CHAPTER II

LITERATURES REVIEW

Gout is a clinical syndrome resulting from deposition of monosodium urate crystals in and around joints, with the subsequent development of variable inflammation response and frequently results in significant short-term disability and occupational limitation[1,6].Gout is predominantly a disease of adult men, with a peak incidence in the fifth decade. The prevalence of self-report gout in the United States was estimated at 13.6/1,000 men, 6.4/1,000 women, also the incidence increased with age especially in woman[1,3,4]. Thus, gout is the most common cause of inflammatory arthritis in men over age 30, and is probably the second most common form of inflammatory arthritis in the United States[1].

Allopurinol, the only inhibitor of xanthine oxidase, has been used extensively to treat patients with chronic gout .It is the best drug to lower serum urate concentration in patients advanced renal failure. However, in patients with renal failure, the dosage should be adjusted depending on CrCl in order to minimize Allopurinol Sensitivity Syndrome (AHS)[1,2,4,7,8,29],which occurs in less than 1 in 1,000 cases[2,8].In 1984, Hande et al.[9] suggested the dosage guideline of allopurinol adjusted depending on CrCl for patients with renal insufficiency. However, in some patients with gout the dose is not sufficient to reduce serum urate level and to halt disease progression[2,21,30].

Gout[1-3,6,31]

Gout, is a disease in which tissue deposition of crystals of monosodium urate occurs from supersaturated extracellular fluids and results in one or more clinical manifestations. These include : 1) recurrent attacks of severe acute or chronic articular

and periarticular inflammation, also termed *gouty arthritis* ; 2) accumulation of articular, osseous, soft tissue, and cartilagilnous crystalline deposits, called *tophi* ; 3) renal impairment, also referred to as *gouty nephropathy* ; 4) uric acid calculi in the urinary tract

Gout occurs primarily in adult men, with a peak onset in the fifth and sixth decades, and is rare in children, premenopausal women and in men younger than 30 years.

Gout typically progresses through four stages :

- asymtomatic hyperuricemia ;
- acute gouty arthritis ;
- intercritical gout (the variable interval between recurrent acute episodes) ; and
- chronic tophaceous gout.

Rarely,patients may present with gouty tophi as their initial manifestation

The diagnosis is base on the characteristic clinical picture – acute onset of an exquisitely painful, swollen, Erythrematous joint – along with the demonstration of needle-shaped, negatively birefringent monosodium urate crystals in an aspirate from the affected joint. An elevated serum urate level is supportive of the diagnosis, but elevated serum urate level may be normal in up 40 % of episodes of acute gout.

Uric acid metabolism[1,3,31]

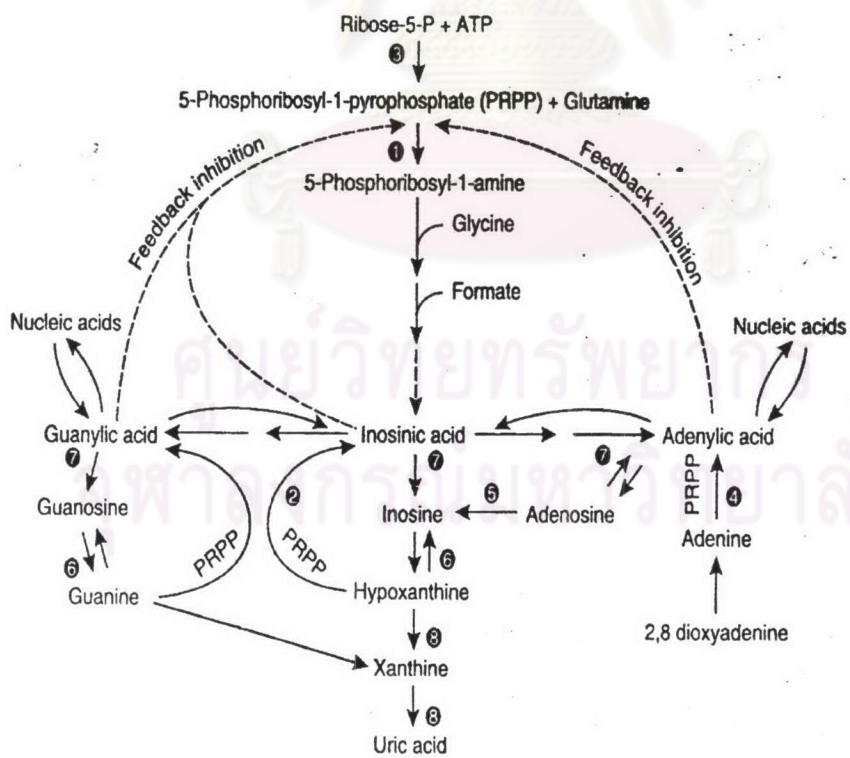
Uric acid is the final breakdown product of purine degradation in humans. It is a weak acid. Urate, the ionized form of uric acid, predominate in plasma extracellular fluid and synovial fluid, with approximately 98 % existing as monosodium urate at Ph 7.4. Plasma is saturated with monosodium urate at a concentration of 6.8 mg/dl at 37°C. At higher concentrations, plasma is therefore supersaturated, creating the potential for urate crystal precipitation. However, precipitation sometimes does not occur even at plasma

urate concentration as high as 80 mg/dl, perhaps because of the presence of solubilizing substances in plasma.

