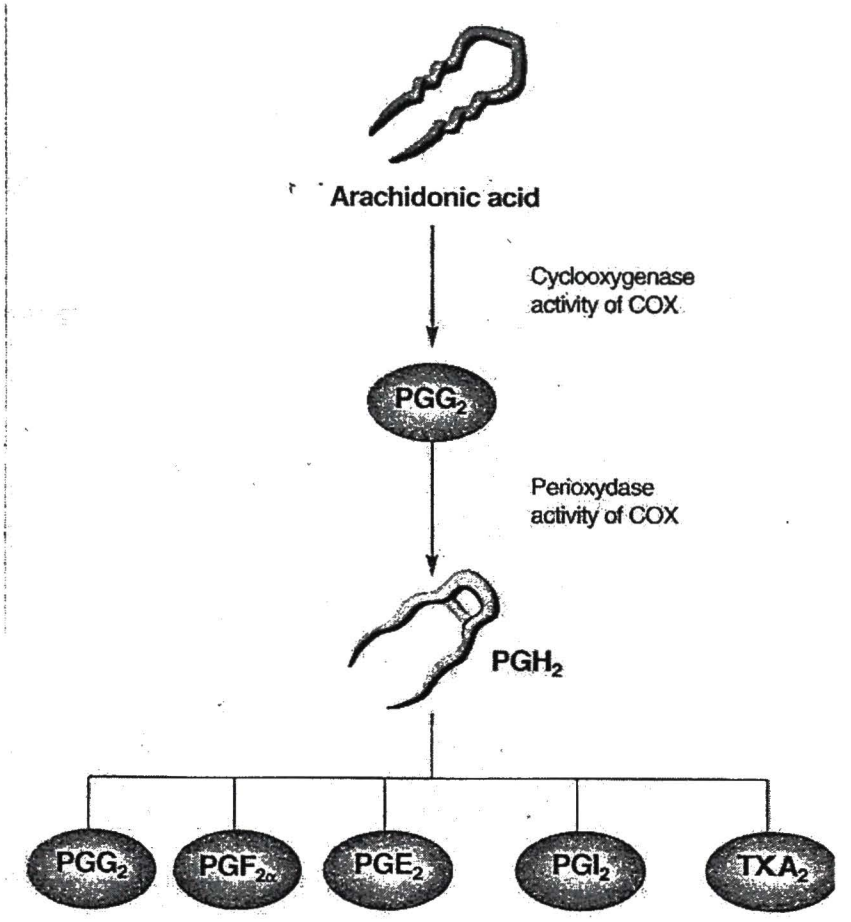


**Figure 3 Roles of COX enzyme in prostaglandin synthesis.** In the first step of prostaglandin synthesis, the cyclo-oxygenase enzyme (COX), oxygenates and isomerizes arachidonic acid, creating an intermediate prostaglandin $G_2$ ($PGG_2$). In the next step, the peroxidase activity of COX reduces $PGG_2$ to $PGH_2$. $PGH_2$ is converted to one of several prostaglandins by distinct synthases or reductases. Prostaglandins formed include prostaglandin $D_2$ ($PGD_2$), prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), prostaglandin $E_2$ ($PGE_2$), prostaglandin $I_2$ ($PGI_2$), and thromboxane $A_2$ ($TXA_2$).[28]

NSAIDs inhibit the binding of arachidonic acid to the enzyme cyclo-oxygenase (Figure 4), thereby decreasing the amount of prostaglandins formed. In mammals, there are two isozymes of COX, COX-1 and COX-2. These isozymes have similar amino acid sequence but have different functions. COX-1 is responsible for prostaglandins that regulate secretion of gastric mucin, a gastric protective agent. The COX-2 isozyme is responsible for prostaglandins that mediate inflammation, pain, and fever[29]. NSAIDs, such as aspirin, ibuprofen, indomethacin, and other older anti-inflammatory drugs, are not specific for there action on the COX enzyme and work to inhibit both isoforms (COX-1 and COX-2). The NSAIDs have rapid onset but may have serious side effects, such as stomach ulcers, gastric hemorrhaging, and renal insufficiency. Side effects of gastric irritation seen with aspirin and ibuprofen are due to the blockade of the COX-1 isozyme which produces prostaglandins with gastro-protective activity. The relatively new class of COX-2 inhibitor NSAIDs are easier on the stomach because they do not inhibit COX-1 prostaglandin synthesis, but inhibit the COX-2 prostaglandins which are responsible for much of the inflammatory process in joints[28](Figure5). Studies have shown that COX-2 inhibitors are just as effective as the classic NSAIDs at reducing inflammation, yet with lower gastrointestinal side effects[15]. For example, etoricoxib, a COX-2 inhibitor, was found to have comparable efficacy to indomethacin, one of the first NSAIDS, with drug related adverse experiences at a lower rate with etoricoxib than indomethacin[30].

