CHAPTER IV

RESULTS

Demographic data

Twenty-seven patients completed this study, their demographic data were summaried in table 7 a and 7 b. the detail characteristics of each individual patient were presented in appendix A.

Table 7 a : Demographic data of the patients

Demographic data	Number of patients N = 27(%)
Sex	
Male	25(92.59%)
Female	2(7.41%)
mean age (yrs.) = 60.37 ± 10.76 (range; 42 - 79)	
mean height (cm.) = 163.96± 7.74 (range; 145 - 181)	
mean weigh (kg) = 66.43 ± 11.46 (range;43-91)	
mean BMI (kg/m^2) = 24.77 ± 4.10 (range; 17.06– 31.12)	
Tophi	
Male	10(37.04%)
Female	-
Duration of gouty arthritis;	
mean±SD = 4.15 ± 4.35 yrs.(range ; 1mth-20 yrs)	
Alcohol use	
Male	8(29.63%)
Female	-
Underlying diseases	
Hypertension	20(74.1%)
Dyslipideamia	18(66.7%)
Chronic renal disease	6(22.2%)
Diabetes mellitus	3(11.1%)
Coronary artery disease	3(11.1%)
Concomitant medications	
ACEI	7(25.9%)
Low dose Aspirin (<2g/day)	6(22.2%)
Prednisolone	4(14.8%)
Thiazide diuretic	3(11.1%)
NSAIDs	1(3.7%)

Table 7 b : Age, sex, weigh, and duration of gouty arthritis of each individual patient.

Patient no.	Age (years)	Sex	Weight (kg.)	Duration of gout
1*	43	Male	83	8 yr.
2*	59	Male	89	8 yr.
3	70	Male	66	1 yr.
4	49	Male	54	3 mth.
5	73	Female	70	1 yr.
6	49	Male	91	1 mth.
7	73	Male	60	1 mth.
8*	70	Male	68	4 yr.
9*	62	Male	65	3 yr.
10*	59	Male	70	3 yr.
11*	47	Male	71	8 yr.
12	51	Female	71	5 yr.
13*	59	Female	74	1 mth.
14*	42	Male	75.5	1 yr.
15	73	Male	43	3 mth.
16*	49	Male	58	5 yr.
17*	65	Male	57	3 yr.
18	69	Male	50	20 yr.
19*	73	Male	66	10 yr.
20*	69	Male	65	2 yr.
21	57	Male	79	9 yr.
22*	68	Male	65	3 yr.
23*	48	Male	57	4 yr.
24*	50	Male	65	5 yr.
25	66	Male	65	3 yr.
26*	58	Male	47	3 mth.
27*	79	Male	69	5 mth.

* tophi

Mean age of patients with tophi (n=10); 56.40±12.33 years, patients without tophi (n=17); 62.71±9.33 years

Mean duration of gout of patients with tophi (n=10); 4.7±2.6 years, patients without tophi (n=17); 3.8±5.2 years

Mean weight of patients with tophi (n=10); 69.65±10.40 years, patients without tophi (n=17); 64.53±11.92 years

There were twenty-five men and two women with a range of age 42-79 years with the mean age equaled to 60.37 ± 10.76 years. Duration of gouty arthritis ranged from 1 month – 20 years and ten patients were chronic tophaceous gout. Eight patients(29.63%) had alcohol intake. Most common underlying diseases were hypertension (74.1%) and dyslipideamia (66.7%).

The laboratory data (BP, WBC, K, Na) of each patient at baseline, before initially received allopurinol therapy, were mostly within normal levels. These data were presented in appendix B

Effect of standard dose of allopurinol (300 mg daily) on renal function in gout patients with renal insufficiency.

The changes in renal function after allopurinol treatment was observed. The variables composed of creatinine clearance (CrCl) measured by 24 hour urine collection, blood urea nitrogen (BUN), serum creatinine (Scr), urine volume, creatinine and protein excreted in 24 hour urine collection . Each outcome was analyzed by pair-T test analysis or Wilcoxon signed rang test.