Uric acid is more soluble in urine than water. The pH of urine greatly influences its solubility.

Uric acid is derived both form the ingestion of foods containing purines and the rate of purine biosynthesis, degradation, and salvage. Normally, two-thirds to three-fourths of urate is excreted by the kidneys, and most of the remainder is eliminated through the intestines. The amount of urate in the body is the net result of the amount produced and the amount excretion. The free purine bases that result from nucleoside clevage are adenine, guanine, hypoxanthine, and xanthine. Hypoxanthine is oxidized to xanthine by xanthine oxidase and then further to uric acid by the same enzyme (shown in figure 1)

Figure 1 outline of purine metabolism



(1)Amidophosphoribosyltransfe rase;(2) hypoxanthine-guanine phosphoribosyltransferase;(20) PRPP synthetase;(4) adenine phosphoribosyltransferase;(5) adenosine deaminase;(6) 5′ nucleotidase;(8) xanthine

Hyperuricemia[1], defined as serum urate concentration more than two standard deviations (SD) above the mean established in the individual labolatory for the sex of the patient (generally above 7.0 mg/dl in males or above 6.0 mg/dl in females).

Causes and classification of hyperuricemia[1,3]

The development of hyperuricemia may be cause by an excessive rate of urate production, a decrease in the renal excretion of uric acid, or a combination of both events. Hyperuricemia and gout may be classified as follows. (as shown in table 1)

Table 1 ; classification of hyperuricemia

Uric acid overproduction	Uric acid underexvretion
Primary hyperuricemia	Primary hyperuricemia
Idiopathic	Idiopathic
HGPRT deficiency (partial and complete)	Secondary hyperuricemia
PRPP synthetase superactivity	Diminished renal function
Secondary hyperuricemia	Inhibition of tubular urate secretion
Excessive dietary purine intake	Competitive anions (e.g. keto- and lactic acidosis)
Increased mucleotide turnover (e.g.myeloproliferative and lymphoproliferative disorders, Hemolytic diseases, psoriasis)	Enhanced tubular urate reabsorption
Accelerated ATP degradation	Dehydration, diuretics
Glycogen storage disease (types I, III , V, VII)	Mechanism incompletely defined
Fructose ingestion, hereditary fructose intolerance	Hypertension
Hypoxemia and tissue underperfusion	Hyperparathyroidism
Severe muscle exertion	Certain drugs (e.g. cyclosporine, ethambutol, pyrazinamide, low dose aspirin ; < 2g/day)
Ethanol abuse	Lead nephropathy

Primary : Cases that appear to be innate, neither secondary to another acquired disorder nor a subordinate manifestation of an inborn error that leads initially to a major disease unlike gout ; although some cases of primary gout have a genetic basis. Others do not

Secondary : Cases that develop in the course of an other diseases or as a consequence of drug use.

Iniopathic : Cases in which a more precise classification cannot be assigned.

Uric acid overproduction[1]

Perhaps 10 % of Patients with hyperuricemia or gout excrete excessive quantities of uric acid in a 24- hour urine collection (more than 1,000 mg excreted while on a normal). Overproduction of uric acid occurs with some frequency in a variety of acquired and genetic disorders.

Uric acid underexcretion[1,3,31]

The great majority of patients with primary hyperuricemia or gout (up to 90%) show a relative deficit in the renal excretion of uric acid. Virtually all plasma urate is filtered at the glomerulus, with greater than 95% of the filtered load undergoing proximal tubular (presecretory) reabsorption. Altered uric acid excretion could theoretically result from decreased glomerular filtration, decreased tubular secretion, or enhanced tubular reabsorption.

Stages of gouty arthritis[1,32]

Four phases can be identified in the evolution of gout :

- Asymptomatic hyperuricemia

Asymptomatic hyperuricemia is a situation in which the serum urate level is high but gout, as manifested by arthritis symptoms, tophi, or uric acid nephrolithiasis, has not yet appeared. The tendency toward acute gout increases with the serum urate concentration.

- Acute gouty arthritis

The first attack of acute gouty arthritis usually occurs between the fourth and sixth decades. Almost all acute attacks before 50 years of age occur in men. The acute gouty athritis of gout is the most common early clinical manifestation. The metatarsophalangeal (MTP) joint of the first toe is involved most often, and is affected at some time in 75 % of patients. The ankle, tarsal area, and the knee are also commonly involved. A wrist or finger joint is less often involved during the early attacks. The first episode of acute gout arthritis frequently begins fairly abruptly in a single joint, often

during the night, so that the patient awakes with dramatic unexplained joint pain and swelling. Affected joints are usually warm, red, and tender. Early attacks tend to subside spontaneously over 3 – 10 days even without treatment. Patients are often conpletely symptom free after an acute attack.

Acute attacks may be triggered by a specific event recognizable by patients, such as trauma, alcohol, drugs, surgical stress, infection, hemorrage, dietary excess. Swings in the level of serum urate,either increasing or decreasing serum urate levels acutely, may precede episodes of gouty arthritis. The often occurs early in the course of treatment with uricosuric drugs or allopurinol. Drugs-induced gout secondary to increased serum urate levels occurs on occasion with diuretic therapy, intravenous heparin, and cyclosporin. Diuretic therapy in the elderly appears to be a particularly important precipitating factor for gouty arthritis.