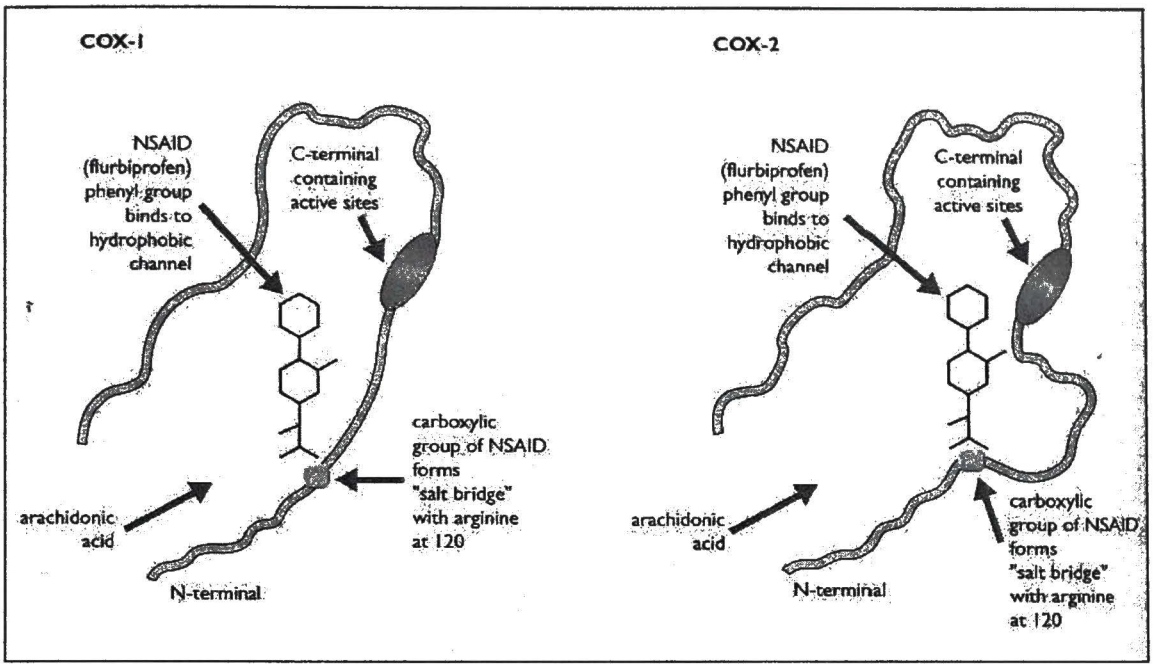


**Figure 4 Cyclo-oxygenase enzyme inhibition.** COX-1 and COX-2 inhibition by classic NSAIDs, arachidonic acid is unable to access the active site.[15]

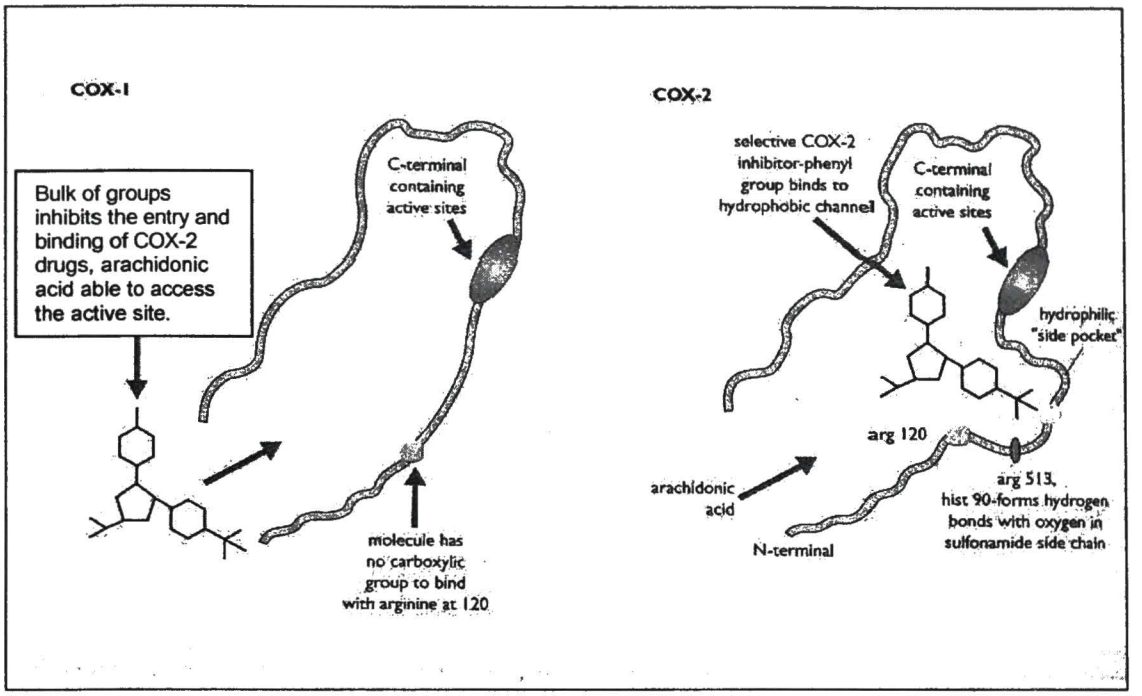


**Figure 5 Cyclo-oxygenase enzyme.** COX-1 enzyme is not inhibited by COX-2 selective inhibitors and arachidonic acid able to bind to the active site. COX-2 enzyme is inhibited by COX-2 selective inhibitors blocking the active site, thus arachidonic acid not able to bind to active site.[15]

Corticosteroids are used increasingly intraarticularly or parenterally in patients, especially if oral drug therapy is not feasible[31, 32]. Corticosteroids block inflammation by inhibiting the enzyme phospholipase $A_2$ from releasing arachidonic acid from phosphotidyl choline, thus blocking the synthesis of prostaglandins locally[11].

Prophylaxis of gout attacks may involve treatment with either colchicine or NSAIDs[31]. Treatment for gout attacks may include administration of colchicine, although this drug is less favored because its onset of action is slow and it causes diarrhea[31]. Furthermore, colchicine toxicity can induce rhabdomyolysis, a fatal disease involving disintegration of skeletal muscle which is found through the spilling of myoglobin in the urine[33, 34, 35].

Correction of hyperuricemia with uricosuric or xanthine oxidase/dehydrogenase (XOD) inhibitors should be commenced with caution as any change in uric acid level, whether increase or decrease, can initiate an acute gout attack. Therefore, patients suffering from an acute episode of gout should not be placed on a uric acid lowering agent until the flare has subsided. Furthermore, a uric acid lowering agent may not be indicated in all patients with gout. Uric acid lowering agents may be started depending on clinician judgment in patients that have the following descriptions: frequent gout attacks, tophi, very high serum uric acid levels, renal calculi, azotemia, treatment of tumors, and occasionally certain diagnoses such as psoriasis[8].