Table 8 : Scr, BUN and 24 hour urine collection before and after receiving allopurinol treatment

patient no.	Scr (mg/dl)		BUN (mg/dl)		24 hour urine collection								
					Urine volume (ml/24hrs)		Creatinine (g/24 hrs)		Proteins (mg/24hrs)		CrCl[a] (ml/min)		
	BL	After Tx.	BL	After Tx.	BL	After Tx.	BL	After Tx.	BL	After Tx.	BL	After Tx.	
1	2.2	2.4	28	32	2344	2940	1.67	1.40	961	1235	45.71	35.57	↓
2	1.5	1.5	16	18	1640	1450	1.35	1.30	98	131	54.00	52.06	↔
3	1.2	1.3	11	16	800	700	1.00	1.10	48	56	59.95	60.15	↔
4	1.2	1.1	13	9	2150	2130	0.85	0.74	344	192	51.70	49.30	↔
5	2.1	1.9	27	20	1630	1030	1.00	0.75	212	175	32.90	27.60	↓
6	1.5	1.4	22	19	870	2900	1.50	1.50	17	59	59.18	63.41	↑
7	1.5	1.5	16	17	900	930	1.10	1.20	63	65	51.80	55.68	↔
8	1.5	1.5	27	21	960	1870	1.40	1.30	451	318	60.00	61.90	↔
9	1.6	1.4	21	19	1700	2090	1.00	0.83	68	84	46.09	44.24	↔
10	1.3	1.4	15	14	2480	1820	0.90	1.10	50	109	48.47	55.00	↑
11	1.3	1.3	17	26	1350	2070	1.00	1.00	3778	4009	51.86	51.86	↔
12	1.6	1.4	30	22	1240	1300	0.83	0.80	87	455	36.70	40.40	↔
13	1.3	1.3	25	28	630	820	0.60	0.70	50	33	31.70	36.99	↑
14	1.3	1.4	35	24	1950	2030	1.30	1.10	1053	345	58.80	49.66	↓
15	1.3	1.1	17	11	920	1120	0.70	0.63	37	45	46.20	47.90	↔
16	1.6	1.4	15	12	2300	2030	1.01	0.80	83	41	49.73	44.87	↓
17	1.3	1.2	13	12	1430	2130	1.00	0.99	57	43	57.00	61.18	↑
18	1.2	1.2	11	16	1910	1440	0.70	0.70	96	58	45.80	44.07	↔
19	1.3	1.3	22	19	950	1180	0.87	0.86	38	35	49.00	48.17	↔
20	1.1	1.1	9	10	2350	2600	0.81	0.88	47	26	51.40	55.08	↔
21	1.8	1.7	26	22	2312	1572	1.50	1.30	486	723	50.30	46.17	↓
22	1.5	1.7	16	19	1180	2550	0.70	0.96	71	77	33.80	40.87	↑
23	1.4	1.5	20	24	1684	1570	0.70	0.79	34	63	38.02	39.52	↔
24	1.3	1.4	15	16	2640	3420	0.85	1.20	53	103	47.70	58.70	↑
25	1.3	1.2	14	20	1330	1830	1.10	1.10	359	238	59.48	64.03	↑
26	2.5	2.6	35	32	1430	1610	0.90	0.80	1487	1256	28.64	24.50	↓
27	1.5	1.3	16	18	830	1200	0.74	0.67	91	108	33.49	34.81	↔
Mean ±SD	1.49 ±0.33	1.46 ±0.35	19.70 ±7.22	19.11 ±6.02	1552 ±603	1790 ±685	1.00 ±0.28	0.98 ±0.25	379 ±771	373 ±798	47.36 ±9.48	47.91 ±10.67	
p-value	0.294[b],0.245[c]		0.527[b]		0.054[b]		0.467[b]		0.891[b],0.801[c]		0.562[b]		

BL = baseline , [a] = CrCl using 24 hour urine collection , [b] = analyzed by pair t-test, [c] = Wilcoxon signed rang test ,

↓= CrCl decreased ≥ 4 ml /min, ↑= CrCl decreased ≥ 4 ml /min, ↔ = changed within ± 4 ml/min

Table 8 showed mean±SD at baseline and after allopurinol treatment of Scr, BUN, urine volume, creatinine in urine, proteinuria and CrCl.

From a statistical point of view, there were no statistically significant difference between before and after allopurinol treatment with respect to mean of measured CrCl using 24 hour urine collection, Scr, BUN, urine volume, proteins and creatinine excreted in 24 hour urine output. These findings were parallel with previous studies[11-15] which

reported that allopurinol 300 mg daily for 6 weeks had no effect on renal function of gout patient with renal insufficiency.

Table 9 : Pharmacokinetic parameters of oxypurinol in 27 patients.