- Intercritical gout

The terms *intercritical gout* and *interval gout* have been applied to the periods between gouty attacks. In most patients, a second attack does occur within 6 months to 2 years (but may not develop until after 27 years). The frequency of gout attacks usually increases with time in untreated patients. Later, attacks have a less explosive onset, are polyarticular, become more severe, last longer, and abate more gradually. Nevertheless, recovery is complete. Roentgenographic changes may develop during the intercritical period despite no sign of tophi on physical examination. These changes are more likely in those with more severe hyperuricemia and more frequent acute attacks.

- Chronic tophaceouse gout

Eventually, the patient may enter a phase of chronic polyarticular gout with no pain-free intercritical periods. At this stage, gout may be easily confused with other types of arthritis. The time from the initial attack to the beginning of chronic symptoms or visible tophaceous involvement is highly variable in studies of untreated patients. Hench reported intervals ranging from 3 to 42 years, with an average of 11.6

years between the first attack and the development of chronic arthritis. The rate of formation of tophaceous deposits correlates with both the degree and the duration of hyperuricemia and also correlates with the severity of renal disease. Deforming arthritis can develop as a result of the erosion of cartilage and subchondral bone caused by crystal deposition and the chronic inflammatory reaction.

Complications and associated diseases[1,3]

The development of hyperuricemia in arterial hypertension appears to be related to an abnormality in uric acid transport by the renal tubules. Diabetes mellitus, cardiac and cerebral atherosclerosis, and hypertrigliceridemia also occur more frequently among patients with gout. The precise explanation for these associations is not known, although a common connection with obesity has been suggested[1]

Diabetes mellitus

Gouty arthritis has been reported in less than 0.1 to 9 persent. Epidemiologic studies have not demonstrated a relation between gout and diabetes or between serum urate and blood glucose concentrations.

Hyperglyceridemia

Hyperglyceridemia has been reported in 75 to 80 percent of patients with gout. A range-order correlation of serum urate and serum triglyceride values has been described but also disclaims. Gouty patients who drink alcohol excessively have mean serum triglyceride levels that are higher than those of their obesity-matched controls and those of non drinking gouty patients. Many studies have been unable to show a correlation between serum irate and cholesterol values. Hypersention does not appear to be associated with a unique lipid phenotype.

Hypertension

Hyperuricemia has been reported in 22 to 38 percent of patients with untreated hypertension. The overall prevalence of gout and hypertension has been variously reported as 2 to 12 percent. In a population study of 6,000 residents of

Tecumseh, Michigan. No correlation was found between blood pressure and serum urate concentration adjusted age, sex, and relative body weight. However, hyperuricemia may be an indication of potential risk of hypertension for adolescent males. The incidence of both moderate and severe hypertension is unrelated to duration of gout.

Treatment

In each stage of gout that may require therapy–acute, intercritical, tophaceous– there is effective medical management, which in most situations should be successful and without excess the complications.

After the diagnosis of gout, the treatment goals should be to provide rapid and safe relief of the pain of acute arthritis, to prevent further attacks, and to prevent destructive arthropathy and the formation of tophi or kidney stones.[1]

Acute gouty arthritis[1,32]

The mainstay of treatment during an acute attack is the administration of an anti-inflammatory drug such as colchicine, nonsteroidal anti-inflammatoiy drugs (NSAIDs), or glucocorsteroid depending on the age of the patient and comorbid conditions.

Prophylactic treatment of intercritical gout[1]

When gouty attacks are frequent or when urate-lowering therapy is being initiated, daily oral colchicine may be given to reduce their frequency. The practice of giving small daily doses of colchicine as prophylaxis against acute attacks of gout, it is approximately 85 percent effective in preventing acute attacks. The use of colchicine at 0.6 mg once or twice a day is generally well tolerated. Prophylaxis usually is continued until the serum urate value has been maintained well within the normal range and there have been no acute attacks for a period of 3 to 6 months. Finally, prophylactic colchicine is not recommended unless one also uses urate-lowering agents. Prophylactic colchicine stops the acute inflammatory response but not the deposition of crystals in tissues.

Control of hyperuricemia in monosodium urate deposition[1,-4,31]

Control of hyperuricemia with antihyperuricemic agents can prevent or reverse urate deposition. In general, the aim of antihyperuricemic therapy is to reduce the serum urate concentration to less than 6 mg/dl at 37°C. Which should allow solubilization of crystalline urate. Lower levels are often needed for resorption of cutaneous or osseous tophi and reduction of attack frequency. When this is achieved, urate deposits resolve. Reduction to this level may be achieved pharmacologically by the use of allopurinol or a uricosuric agent. Antihyperuricemic drugs do not have anti-inflammatory properties. Allopurinol inhibits xanthine oxidase, the enzyme that catalyzes the oxidation of hypoxanthine to xanthine and xanthine to uric acid. Uricosuric agents reduce serum urate concentrations by enhancing the renal excretion of uric acid. Although a large number of drugs exhibit this property, the most effective agents are probenecid , sulfinpyrazone, and benzbromarone.