Uricosuric agents are drugs of choice in patients that are underexcretors, while uricosurics are harmful in overproducers because they increase the risk of renal calculi. Common uricosurics are Probenecid, Sulfinpyrazone, high dose Salicylate, Diflunisal, and

Benzbromarone (not approved in the United States of America). Uricosurics such as probenecid are weak acids which interfere with distal tubular uric acid reabsorption, causing uricosuria, and decrease in serum uric acid levels. Probenecid requires normal kidney function to work properly and is ineffective in patients with creatinine levels over 2 mg/dl. Concomitant use of salicylates also renders probenecid ineffective. The dosage of probenecid is twice daily, which is sometimes problematic due to lack of patient compliance. Side effects of probenecid include skin rashes, gastrointestinal intolerance, nephrolithiasis, and rarely hepatic necrosis and proteinuria[20].

XOD inhibitors, such as allopurinol, are the drugs of choice to treat hyperuricemia when the distinction between overproduction and underexcretion is not clear[31]. Allopurinol is also used in patients with renal insufficiency, history of renal calculi, and allergy or failure to respond to uricosurics. Allopurinol is a potent inhibitor of xanthine oxidase, thereby blocking the transformation of hypoxanthine into xanthine, and xanthine into uric acid. There is a build up of xanthine and hypoxanthine when XOD inhibitors are used this seems to result in few ill effects. Allopurinol is metabolized into oxypurinol which is also a xanthine oxidase inhibitor. 17-40 hours after initial dosing, at least one half of the oxypurinol will remain in the body, thus dosing of allopurinol occurs once a day. Side effects of allopurinol are infrequent and generally mild and include rashes, gastrointestinal distress, diarrhea, and headache. Allopurinol may interfere with the metabolism of certain drugs that are purine based metabolites, such as azathioprine (Imuran) or 6-mercaptopurinol (Purinethol), allopurinol may interfere with other drugs such as theophylline and warfarin

due to altered hepatic metabolism. Cyclophosamide toxicity and bone marrow suppression are enhanced with allopurinol due to an unclear mechanism.

About 0.1% to 0.4% of patients taking allopurinol develop a severe allopurinol hypersensitivity syndrome (AHS) which can be fatal. Characteristics of this reaction are fever, rash, hepatitis, leukocytosis with eosinophilia, and worsening renal function. Fever is usually in the range of 102 to 103 F). Skin rash may be exfoliative erythroderma, palmar/plantar hyperkeratosis, Stevens-Johnson syndrome, or toxic epidermal necrolysis. Eighty percent to ninety percent of patients with AHS have elevated liver functions with a few progressing into hepatic failure. Death is reported in 25% to 30% of these cases. Causes of death in AHS include acute renal failure, gastrointestinal bleeding, and sepsis associated with skin exfoliation. Eighty percent of patients that develop AHS have mild renal dysfunction and about 50% are taking thiazide diuretics. Average onset of AHS is about 3 weeks after starting a standard dose of 300mg[36].

There has not been a new commercially available drug to inhibit the pathway leading to accumulation of uric acid (i.e., hyperuricemia) since allopurinol was first introduced in 1966. The novel xanthine oxidase inhibitor under investigation will be the second of this type to be used in the U.S. should it gain FDA approval[37]. While allopurinol can be used safely in many patients, there are some situations, such as patients with renal insufficiency, who may experience allopurinol hypersensitivity syndrome (AHS) due to a reduced creatine clearance or prolonged half-life of oxypurinol [38]. If the novel drug being tested in current clinical trials proves to be safe, it would be beneficial to patients who have renal insufficiency or are taking thiazide diuretics.

CHAPTER II

## Materials and Methods

### *Internship Activities*

Activities performed during the internship will be under the direct supervision of Cynthia Jimenez-Williams, R.N., B.S.N, the Department of Internal Medicine at the University of North Texas Health Science Center in Fort Worth. The activities focus on the role of Clinical Research Coordinator in Clinical Trials that are conducted in phase two, three, and four clinical trials. The following are activities that I engaged in during the internship.

I prepared for a site selection meeting by making copies of curriculum vitae and licenses for the investigator, site staff, and pharmacist. The study protocol was reviewed to see if there were any questions the site has for the sponsor. Rheumatoid arthritis study. (28 August 2003)

I participated in a site selection meeting with a clinical research associate (CRA) from a contract research organization (CRO) Quintiles for pharmaceutical company Centocor. The CRA goes over the purpose of the meeting and verifies that the site does not currently have a competing study in progress. The CRA verifies that the site facilities and staff are equipped to handle the study. A tour of the facility is taken including clinic visit rooms, lab processing area, cold and freezer storage, drug storage areas, and pharmacy. The CRA sends the site a

letter detailing problems/questions and submits the findings to the sponsor. Rheumatoid arthritis study. (29 August 2003)

I compiled a study budget to see if pharmaceutical company will pay a sum that will cover the costs that will be accrued during the course of the study for new Centocor study. I met with Donna Wilson, Clinical Trials Administrative Secretary to review clinical trials accounting system. All studies. (22 August 2003)

I reviewed the protocol, investigator brochure, and coordinator binder for the gout novel xanthine oxidase inhibitor study. This included a review of the inclusion/exclusion criteria, procedures, visits, and purpose of the study. Proper measurement of tophi, subcutaneous collections of uric acid in the skin, was also reviewed. Tophi are found on the elbow, ankles, wrists, and helix of ear. Drugs used to treat gout and their purpose including allopurinol, naproxen, and colchicines were reviewed. I became familiar with the wash out schedule of allopurinol, before study drug could be started. I also became familiar with concomitant medications that are prohibited during course of the clinical trial as well as eligibility criteria, including history of gout attacks. (09 June 2003).

