CHAPTER I

INTRODUCTION

Gout is a disease due to tissue deposition of monosodium urate crystals and is the common cause of inflammatory arthritis which frequently result in significant short-term disability and occupational limitations[1]

Allopurinol is an effective urate lowering drug, that is most frequently used in patients with gout and other hyperuricemia condition. Allopurinol is the only xanthine oxidase inhibitor, it blocks the final step in urate synthesis, that should be reserved for patients in whom there is urate overproduction, nephrolithiasis or other contraindications to uricosuric therapy and it is the preferred drug in renal insufficiency[1-4]. In general, the initial dosage of allopurinol is recommended as 100 mg daily and that this daily dose should be increased by 100 mg weekly until the serum urate concentration falls below 6 mg/dl (less than 5 mg/dl in patients with tophaceous gout) [2,4-6] or until the maximum recommemded dasage of 800 mg daily is reached[7]whichever appear first. The average maintenance dosage is 300 mg daily. However, the dose of allopurinol should be reduced in proportion to the glomerular filtration rate (GFR) as assessed on the basis of the creatinine clearance (CrCl), to avoid the development of allopurinol hypersensitivity syndrome[2,4,7-9]. In renal insufficiency, although, allopurinol is the drug of choice.

To date, limited data have been published to show the influence of this drug upon renal function and there are no studies investigate the relationship between serum oxypurinol concentrations after standard doses of allopurinol and the changes in GFR of patients with renal insufficiency.

In 1966, Levin et al[11] observed serial CrCl in 29 patients who had CrCl less than 70 ml/min and on allopurinol treatment during 3-12 months. They found that CrCl in this group were not significantly change and did not show any consistent deterioration renal function.

Rundle et al[12] reported that renal function tended to stabilize and in some in stances seemed to improve with allopurinol treatment. Moreover, this improvement could occur at an early stage of gouty nephropathy, but would be unlikely to occur in advanced renal disease.

In 1967, Wilson et al[13]concluded that there was no significant improvement in renal function in gout patient with average CrCl below 68 ml/min during 4-48 weeks of allopurinol treatment period. However, in 2 patients, their CrCl were increased from 52 to 98 ml/min and from 31 to 56 ml/min, respectively.

Bowie et al[14] observed 12 patients with severe gout and chronic renal function (CRF) and found that there were no significant change in CrCl after receiving allopurinol 300-600 mg/day for 6, 12 and 18 months.

In 1979, Briney et al[15] studied in 7 gout patients with renal impairment and average CrCl of 34.3 ml/min, taking allopurinol 200-800 mg/day for 6-32 months and found that there were significant increase in CrCl after allopurinol treatment.

Although, allopurinol is generally well tolerated with few siginificant adverse effect, the main clinical practice problem of allopurinol is the occurrence of Allopurinol Hypersenitivity Syndrome (AHS). Eventhough this toxicity syndrome is rare but it is life threatening[8,9,16].The syndrome is consists of maculopapular or desquamative rash, fever, hepatitis, eosinophillia and worsening of renal function . Early studies suggested that the development of this syndrome was associated with the use of allopurinol in patients with renal insufficiency and in patients concomitantly receiving thiazide diuretic[9,17-21]. There is also evidence of cross reactivity between allopurinol and oxypurinol, active metabolite of allopurinol[19,21]. In 1982, Hande et al[9] reviewed the histories of 78 case reports in whom severe reaction to allopurinol were occurred and concluded that the development of this syndrome was possible to associated with the use of standard dose of allopurinol (200-400 mg/day) in patients with renal insufficiency. Moreover, they proposed adjusting the dose of allopurinol according to the rate of CrCl but only for the purpose of preventing the risk of AHS. However, the mechanism of AHS is unknown[8-10] and some

patients with gout receiving allopurinol in dose adjusted to CrCl may not be benefit from the lower doses since the higher doses are needed to reduce the serum uric acid level[22,23]. Several survey studies[22-24] showed significant proportion of patients required dosages of allopurinol that were exceed the recommended dosage in the guideline in order to control their uric acid level without occurring AHS. They also found that increased doses in such cases do not appear to be related to a higher prevalence of serious adverse reactions, and AHS can occur in some cases who have normal renal function[25-27]. The incidence of AHS is unknown, although it is thought to be very low. There are about 100 cases of AHS described in the literatures. Approximately 3-5 percent of patients taking allopurinol develop severe cutanous reaction, eosinophilia, nephritis and hepatotoxic effect[28]. AHS developed, on average, 2 to 6 weeks after initial allopurinol therapy[8,21,27,29]

In our previous survey of allopurinol dosage prescribing in gout patients at out-patient department of Rajavithi hospital during January 2002 to April 2002, we found that 64.2% of patients received higher than standard maintenance dose of allopurinol. Six cases (the total was 205 cases) occurred mild skin rash after treatment but did not develop to serious adverse events.

The purpose of this study

1. To study the renal effect of allopurinol after standard dose 300 mg daily in gout patients with renal insufficiency.
2. To examine the relationship between plasma oxypurinol concentrations and the change in serum urate levels in gout patients with renal insufficiency.
3. To examine the other adverse effects of allopurinol .