The treatment of hyperuricemia in gout is ordinarily carried on indefinitely. For those patients with gout who excrete less than 700 mg of uric acid per day and have normal renal function, reduction of serum urate concentration can be achieved equally well with allopurinol or a uricosuric drug. These agents are equally effective in preventing deterioration of renal function in patients with primary gout. In most cases, allopurinol is probably the drug of choice because it can be used with fewer restrictions compared with uricosuric agents.

In general, the candidate for uricosuric agents is the gouty patient who is younger than 60 of age and has normal renal function (creatinine clearance greater than 80 ml/min), uric acid excretion of less than 700 mg/24 hours on a general diet, and no history of renal calculi. In certain situations, allopurinol is clearly the drug of choice in the gouty patient (as shown in table 2).Gouty individuals with a history of renal calculi of any type should be treated with allopurinol. Likewise, patients with tophi generally should receive this agents to decrease the load of uric acid that must be handled by the kidney. Patients with gout and mild renal insufficiency may be given either type of

agent, but uricosuric agents would not be expected to work when the glomerular filtration rate is less than 30 min/min. Allopurinol doses must be decreased in the presence of reduced glomerular filtration.

Table 2. Indications for allopurinol

Hyperuricemia associated with increased uric acid production
Urinary uric acid excretion of 1000 mg or more in 24 hours
Hyperuricemia associated with HPRT deficiency or PRPP Synthetase overactivity
Uric acid nephripathy
Nephrolithiasis
Prophylaxis before cytolytic therapy
Intolerance or reduced efficacy of uricosuric agents
Gout with renal insufficiency (GFR < 60 ml/min)
Allergy to uricosurics

Abbreviations : GFR, Glomerular filtration rate ; HPRT, hypoxanthine-guanine phosphoribosyltransferase ; PRPP, phosphiribisylpyrophisphate.

A final indication for allopurinol is the failure of uricosuric agents to produce a serum urate concentration lower than 7 mg/dl or patient intolerance of the uricosuric agent. Allopurinol and a uricosuric drug may be used in combination for the patient with tophaceous gout in whom it is not possible to reduce the serum urate below 6.4 mg/dl with single agent. In other settings, if 400 mg of allopurinol per day does not cause the serum urate to drop below 6.4 mg/dl, one should question the compliance of the patient.

Allopurinol therapy is indicated for the gouty patient who excretes large amounts of uric acid in the urine. The incidence of renal calculi is about 35 percent in patients with primary gout who excrete more than 700 mg/day of uric acid. Similarly, it is the magnitude of uric acid excreted per day that correlates best with the development of acute uric acid nephropathy. Therefore, these patients risk development of renal disease. There is also greater risk for uric acid stones on initiation of uricosuric therapy. Allopurinol, which decreases uric acid excretion, is the logical choice of therapy in these patients. For the same reason, patients with certain neoplastic diseases that are associated

with hyperuricemia caused by increased mucleotide catabolism may be treated with allopurinol.

Allopurinol Hypersensitivity Syndrome (AHS)[8,17-21]

Allopurinol , an analog of hypoxanthine, has been widely used in clinical practice for over 20 years for the treatment of hyperuricemia and gout. Allopurinol is generally well tolerated, approximately 2 percent of patients taking the drug develop a mild cutaneous rash and 3% to 5% develop severe cutaneous reactions, eosinophilia, nephritis, and hepatotoxic effects[8,28]. Mcinnes et al.[29] reported that 1.8 percent of a sample of hospitalized patients taking allopurinol experienced an adverse reaction secondary to the drug, and that it induces a severe reaction in 1 of 260 patients (0.4 percent). Allopurinol hypersensitivity syndrome (AHS) is an infrequent but life-threatening adverse effect of allopurinol therapy.The incidence of AHS is unknown, although it is thought to be very low. There are about 100 cases of AHS described in the literature, and it is estimated that 240 million doses of allopurinol are administered annually. Although rare, AHS can be life threatening, may require prolonged hospitalization, and occasionally involves residual morbidity.

Pathogenesis

The exact mechanism responsible for the development of AHS is unknown. However, existing data support the coexistence of three mechanism : immunologic factors, genetic predisposition, accumulation of the drug.

The accumulation of allopurinol is considered a risk factor for the development of AHS. Allopurinol is rapidly metabolized to oxypurinol, which is responsible for most of the drug's pharmacologic actions. Oxypurinol serum concentrations vary widely among patients, depending primary on renal function. The elimination half-life of oxypurinol is approximately 24 hours in patients with normal renal function, and there is

a strong correlation between serum oxypurinol concentrations and creatinine clearance (ClCr). Some authors have suggested the existence of a relationship between elevated serum oxypurinol concentrations and the development of AHS.

However, most reports have described individual cases or series of patients with adverse events related to allopurinol and patients receiving allopurinol who did not develop adverse events were not included. There is only one reporting allopurinol associated adverse reactions in hospitalised patients with comorbid conditions and receiving multiple treatments.[22,23]

Manifestation of AHS

The allopurinol hypersensitivity syndrome is characterized by fever, eosinophilia, abnormalities of liver function, rapidly progressive renal dysfunction, and a skin eruption which may take the form of erythema multiforme, Stevens-Johnson syndrome or, in the worst cases, toxic epidermal necrolysis. The average time of onset of the syndrome after starting allopurinol is two to six weeks but can be considerably longer.[8,33,34]

In 1993, however, Arellano and Sacristán[8] reviewed the pathophysiology, pathology, and clinical findings from 101 cases of AHS reported in the literature. They suggested that the clinical picture of AHS included a rash and at least one of the following criteria: worsening of renal function, acute hepatocellular injury, or marked eosinophilia without reference values (table 3).