Pre-screens or chart audits were done to determine the eligibility if a subject for the study. Patient names are given to the coordinator by the investigators, other physicians, or are obtained from previous trials that have terminated. Subjects are screened that have responded to advertisements and are inquiring about possible study participation. Patient

charts are reviewed from beginning to end and most of the findings are recorded on a patient past medical history form. Previous surgeries as well as minor illnesses are also recorded. Also, a current list of patient medications is ascertained. I called subjects on the phone and explained the nature of the study including study schedule, why the study is being done, I discussed inclusion/exclusion criteria, and lab testing, as well as follow up. Copies of the informed consent were sent to patients to read before the screen visit. This gives the patient time to read the consent in a familiar environment. Actual consent is only performed at the screen visit and patients are instructed not to sign the consent form that is sent to them. I performed about 45 pre-screens during the internship practicum. All studies including gout study. (01 July 2003)

The coordinator is contacted when patients in the clinic meet eligibility criteria for a study and they are interested in participating in a clinical trial. Some patient clinic visits may turn into actual study screen visits under the correct protocol. The coordinator must be ready to screen patients at any time for any of the ongoing studies. All studies. (01 July 2003)

We coordinated schedules with the coordinator, investigator, sub-investigator, and the study protocol to see when the gout subjects are able to come for their visits. This study has particular windows in which to bring the patients in, screen them, and then randomize them to study drug. It was important to schedule subjects at times that the coordinator, sub-investigator, and the subject would all be able to make. It was decided that due to the work schedules of the subjects, many of the visits would occur at 7:00 am or 7:30 am. Additional

protocol restrictions limit the time of day in which the patient must be seen to the morning hours. Once subjects randomized, visit dates and windows were recorded for easy reference later in the study. Gout study. (11 June 2003)

Study source documents are the clinical trial records detailing what occurred during the study. Completed case report forms (CRFs) are returned to the pharmaceutical company. The source and the CRF should match each other in the information that is documented. Source documents are created by the coordinator of the study, while CRFs are provided by the pharmaceutical company. Source documents are created as is someone who doesn't know the protocol could understand and complete the subject's visit. Source binders are prepared prior to screening each subject. Several binders can be prepared at one time. I reviewed electronic data capture (EDC) for CRFs. EDC is a way to capture the CRF data through application of computers and online submission of the data. I created paper source documents for an opioid induced constipation study being conducted in family medicine whose study had not yet screened subjects. Subject source binders were assembled for five studies including the gout study. (01 July 2003 and 25 July 2003)

Investigators are informed of the times of the next day's study visits by email reminders. The investigators are also informed of the scheduled monitoring visits. All studies. (02 July 2003)

Informed consents are signed by subjects only after subjects have thoroughly read the document, the principle investigator reviews the consent with the subject, and the subject's questions are answered. The subject initials and dates each page, signs the end of the document, dates, and writes the time consent was obtained. The principle investigator and a witness would also sign the consent. I acted as a witness to several consents during the internship. All studies. (11 June 2003)

A new informed consent was created to include the Health Insurance Portability and Privacy Act (HIPPA). Part of HIPPA protects the privacy rights of patients. Thus, the informed consents of all studies were revised to include the HIPPA language. Subjects were required to sign new informed consents with this language on their next scheduled study visit. All studies. (11 June 2003)

A rheumatoid arthritis and osteoarthritis study has an optional tube of blood collected for genetic testing in the future. This tube of blood will be frozen and stored. This tube of blood was not required for participation in the study, any subjects who were not comfortable with storage of their blood were not required to have this additional tube of blood taken. There was an additional consent form that was required for this tube of blood to be drawn and stored for genetic testing. As this part of the protocol was added later in the study, after the Institutional Review Board (IRB) approved the amendment to the protocol to account for the storage of blood for genetic testing, subjects signed the additional genetic consent form on their next scheduled study visit. (11 June 2003)

Subjects brought study drug and empty study drug containers with them to each study visit. Study drug was counted in order to assess subject compliance with the dosing schedule. Pill counts are done to insure the protocols are being followed properly by the subjects and the investigators. Pill counts also assure patient safety by following proper dosing schedules, making sure the patient is not taking too many or too few pills, and to assure the patient will have enough supply of medication until the next study visit. All studies. (daily)

An osteoporosis study utilizes electronic pill caps that count the number of times the bottle is opened, thus equaling one dose. The information in the pill cap is then transferred electronically through the phone line to the pharmaceutical company. Patients are instructed on proper usage of bottle cap in order that unnecessary opening does not occur. (daily visits from 09 June 2003 until 31 October 2003)

Interactive Voice Response System (IVRS) was used on a daily basis. IVRS was used to get allocation/randomization numbers for patients. This system assigns study drug to dispense to the patient based on the numbers on each study drug container. New study medication can then be dispensed at each visit, if the protocol calls for it. All studies. (daily)

IVRS helps the sponsor keep track of study medication and when to send new supply to the sites. In certain cases, the sponsor can put a hold on study medication dispensing by not assigning any new drug to subjects. In one case, the sponsor had issues with expiration dates

on some of the medication and the sponsor contacted IVRS to temporarily discontinue dispensing drug. This causes a problem for subjects that are scheduled for visits in which dosing is to take place at a certain time. Multiple phone calls to the sponsor and IVRS company cleared up the issue after the patient and left. Study drug dispensing occurred outside protocol times, however, there was no other option. All studies. (11 September 2003)

A subject discontinued from the study, they were withdrawn by the investigator for noncompliance. The subject did not take the study medication as the protocol delineates and indicated that they would not take the study medication and prophylactic medication as indicated. The subject was withdrawn for their own safety. Gout study. (05 September 2003)

I took part in regular study visits which I had an active role in taking vital signs, collecting blood and urine, assessing study drug compliance-pill counts, dispensing study drug, determining if any adverse events occurred since the last visit, and scheduling the next study visit. Over 50 regular study visits took place during the internship practicum. All studies. (daily)

Some studies call for subjects to complete surveys to give the company and idea of patients' pain level, changes in quality of life, or changes in health. One study calls for the Minnesota quality of life questionnaire to be completed. Another study calls for the SF-36 survey to be

completed. Another study has subjects complete the Survey of Dyspepsia Assessment (SODA). The SODA asks subjects about the level of stomach discomfort or dyspepsia before and after the study. Osteoarthritis/Rheumatoid arthritis study. (11 June 2003)