Patient no.	C_{max} (µg/ml)	C_{min} (µg/ml)	Kd (hr^{-1})	$T_{1/2}$ (hr.)	Vd (l.)	Cl(ml/min)
1.	27.73	20.34	0.016	42.48	26.64	7.17
2.	29.48	23.37	0.012	56.69	32.73	6.50
3.	22.24	15.33	0.020	35.39	28.32	9.17
4.	17.23	9.33	0.032	21.46	23.28	12.33
5.	35.09	25.43	0.017	40.89	19.47	5.50
6.	17.41	11.39	0.022	31.03	32.22	11.67
7.	34.02	31.12	0.005	147.78	66.30	5.17
8.	28.27	16.56	0.028	24.69	16.03	7.50
9.	27.66	16.76	0.026	26.28	17.86	7.67
10.	16.81	8.94	0.033	20.85	23.34	13.00
11.	23.26	13.15	0.030	23.09	18.63	9.33
12.	41.70	35.40	0.009	80.39	31.32	4.50
13.	47.36	38.47	0.011	63.33	22.19	4.00
14.	48.13	35.18	0.016	42.01	15.40	4.16
15.	22.74	18.09	0.012	57.56	42.29	8.50
16.	25.69	18.05	0.018	38.50	25.64	7.67
17.	29.82	21.84	0.016	42.28	24.81	6.67
18.	34.88	21.85	0.025	28.15	14.26	6.00
19.	36.70	27.79	0.015	47.38	21.41	5.17
20.	25.72	19.36	0.015	46.35	30.73	7.67
21.	26.62	19.91	0.015	45.33	29.88	7.50
22.	43.99	33.66	0.016	44.22	17.38	4.50
23.	27.33	22.16	0.011	62.79	38.52	7.00
24.	30.96	21.07	0.020	34.21	19.75	6.67
25.	17.98	7.10	0.049	14.17	16.14	13.17
26.	88.85	78.18	0.007	102.92	18.63	2.17
27.	30.18	23.62	0.013	53.72	29.19	6.33
Mean (±SD)	31.77 (±14.31)	23.46 (±13.71)	0.019 (±0.010)	47.18 (±27.86)	26.01 (±10.82)	7.28 (±0.17)

C_{max} = maximum oxypurinol concentration at steady state

C_{min} = minimum oxypurinol concentration at steady state

Kd = elimination rate of constant

$T_{1/2}$ = half life

Vd = volume of distribution

Cl = clearance of oxypurinol

Table 9 showed the trough and peak plasma oxypurinol concentrations of each individual patient along with his/her pharmacokinetic parameters.

Figure 3 : Relationship between CrCl (ml/min) and clearance of oxypurinol (ml/min).

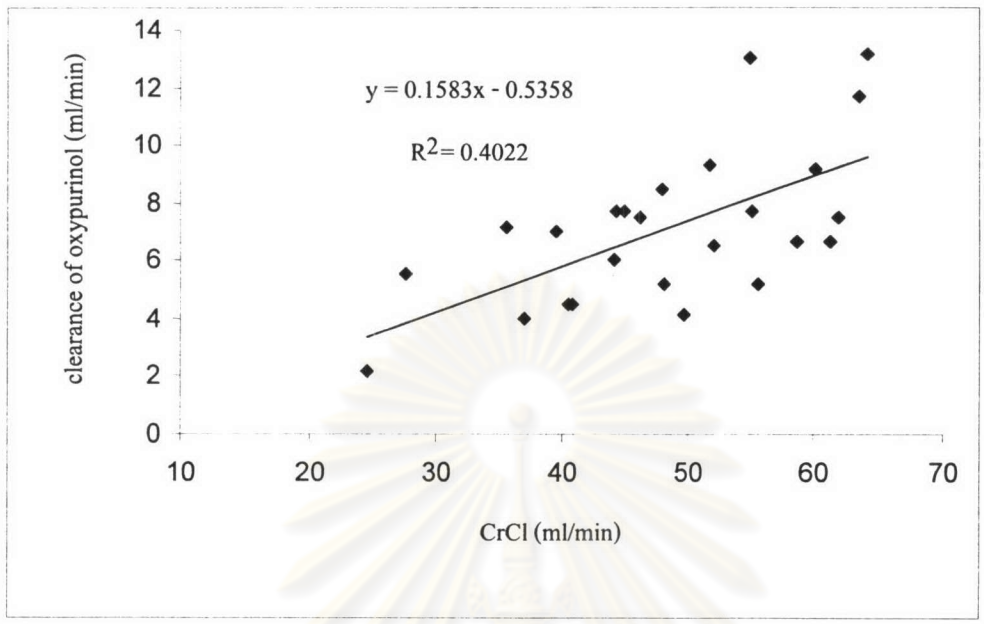


Figure 3 showed that there were significantly linear correlation between CrCl and clearance of oxypurinol (R^2= 0.402, r = 0.634, p=0.001, n=25 when patient no. 4 and 27 were excluded because of Cr/LBW less than 15.0 mg/kg). Clearance of oxypurinol could be predicted from CrCl by the equation:

$$y = 0.1583x - 0.5358$$

where y = clearance of oxypurinol and x = CrCl

Effect of plasma oxypurinol concentrations on the changes in CrCl.