Table 3 : proposed criteria for the definition of allopurinol hypersensitivity syndrome

1.A clear history of exposure to allopurinol
2.A clinical picture including :
a rash consisting of either TEN, erythema multiforme, or a diffuse maculopapular or exfoliative dermatitis and at least one of the following:
- worsening of renal function
- acute hepatocellular injury without reference value
- marked eosinophilia
3.Lack of exposure to another drug that may cause a similar clinical picture

The risk of developing AHS

In 1974, Young et al[35] described two cases of severe allopurinol toxicity seen at our medical center and reviewed the histories of an additional four patients previous described in the literature. They suggested that the development of this syndrome was associated with the use of allopurinol in patients with renal insufficiency and in patients receiving thiazide diuretics[9,17-21]. Although AHS may rarely occur in patients with oxypurinol concentrations with in the therapeutic range, it is clear that the syndrome is much more likely to develop in patients with renal insufficiency in whom the dosage of allopurinol has not been reduced appropriately, resulting in excessive elevation of plasma oxypurinol concentrations.[8,9]

Because oxypurinol, active metabolite of allopurinol, accumulates in renal failure, and raised serum levels of the metabolite have been found to correlate with risk of developing the toxicity syndrome.[8,9] Furthermore, renal function declines steadily with age but loss of function is not always reflected by rise in serum creatinine concentration. Thus, the elderly are most vulnerable to developing hypersensitivity reaction.[34]

The coadministration of thiazide diuretics with allopurinol has been reported to be a risk factor for the development of AHS. These agents inhibit uric acid secretion, and it has been suggested that they may impair oxypurinol clearance. However, studies performed in healthy volunteers have not shown this to be the cases.[9]

Treatment[8,4,18,

There is clearly no cure for AHS. Patients should be warned to watch for a rash or fever, which should prompt discontinuation of the drug and be received appropriate supportive therapy. Prednisolone (60-100 mg/day) has been used successfully to treat allopurinol-induced renal insufficiency. However, the potential risks and benefits of steroid therapy remain to be determined. Cyclosporin has been used successfully in cases of TEN, and its therapeutic role in AHS should perhaps be considered in the future

Dosage guideline of allopurinol for renal impairment patients

In 1984, Hande et al[9] have reviewed 6 case reports of AHS and 72 patients with severe reaction to allopurinol described in the literature. They found that most of patients were given standard dose of allopurinol (200 to 400 mg/day) and approximate 81 percent of patients had evidence of renal insufficiency, defined as a serum creatinine concentration $\geq$ 1.5 mg/dl and/or BUN $\geq$ 40 mg/dl, before initiation of allopurinol therapy. However, only 52.6 percent of these patients had a clear history of renal insufficiency.

They also compared creatinine clearance values with serum oxypurinol concentration in 28 patients receiving oral allopurinol therapy with 300 mg/day for more than 2 weeks. An inverse linear relation exists between the serum oxypurinol concentration and the creatinine clearance

Although a specific mechanism or causative agent producing toxicity has not been identified, elevated serum concentrations of oxypurinol appear to correlate with the development of this toxicity syndrome. The accumulation of oxypurinol may be a primary mechanism for the development of AHS. The use of standard (300 to 400 mg/day) doses of allopurinol in patients with renal insufficiency results in plasma oxypurinol concentrations several times greater than what is needed the inhibit xanthine oxidase and prevent increased uric acid formation in most instances. Therefore, they have suggested that the initial maintenance dose of allopurinol should be reduced on the basis of the creatinine clearance to prevent occuring AHS. Dose adjustments, according to the guidelines in table 4 , have resulted in therapeutic serum oxypurinol concentrations (20 to 100 μM or 5-15 μg/ml) in only six patients with renal failure whom they have studied after proper dosage modifications. Furthermore, this dosage guideline of allopurinol has been widely recommended.

Table 4 : maintenance doses of allopurinol for adults based on individual creatinine clearance measurements

Creatinine clearance (CrCl : ml/min)	Maintenance dose of allopurinol
0	100 mg every three days
10	100 mg every two days
20	100 mg daily
40	150 mg daily
60	200 mg daily
80	250 mg daily
100	300 mg daily
120	350 mg daily
140	400 mg daily

Unfortunately, using these dosage guideline in some patients with gout , receiving allopurinol in doses adjusted to the creatinine clearance rate, may not benefit from the use of lower doses of the drug , and higher doses are needed to reduce the serum uric acid level, especially in the elderly, because of xanthine oxidase inhibition by oxypurinol appears to be reduced in old age[41]. Increased doses in some cases do not appear to be related to higher prevalence of serious adverse reactions and frequency of adverse events are similar to that found in patients receiving dose adjusted to the creatinine clearance rate. The several studies show a significant proportion of patients surveyed the allopurinol dose exceeded that recommended in Hande's published guideline, but severe toxicity is rare.[4,8,22-24] In contrust, minor adverse reactions to allopurinol probably occur is 1.8-2.0 % of patients receiving the drug.[22]