Screen visits for subjects varied from protocol to protocol but in general, I obtained patient vital signs including blood pressure, pulse, respirations, temperature, height, and weight. Informed Consent was obtained before any study procedure was started. Subjects would then have their medical history, concomitant medications, and protocol inclusion/exclusion criteria reviewed. Generally protocols call for blood to be drawn, EKG, and patient urine sample. The investigator would then perform a physical exam and complete required documentation. The patient would be given special instructions regarding their current medications, and any other protocol requirements. The patient would then be set up for their next visit and given any pertinent information about what they can expect at that visit. All studies. (16 June 2003)

Pharmaceutical company contacted to obtain approval of a protocol departure. The subject will need to start study medication one day later than the protocol delineates. The randomization visit could not take place on the required timeline due to the clinic being closed for a holiday. The approved protocol departure form is kept in the CRF for the subject. Gout study. (30 June 2003)

Randomization visits vary from protocol to protocol. Most visits involve calling IVRS to get a randomization or allocation number. Study drug is then usually assigned by component identification number. Most studies call for lab draw and urine collection. Some studies require specific measurements such as bone scans or as in the gout study tophi measurement. Some studies call for patients to obtain stool samples at home and brought in to the randomization visit in order to determine if the subject has any lower intestinal bleeding. Study drug as well as any prophylaxis medications or placebos are dispensed during randomization. Subjects receive instructions on dosing of the drugs according to protocol. Some instructions are verbal, some are written. Written handouts given to patients regarding dosage or anything else must receive prior approval from the IRB. Subjects are asked to repeat back instructions of dosing to ensure they understand how to properly take the medications. Approximately 17 patients randomized during internship practicum. All studies. (16 June 2003)

Lab specimens are generally processed after the morning patients have been seen and blood has had sufficient time to clot. Depending on the lab company each study will use, some lab work is processed and sent down stairs to an onsite collection facility; other lab work is packaged and sent via Airborne Express to labs that are out of city, county, state, etc. Labs that must be sent via Airborne Express, must be frozen if necessary and prepared for pickup by 4:00pm in order for timely processing. Lab-work collected on Fridays must have special labeling for the package to be delivered on Saturdays; otherwise the lab specimen will sit over the weekend and not be delivered. For these reasons of lab collection and processing,

scheduling of patients in the afternoon and on Fridays was avoided. All studies. (16 June 2003)

The Office of Clinical Trials has dry ice delivered weekly. Specimens that must be sent frozen should be packed on dry ice. Dry ice was also obtained from a supplier of dry ice when the office of clinical trials did not have sufficient dry ice for packing. Osteoporosis and gout study. (02 July 2003)

Clinical Research Associates (CRAs) from pharmaceutical companies are responsible for the interim monitoring visits at each site. These visits usually take place after the first patient has been randomized at the site, then periodically afterwards. CRAs review the regulatory binders to assure that the enrollment log is up to date, correspondence/newsletters from the company are being kept, up to date curriculum vitae and license for each investigator, proper documentation has been sent to the IRB and has been approved by the IRB, lab manual is up to date with the latest CLIA certifications, latest addition of the investigator's brochure is on hand, and so on. Additionally, documentation in both the source documents and the case report forms (CRFs) should be up to date. All of the above items are checked before the next monitoring visit. Approximately 8 or more interim monitoring visits were performed during the internship practicum. (09 June 2003 to 30 October 2003)

A letter from the gout study sponsor was received. This letter indicated that enrollment was closing due to enough subject participation. Two subjects were coincidentally scheduled for screen visits the day of the deadline for enrollment. (26 August 2003)

The coordinator and investigator monitor the subject lab work when it is returned. The subject's safety is taken into account and precaution is taken when lab work is abnormal. Sometimes the protocol requires that the subject discontinue if a lab value is extremely out of range. Other times, lab values that are mildly elevated or depressed are repeated on a regular basis until the value normalizes. Two subjects experienced this course of events while participating in a study during the internship practicum. Rheumatoid arthritis study and gout study. (02 July 2003)

The patient completed study protocol, and the last visit was completed. The study drug was collected from the patient. Study lab work was collected and final electrocardiogram (EKG) was performed. A cardiologist read the EKG, by prior agreement. The patient's regular clinic chart was retrieved from medical records to confirm the patient's medications prior to the study. Discussed with patient need to continue back on a non-steroidal anti-inflammatory (NSAID). A prescription was given to the patient for the same NSAID they were on prior to the study. It was explained that the result of the study would not be done for about a year. Investigator let patient know that they would not know which drug the patient was on until the study becomes unblinded. Finally, coordinator informed the patient that they would receive a phone call in 28 days to see if any events had occurred since going off the

medication. The patient then set up a regular clinic appointment for continuity of care. Approximately 6 subjects completed study termination visits during the internship practicum. Rheumatoid arthritis and osteoarthritis studies. (11 June 2003 to 30 October 2003).

Preparation for the next days' patients is always done before leaving the office/clinic for the day. Preparation includes pulling the appropriate lab kits for each visit that is scheduled or anticipated, making sure phlebotomy supplies are readily available, pulling subject source binders or case report forms (CRF), and calling to remind patients of their scheduled visits. This allows the coordinator additional time to deal with issues as they may present themselves during the day. The coordinator prepares for possibility that a subject may withdraw from the study or continue with the study based on previous conversation with the subject. Lab kits for both occurrences are pulled, and the coordinator reviews protocol for the withdrawal visit. All studies. (16 June 2003 and daily)

The coordinator takes steps towards being prepared for a serious adverse event (SAE) before they occur. Subjects complete information forms during screen visit with the names and numbers of emergency contacts as well as physician names and numbers. Subjects also sign a release giving permission for medical records to be released to the coordinator should something happen to the patient. All studies. (27 June 2003)

I prepared for the absence of the study coordinator. A list of subjects was prepared with subject names, visit number in the protocol, and sponsor contacts if needed. Instructions for

SAEs were also left with the investigator should and SAE occur. Also, a list of study visit protocols was reviewed with the sub-investigator for a gout study visit in the absence of the coordinator. (04 August 2003).

Pharmaceutical companies send queries to the site regarding CRFs and the source documentation. These queries seek to clear up any inconsistencies in the source documentation or the CRFs. Queries must be responded to in a timely manner. Each company has a certain protocol for the response, many of which can be faxed back to the company. All studies. (07 July 2003)

I assisted the coordinator with maintaining correspondence with the study monitor by sending latest IRB submissions, including but not limited to new study protocols, patient handouts, protocol amendments, revised investigators brochures, periodic project reviews, and the approval of the IRB of the aforementioned items. Some companies will disable access to the IVRS system if they do not receive continued IRB approval documentation. All studies. (09 July 2003)

The coordinator and a study monitor at the sponsor company discussed the wording of the exclusion criteria to see if a patient could enroll in the study. They also spoke about over enrolling for the study and getting approval to enroll more subjects than the original projection. Permission was obtained to over enroll and documentation verifying the approval was filed in the correspondence section of the regulatory binder. The potential subject did

not qualify for the study, as medication dosage was not stable for the required time period. Osteoporosis study. (18 July 2003)

I helped maintain the study regulatory binders with frequent filing of appropriate study documentation and correspondence. I also assembled new regulatory binders as needed when space was limited. All studies. (09 July 2003)

Patients can withdraw voluntarily at any time from a study. The investigators also can withdraw a patient from a study. Subjects that are not compliant with dosing of study drug or compliant with rescue medication may be withdrawn from the study at the discretion of the investigator. Subjects may also be withdrawn if they experience any adverse event while on the study medication at the discretion of the investigator. All studies. (16 June 2003)

I assisted with maintaining storage space by disassembling expired lab kits. Contents of the kits were properly discarded in sharps containers if required. Some contents of kits were salvaged such as plastic bags or extra pipettes. All studies. (17 June 2003)
I organized the storage cart for study visits. Phlebotomy supplies were restocked and organized in a manner that allows efficient use. (14 July 2003)

Lab supplies are continually accounted for. Supplies are reordered on a limited basis as there is only limited storage space for lab kits and packing supplies. Lab supplies are sent to the coordinator through the mail. Study drug is also sent to the site in the mail. Most protocols

require IVRS to be contacted to register shipments of drug received. Shipments of drug and lab supplies come with packing slips which are double checked against the shipment for accuracy and then filed into the appropriate section in the regulatory binder. Lab kits are checked for expiration dates and new supplies are ordered when needed. All studies. (30 June 2003)

Extra medications that are not study drug such as over the counter aspirin or tums must be taken to the university pharmacy in order for the drug to be destroyed. All studies. (30 June 2003)

Copies of subject face sheets with contact information are kept in the coordinator's office to keep track of subject's information after study closure. Keeping a file of this contact information allows the coordinator to contact subjects after the study has been unblended. This list can also be used to contact subjects if problems arise with the study medication after the study is closed. Moreover, the coordinator can use the subject information sheets to contact subjects during adverse weather conditions. All studies. (30 June 2003)

Study lab work results is copied and placed in the subject's regular clinic charts in order to continue patient care such as medication refills and lab draws that are not covered by the study. All studies. (30 June 2003)

Subjects give consent for coordinator to notify their primary care physician (PCP) that the subject is participating in the clinical trial. PCPs are sent a copy of the patient's mist recent lab work and EKG, if applicable, as well as a protocol synopsis which contains information regarding the study which the PCP may find helpful in treating the patient. All studies. (11 July 2003)

A subject had an elective foot surgery which required hospitalization. The proper forms were completed regarding SAE to the IRB. Hospitalizations for any reason, even if not related to study drug must be reported as an SAE. Osteoporosis and gout study. (15 October 2003)

I assisted in preparing documentation for the local institutional review board (IRB) regarding serious adverse event (SAE) from other sites within 10 days of site notification. Informing the IRB of new SAEs is important in clinical research. The local IRB considers the SAE and if the existing informed consent form should be amended. While paperwork is involved and extra steps are required in processing SAEs, this is done for continued subject safety in ongoing clinical trials. Under the direction of the coordinator, I prepared over 65 SAEs from other sites to be submitted to the local IRB during the internship practicum. The principle investigator of the specified study signs each form to acknowledge they are aware of the current safety issues with the study medication. The IRB receives a copy of this notification and a copy is maintained in the study regulatory binders. All studies. (17 June 2003 to 30 October 2003)

I prepared periodic project reviews to be submitted to the local IRB. These reviews allow studies to be evaluated on a regular basis to ensure that subject safety is being met. The review requires the number of subjects participating in the study, the number of new enrollments since the last review, how many subjects are on study drug or are in follow up stage of the trial, the number of minorities enrolled, and the SAEs that were reported. About five periodic project reviews were completed including a study closure. All studies. (10 July 2003)

I prepared an amended FDA form 1572 in order to add a sub-investigator. This form was submitted to the sponsor company and to the local IRB. Osteoporosis study. (24 July 2003)

I attended monthly rheumatology division meetings to learn specific issues in the rheumatology clinic. The meetings are an opportunity for employees to voice concerns and for the physicians to educate the staff on changes in clinic practice or patient service issues. (July, August, September 2003)

After the last subject has completed the last study visit, a study site closure is scheduled with the monitor. The monitor will indicate any further requirements. Study source documents and all other study materials the monitor does not send back to the company are boxed and prepared for storage in the clinical trials storage facility. Boxes are labeled with the sponsor company name, study name and number, the investigator name, and the coordinator number

in order that materials can be retrieved when needed. Storage must be maintained for several years under federal drug administration rules. Rheumatoid arthritis study. (21 October 2003)