Therapeutic range of oxypurinol concentration

An optimal concentration range for steady-state plasma oxypurinol concentrations has not been established formally. While the relationship between plasma levels of oxypurinol and urate in not well-defined[36]. The serum urate concentration depends on many factors, chiefly those affecting either urate production (both endogenous and exogenous) or the renal elimination of urate. In most patients,

hyperuricemia, whatever its cause, is responsive to allopurinol therapy. However, in some patients, the usual doses of allopurinol are not effective in restoring the plasma urate to normal[37]. Emmerson et al[37] have suggested that plasma oxypurinol concentration between 30 to 100 μmol/l (5 – 15 μg/ml), were generally effective in controlling hyperuricemia in patients with normal renal function. Unfortunately, the effective oxypurinol level in patients with renal insufficiency was not examined.

However, No data are available concerning allopurinol plasma concentrations in overdosage or acute in toxication[38]

In 1987, Emmerson et al.[37] were studied the level of plasma oxypurinol concentration in 66 gout patients with normal to moderate renal function receiving the usual dose of allopurinol varied between 100-400 mg/day. They found that plasma oxypurinol concentration correlated significantly with allopurinol dose in patients whose plasma creatinine within normal range. However, no such correlation was demonstrable in patients with renal insufficiency and plasma oxypurinol concentrations at each allopurinol were all higher than and significantly different from patients with normal plasma oxypurinol concentrations. Moreover, they was a significant correlation between plasma oxypurinol concentrations and serum uric acid level ($r=0.41$, $p=0.001$). In addition, there was a significant association between desirable serum urate level (0.42 mmol/l) and plasma oxypurinol concentrations ($p=0.03$). From these result, therefore, they suggested that the upper limit of the therapeutic range of plasma oxypurinol concentrations could be up to 100 μmol/l (15 μg/ml) and renal function remains one of the dominant factors in determining the plasma oxypurinol concentration.

In 1988, Day et al.[39] observed the range of plasma oxypurinol concentrations in 50 patients of rheumatology department taking long-term allopurinol therapy, 85% of patients taking 300 mg/day. The result was found a wide range of steady-state plasma oxypurinol concentrations from 2.8-55.8 μg/ml(mean±SD=15.2±11.7μg/ml) without

developed serious adverse events and 32% of patients had plasma oxypurinol concentrations excess of 15 μg/ml. Also, there was a significant correlation between plasma oxypurinol concentrations and CrCl ($r=0.57$; $p<0.005$: $n=31$), this finding is similar to result from previous investigation by Hande et al.[9]

In addition, twenty-four hours urine urate excretions were available in 32 patients and showed an exponential relationship to plasma oxypurinol concentrations ($r=0.86$). Although there was no significant relationship between serum urate level and plasma oxypurinol concentrations, this results disagree with a previous study of Emmerson et al, but the majority of plasma urate values were in the normal range and there was little decrement in serum urate level with higher plasma oxypurinol concentrations. In study of Emmerson et al., they suggested that the concentrations of oxypurinol achieved at 30-100 μmol/l (5-15μg/ml) may be optimal for effective control of hyperuricemia in patient with normal renal function. Unfortunately, the results of this study which included high proportion of patients with renal impairment show that the plasma oxypurinol concentrations in some patients should be increased up than 15 μg/ml to bring the plasma urate into the goal standard of urate-lowering treatment. Therefore, it is possible that the plasma oxypurinol level at 5-15 μg/ml may be lower effective to reduce serum urate into the goal standard of urate-lowering treatment, especially in patients with renal insufficiency. However, an optimal concentration range for steady state plasma oxypurinol concentration has not been established formally and need to define precisely the optimal concentrations for efficacy with a low risk of toxicity in patients with renal insufficiency.

In 1990, Peterson et al.[36] examined dosage prescribing and steady state plasma oxypurinol concentration in 66 patients receiving allopurinol therapy, 65% taking 300mg/day, and most patients were renal impairment. The results of this study, similarly study of Day et al., they found that 35% of patients were receiving excess dosage allopurinol and plasma oxypurinol concentration were often very high was in range 28-

486 μmol/l (4.3-73 μg/ml) ; mean±SD=156±109μmol/l (24±16.5 μg/ml). Also, plasma oxypurinol concentration and serum urate were no significantly related. However, most patients (33/42:79%) with oxypurinol level higher than 100 μmol/l (15μg/ml) had urate concentrations within the normal reference range, but not significant improved in patients with oxypurinol level up to 100 μmol/l. In addition, the oxypurinol concentration was moderately related to CrCl ($r=-0.45$, $p<0.001$).

They suggested that 100 μmol/l (15 μg/ml) should be taken as the upper limit of the therapeutic range for oxypurinol concentration to control serum urate and avoid the AHS

From these previous studies, nevertheless, the relationship between the changes of serum urate level at before and after allopurinol therapy and plasma oxypurinol concentration at vary dosage of the drug was not examined. Therefore, the reference range of oxypurinol concentration may be not the optimal range to reach normal serum urate.