I met with IRB regulatory document coordinator whose job description includes drafting informed consents for sponsor approval, ensuring that protocol signature page is signed, FDA form 1572 is completed, principal investigator (PI) and sub-investigators have signed financial disclosure forms, updated curricula vita and licenses for PI and sub-investigator, listing of IRB board members, CLIA and lab reference ranges, IRB approval, IRB approved informed consent, and business contracts with the sponsor. (11 July 2003)

I attended a local IRB monthly meeting. I observed as investigators and coordinators presented studies to the board to be approved to be started or continued. (05 August 2003)

I obtained HIPPA 2003 privacy training through UNTHSC. (21 July 2003)

I attended a nationwide teleconference regarding recruitment into an ongoing study. Issues regarding protocol were discussed. High enrolling sites gave ideas of how to overcome obstacles. Rheumatoid arthritis/ Osteoarthritis study. (05 September 2003)

I shadowed Dr. Forman in rheumatology clinic at John Peter Smith Hospital in order to get baseline knowledge of rheumatology. I also shadowed Dr. Rubin, Dr. Pertusi, and Linda

Davis, PA in the rheumatology clinic at UNTHSC department of internal medicine. (10 June 2003 to 30 October 2003)

Observed bone scan or DEXA scan done for study purpose. This specialized x-ray compares the density in the hip and lumbar spine of a patient to the density of an average 20 year old, the age at which one has peak bone mass). A score is then given to the patient based on how far away from the standard deviation his/her bone density is. Most scores are given in standard deviations from the mean. -1 to 1 is considered good or normal. -1 to -2.4 is considered osteopenia. -2.5 and lower is considered osteoporosis. For the exam to be accurate, positioning of the patient must be accurate. Moreover, the radiology technician must be able to determine areas on the spine that must be avoided such as the lumbar sacral spine where injury is common. Patients receive an explanation of the test and the results of their test. (27 June 2003)

I was instructed on blood specimen processing. Tiger tops used for chemistry type labs. Purple tops frequently are EDTA preservative tubes and are used for CBCs frequently. Coloring of specimen tube tops can vary; usually instructions from the lab company are included with the lab requisition form, in the lab handbook, or in correspondence from the company. Blood that is drawn by coordinator is allowed to clot for at least 30 minutes. Chemistry/tiger top tubes are centrifuged for 15 minutes, after which, the serum is transferred to a plastic tube using a pipette and universal precautions for blood borne pathogens. Most of

the time, purple tops are not centrifuged and are sent as is to the lab company. However, some protocols require purple EDTA and blue Na Citrate tubes to be centrifuged. Transfer of plasma from these tubes after centrifugation is more difficult as there is no separation layer between the cells and the plasma. Some protocols call for blood smears to be done using the blood in the purple top and slides that are usually provided. I was instructed on proper technique for blood smears. Also, some study protocols call for some specimens to be frozen and some specimens to be sent ambient. I was instructed on proper freezing procedures, maintenance of temperature logs of freezers, refrigerator, and drug storage areas. I was also instructed in proper packaging of both ambient and frozen specimens for shipping, for example the amount of dry ice a package contains in kilograms is important to label on the outside of the box to be compliant with IATA packaging. (11 June 2003)

# CHAPTER III

## Limitations

Due to the proprietary nature of the study that is ongoing, the protocols, specific methods, and data from the novel XOD inhibitor compound will not be reported.

## Discussion

During the course of a clinical trial, the clinical coordinator would attend an investigator meeting for all the principle investigators, clinical research coordinators, and other required personnel. This would follow the site selection visit after the site had been selected by the pharmaceutical company to participate in the trial. This meeting allows the sponsoring pharmaceutical company to educate the site personnel on the study procedures. Investigator meetings occur only at the beginning of new studies. No investigator meetings for the coordinator were scheduled during the internship practicum. This was essentially the only clinical trial activity that was not participated in as part of the internship.

Roles of clinical research personnel were quickly elucidated during the internship practicum. Several ongoing studies allowed for the participation in various aspects of clinical research from the start of the study to the end of a study. Knowledge regarding rheumatology diseases, treatment, and prevention was gained through shadowing clinicians. Finally, the outcome of the XOD inhibitor trial should provide interesting debate about the necessity of a new XOD inhibitor, its safety and efficacy.

## REFERENCE CITATIONS


1. Schumacher HR Jr.: Acute Inflammatory Arthritis, In Clinical Care in the Rheumatic Diseases. First Edition. Edited by ST Wegener, BL Belza, EP Gall. Atlanta, American College of Rheumatology, 1996, pp 186-187.
2. Porter R, Rousseau GS: Gout, The Patrician Malady. Yale University Press. New Haven and London, 1998.
3. Copeman WSC: A Short History of the Gout and the Rheumatic Diseases. University of California Press. Berkeley and Los Angeles. 1964.
4. Bynum B: Irregular Gout. The Lancet 2000; 356:948.
5. Yu KH, Luo SF: Younger age of onset of gout in Taiwan. Rheumatology 2003; 42(1):166-170.
6. Van Doornum S, Ryan PFJ: Clinical manifestations of gout and their management. Medical Journal of Australia 2000; 172:493-497.
7. Sah SP, Rani S, Mahto R: Fine Needle Aspiration of Gouty Tophi: A Report of Two Cases. Acta Cytologica 2002; 46(4):784-785.
8. Terkeltaub RA, Edwards NL, Pratt PW, Ball GV: In, Primer on Rheumatic Diseases, Eleventh Edition. Edited by JH Kippel. Atlanta, Arthritis Foundation, 1997, pp.230-243.
9. Fantone JC, Ward PA: Mechanisms of Inflammation, In Rheumatology and Immunology. Second Edition. Edited by Cohen AS, Bennett JC. Grune and Stratton, Inc., 1986, pp403-417.

10. Kelley WN, Wortmann RL: Gout and Hyperuricemia, In Textbook of Rheumatology. Fifth Edition. WB Saunders Company, 1997, pp1313-1347.

11. Iwamoto I: Drugs and the Inflammatory and Immune Response, In Integrated Pharmacology. Second Edition. Edited by Page C, Curtis M, Sutter M, Walker M, Hoffman B. Mosby, London, 2002, pp 327-341.

12. Roth SH, Calabro JJ, Ehrlich GE, Hukisson EC, Paulus HE: Handbook of Drug Therapy in Rheumatology. PSG Publishing Company, Inc. Littleton, Massachusetts, 1985, pp45-59.

13. Park YB, Park YS, Lee SC, Yoon SJ, Lee SK: Clinical analysis of gouty patients with normouricaemia at diagnosis. Ann Rheum Dis 2003; 62:90-92.

14. Lin KC, Lin HY, Chou P: The Interaction Between Uric Acid Level and Other Risk Factors on the Development of Gout among Asymptomatic Hyperuricemic Men in a Prospective Study. J Rheumatol 2000; 27(6):1501-1505.

15. Wade JP: Drugs and the Musculoskeletal System, In Integrated Pharmacology. Second Edition. Edited by Page C, Curtis M, Sutter M, Walker M, Hoffman B. Mosby, London, 2002, pp 437-454.

16. Nelson DL, Cox MM: Biosynthesis of Amino Acids, Nucleotides, and Related Molecules, In Lehninger Principles of Biochemistry. Third Edition. Worth Publishers, New York, 2002, pp 861-863.

17. Perez-Ruiz F, Calabozo M, Garcia Erauskin G, Ruibal A, Herrero-Beittes AM: Renal Underexcretion of Uric Acid Is Present in Patients With Apparent High Urinary Uric Acid Output. Arthritis & Rheumatism 2002; 47(6):610-613.

18. Lin JL, Tan DT, Ho HH, Yu CC: Environmental Lead Exposure and Urate Excretion in the General Population. The American Journal of Medicine 2002; 113(7):563-568.

19. Shadick NA, Rohko K, Weiss S, Liang MH, Sparrow D, Hu H: Effect of Low Level Lead Exposure on Hyperuricemia and Gout Among Middle Aged and Elderly Men: The Normative Aging Study. J Rheumatol 2000; 27(7):1708-1712.

20. Canoso JJ: Crystal Induced Arthritides, In Rheumatology in Primary Care. WB Sauders Company, 1997, pp150-157.

21. Wortmann RL: Gout and Hyperuricemia. Current Opinion in Rheumatology 2002; 14:281-286.

22. Moriwaki Y, Yamamoto T, Takahashi S, Yamakita JI, Tsutsumi Z, Hada T: Spot Urine Uric Acid to Creatine Ratio Used in the Estimation of Uric Acid Excretion in Primary Gout. J Rheumatol 2001; 28(6):1306-1310.

23. Kling CW, Helm TN, Narins RB: The Diagnosis: Intradermal Tophaceous Gout. Cutis 2001; 67(3):205-206.

24. Kelley JT, Agudelo C: Subcutaneous Tophaceous Nodule Formation Due to Deposition of Cholesterol Crystals. J Rheumatol 2002; 29(8):1798-1799.

25. Fam AG: Gout, Diet, and the Insulin Resistance Syndrome. J Rheumatol 2002; 29(7):1350-1355.

26. Dessein PH, Shipton EA, Stanwix AE, Joffe BI, Ramokgadi J: Beneficial effects of weight loss associated with moderate calorie/carbohydrate restriction, and increased proportional intake of protein and unsaturated fat on serum urate and lipoprotein levels in gout: a pilot study. Ann Rheum Dis 2000; 59:539-543.

27. Cardona F, Tinahones FJ, Collantes E, Escudero A, Garcia-Fuentes E, Soriguer FJ: The elevated prevalence of apolipoprotein E2 in patients with gout is associated with reduced renal excretion of urates. Rheumatology 2003; 42: 468-472.

28. Adelizzi, RA: COX-1 and COX-2 in health and disease. JAOA 1999; 99(11):S7-S12.

29. Nelson DL, Cox MM: Lipid Biosynthesis, In Lehninger Principles of Biochemistry. Third Edition. Worth Publishers, New York, 2002, pp 785-788.

30. Schumacher HR, Boice JA, Daikh DI, Mukhopadhyay S, Malmstrom K, Ng J, Tate GA, Molina J: Randomized double blind trial of etoricoxib and indomethacin in treatment of acute gouty arthritis. BMJ 2002; 324(7352):1488-1492.

31. Emmerson BT: The Management of Gout. NEJM 1996; 334(7):445-451.

32. Taylor CT, Brooks NC, Kelley KW: Corticotropin for Acute Management of Gout. Ann of Pharmacotherapy 2001; 35(3):365-368.

33. Kubler PA: Fatal Colchicine Toxicity. Medical Journal of Australia 2000; 172:498-499.

34. Chattopadhyay I, Shetty HGM, Routledge PA, Jeffery J: Colchicine induced rhabdomyolysis. Postgrad Med J 2001; 77:191-192.

35. Boomershire K: Colchicine-Induced Rhabdomyolysis. Ann of Pharmacotherapy 2002; 36: 824-826.

36. Boulware DW, Becker MA, Edwards NL: Gout and Crystal-induced Synovitis, In Clinical Primer of Rheumatology. Edited by Koopmen WJ, Boulware DW, and Heudebert GR. Lippincott Williams and Wilkins, 2003, pp262-277.

37. Horiuchi H, Ota M, Nishimura S, Kaneko H, Kasahara Y, Ohta T, Komoriya K: Allopurinol Induces Renal Toxicity By Impairing Pyrimidine Metabolism in Mice. Life Sciences 2000; 66(21);2051-2070.

38. Mellado JV, Meono Morales E, Pacheco-Tena C, Burgos-Vargas R: Relation between adverse events associated with allopurinol and renal function in patients with gout. Ann Rheum Dis 2001; 60:981-983.