The influence of allopurinol on renal function

Allopurinol is metabolized by xanthine oxidase to oxypurinol. Unlike allpurinol, a large part of oxypurinol is reabsorbed by the renal tubules. However, About 70 % of the administered daily dose is excreted in urine as oxypurinol[7]. The normal renal clearance of oxypurinol is 16.5 ml/min. this has been found to be greatly diminished in renal insufficiency[21]. Therefore, using long-term maintenance dose of allopurinol or an accumulation of serum oxypurinol concentration in gout patients with renal insufficiency may be effect to renal function or allergic reactions induce renal damage.

Furthermore, acute interstitial nephritis (AIN), a cause of acute renal failure characterized by interstitial inflammation and renal tubular damage, has also been described in association with the allopurinol hypersensitivity syndrome, a cell-mediated hypersensitivity response similar to antibiotic-induced nephritis[27].

However, the direct effect of allopurinol to renal function has never been clarified and to date little data have been published to show this effect.

- Studies of allopurinol treatment on renal functions

Karl-Holger Sjöberg[40] studied in ten male patients with gouty kidney involvement. The eight patients had slight to moderate renal insufficiency with serum creatinine of 1.5 to 3.5 mg/dl. The average duration of allopurinol treatment was 5 to 6 months (range 2 weeks to 18 months). It was found that their kidney function did not change during allopurinol treatment except in one patient who showed signs of improvement and none of them developed any adverse events of allopurinol. This case was 47 year old man who had a severe tophaceous gout and nephrocalcinosis. When allopurinol treatment was started, there was a slow improvement of renal function with inulin clearance increased from before treatment 31 ml/min to 55 and to 70 ml/min, after allopurinol therapy for 2 months and 17 months respectively. The dose of allopurinol was increased until 600 mg daily. However, three patients died during treatment (two in uraemia and the third from cerebral haemorrhage) after having taken allopurinol for 2 weeks, 2 months, and 11 months respectively.

Rundles et al[12] studied in 46 patients with intermittent or/and chronic gout. This study was close observation for periods of 1 to 28 months. The dose of allopurinol required to normalize the hyperuricemia in this group of patients with gout range from 200 to 1,000 mg/day (average dose of 500 mg/day)

This study found that eight patients who had complication of azotemia or renal disease involvement, also used in standard maintenance dose of allopurinol (range 300 to 600 mg/day) for control serum uric acid concentration to normal level. In addition, in these patients who had some impairment of renal function before treatment was begun, there was no evidence of progression during allopurinol therapy, and in some instances renal function seemed to improve. However, five patients developed mild skin reaction.

Two patients of these cases being treated with allopurinol and also impaired renal function and elevated BUN concentration.

Levin et al.[11] carried out in 33 patients and 22 patients of these had endogenous creatinine clearance rate less than 70 ml/min before starting allopurinol. The renal function was evaluated before and after allopurinol therapy 300 to 400 mg/day. The duration of study was for at least 3 months (21 for 6 months, 13 for 9 months and 9 for 12 month).

The result of allopurinol treatment on renal funtion, shown as the change of mean endogenous creatinine clearance at the beginning and the end of allopurinol treatment, was found that there was no significant change in creatinine clearance of 29 patients, the other four patients clearances were 51, 60, 56, and 64 ml/min,initially and 70, 67, 64, and 63 ml/min 5, 5, 1, 5 and 4 months later respectively. Certainly those patients with impairment of renal function showed no consistent deterioration. Moreover, there was no significant change in the percentage blood urea level and in urinary protein excretion. Thus, it can be concluded that there was no significant change in renal function as measured by these parameters. However, two patients developed maculopapular rash which disappeared immediately after cessation of treatment. In one patient did not reappear after therapy reinstituted. Both of patient had impaired renal function, creatinine clearance being 11 and 33 ml/min, respectively.

Willson et al[13] described the result of the using allopurinol over many months in 12 uraemic patients with severe gout. Allopurinol was given in a dosage of 100 to 400 mg/day. All patients had renal disease, with an endogenous creatinine clearance below 68 ml/min. (average 33 ml/min) and a serum urea above 44 mg/dl. Duration of treatment was in range 4 to 48 weeks. The degrees of renal damage as judged by the endogenous creatinine clearance.

The result of study was found that there was no significant improve in renal function which can certainly be attributed to allopurinol in gout patients with ureamia.

However, in two patients, there was a significant improve in renal function, increasing creatinine clearance from 52 to 98 and from 31 to 56 ml/min, respectively. The serum urea and the urinary sediment were not altered significantly. Two patient died of terminal renal failure after 4 and 24 weeks treatment, the serum urea in both was above 240 mg/dl before treatment. Transient diarrhea, rash and persistent reticulocytosis were minor side-effects.

Bowie et al.[14] reported the long-term effect of allopurinol treatment on renal function in 14 gout patients with chronic renal failure. the results of renal function tests and biochemical studies of these patients after treatment for periods up to 19 months with an average of 12 months. Allopurinol was started at 300 mg daily to divided doses and was increased over subsequent weeks until the serum uric fell below 6 mg/dl, one patient given 600 mg/day, two for 400 mg/day and all others 300 mg/day. Renal function was assessed at six-monthly intervals using serum urea, serum creatinine, creatinine clearance, urinary protien, cellular excretion and urine cultures.

The changes in serum urea, serum creatinine and creatinine clearance in patients on treatment were observed for 6, 12 and 18 months respectively.

There was no siginificant change in creatinine clearance, however ; the plasma creatinine and serum urea both rose slightly during the first 12 months of treatment.

Proteinurea appeared during treatment in two patients and increased in seven other. The biggest increase in proteinurea was seen in the patient who had previously had a nephrotic syndrome. There was no significant change in urinary cellular excretion or bacteriology throughout the trial. All other biochemical invastigations at the end of trial were normal.Three of 14 patients died during the course of the study and six of the 14 patients developed an itchy maculopapular rash which subsided over two to 12 weeks while allopurinol was continued.

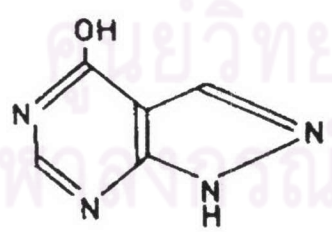
Briney et al.[15] evaluated the effect of continous of allopurinol on renal function in 10 gouty patient with gouty nephropathy. The dosage of allopurinol varied from 200 to

800 mg/day,with an average of 400 mg/day. Serial renal function was tested at 6- to 12-month intervals, glomerular filtration rates (GFR) measured by the clearance of inulin (Cin) and effective renal plasma flow measured (ERPF) by the clearance of ρ-aminohippurate (CPAH). Following therapy that ranged from 6-38 months (average:23 months), prior to therapy the GFR varied from 17.4 to 59.7 ml/min (average 34.3 ml/min) and ERPF valued varied from 64.2 to 256 ml/min (average :168 ml/min).

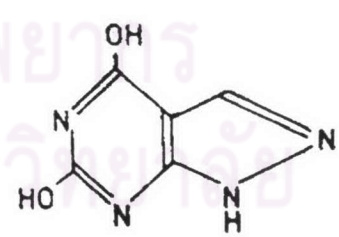
At the time of the study period the observed mean increase in GFR of 11.4 ml/min was a statistically siginificance from the borderline ($p<0.10$), but the observed mean increase in ERPF of 41.8 ml/min was not significant. In four of 10 patients both the GFR and ERPF valued increased more than 2% from those obtained in the pretreatment period. In no instance did both the GFR and REPF values decrease by more than 20%.

Pharmacokinetic of allourinol[7,38]

Allopurinol [1H-pyrazolo (3,4-d) pyrimidin-4-ol] is an oxypurine base with a molecular weight of 136.11. it is a polar compound which is slightly soluble in water and ethanol and has a pKa of 10.2.Its metabolite, oxypurinol, is less soluble in water.



Allopurinol



Oxypurinol

Absorption

With single oral dose, peak allopurinol concentration occur after 1 hour. Oxypurinol is detected in plasma within 15 minutes and peak plasma concentrations are observed after 3 to 5 hours[39,41,42]

Distribution

Allopurinol and oxypurinol are substrates for the enzyme xanthine oxidase, which is present in the cytoplasm of endothelial cells of capillaries, including sinusoid, with the highest activity in the liver and intestinal mucosa.Tissue concentrations of allopurinol have not been reported in humans, but it is likely that allopurinol and oxypurinol will be present in the highest concentrations in these tissues. Allopurinol and oxypurinol are negligibly bound by plasma proteins and therefore variations in protein binding are not thought to significantly alter clearance. The apparent volume of distribution is about 1.6 L/kg which suggests relatively extensive uptake by tissues. No data are available on allopurinol or oxypurinol concentrations in breast milk, although xanthine oxidase has been found in high concentration in milk-secreting epithelial cells, nor are data available concerning distribution and tissue concentrations of the oxypurines in fetal and placental tissues.

Elimination

Allopurinol is rapidly converted to oxypurinol by xanthine oxidase.Both allopurinol and oxypurinol inhibit the action of this enzyme. The half-life of allopurinol and oxypurinol are 1to3 hours and 18 to 30 hours, respectively. Following oral administration, plasma allopurinol and oxypurinol concentration decline in an exponential fashion consistent with a first-order profile. The elimination half-life is not dose-dependent according to available data. However, the possible occurrence of dose-dependent elimination has not been explored at higher dosages. Oxypurinol has a long elimination half-life and is eliminated unchanged in urine. Variation in protocols and/or creatinine clearance may account for the large discrepancies in reported valued of the elimination half-life are not clear. Renal clearance of oxypurinol is about 30 ml/min.

A mumber of factors may influence the renal elimination of oxypurinol. As the renal clearance of oxypurinol is similar to those mechanisms controlling secretion and reabsorption of uric acid, it follows that changes in urine pH, glomerular filtration and uric acid concentrations may influence oxypurinol elimination. Therefore, decreased uric

acid excretion with long term allopurinol therapy may be expected theoretically to alter the tubular reabsorption of oxypurinol, although this has not been demonstrated in the therapeutic setting.

In patients with severe renal dysfunction the elimination half-life of oxypurinol is prolonged to 1 weeks. No data are available on the influence of hepatic disease or age on the kinetics of allopurinol