Although the means CrCl showed no statistically significant difference between before and after treatment, there were several patients whose CrCl were decreased or increased more than 4 ml/min, the data were then further analyzed to investigate whether or not there were any relationship between the levels of plasma oxypurinol and the changes in CrCl.

Table 10 : Percentages of patient with decrement and increment of CrCl ≥4 ml/min and within 4 ml/min after treatment within various levels of trough plasma oxypurinol concentration.

Trough plasma oxypurinol concentration (μg/ml)	Number of patients within the plasma concentration ranges (n)	Number of patients with change in CrCl n(%)		
		CrCl ↓ ≥4 ml/min.	CrCl ↑ ≥4 ml/min.	CrCl ± 4 ml/min.
< 5	0	0	0	0
5 – 15*	5	0	3(60.0%)	2(40.0%)
15 – 25	14	3(21.4%)	2(14.3%)	9(64.3%)
25 – 35	4	1(25.0%)	1(25.0%)	2(50.0%)
> 35	4	2(50.0%)	1(25.0%)	1(25.0%)
total	27	6(22.2%)	7(25.9%)	14(51.9%)

* = proposed therapeutic range of oxypurinol concentration

In table 10, the patients were stratified into five groups according to their through plasma oxypurinol concentrations. The percentages of patients whose CrCl were decreased more than 4 ml/min tended to increase with increasing trough plasma oxypurinol concentrations. However, no statistically difference among groups were found (p=0.356). At the same time, even though the percentage of patients whose CrCl were increased more than 4 ml/min was highest at the lowest level of plasma oxypurinol concentration range, the percentages did not decrease consistently with the increase in plasma concentrations.

Table 11 : Percentages of patient with decretment and increment of CrCl ≥4 ml/min and within 4 ml/min after treatment within various levels of peak plasma oxypurinol concentration.

peak plasma oxypurinol concentration (μg/ml)	Number of patients within the plasma concentration ranges (n)	Number of patients with change in CrCl n(%)		
		CrCl ↓ ≥4 ml/min.	CrCl ↑ ≥4 ml/min.	CrCl ± 4 ml/min.
< 5	0	0	0	0
5 – 15*	0	0	0	0
15 – 25	7	0	3(42.9%)	4(57.1%)
25 – 35	13	3(23.1%)	2(15.4%)	8(61.5%)
35 - 45	4	1(25.0%)	1(25.0%)	2(50.0%)
> 45	3	2(66.7%)	1(33.3%)	0(0%)
total	27	6(22.2%)	7(25.9%)	14(51.9%)

* = proposed therapeutic range of oxypurinol concentration

Table 11 stratified the patients into six groups according to their peak plasma oxypurinol concentrations, percentages of patients whose CrCl were decreased or increased or changed within 4 ml/min after allopurinol treatment for 6 weeks were demonstrated. Same as trough concentration, the percentages of patients whose CrCl were decreased more than 4 ml/min tended to be increased with higher peak plasma concentration ranges. However, no statistically significant difference among groups were found (p=0.142).

Relationship between pharmacokinetic parameters (Kd, $T_{1/2}$, Vd and Cl) and the changes in CrCl.

The patients were divided into three groups, group 1 consisted of patients whose CrCl were changed within 4 ml/min (n=14), group 2 consisted of patients whose CrCl were decreased more than 4 ml/min (n=6), and group 3 composed of patients whose CrCl were increased more than 4 ml/min (n=7).

Table 12 : Comparisons of pharmacokinetic parameters among patients whose CrCl were decreased, increased and changed within 4 ml/min after allopurinol treatment.

pharmacokinetic parameters	Mean ± SD			p-value
	Gr.1	Gr.2	Gr.3	
Kd(hr^{-1})	0.019±0.010	0.015±0.004	0.024±0.013	Gr.1 vs Gr.2 = 0.492 Gr.1 vs Gr.3 = 0.189 Gr.2 vs Gr.3 = 0.095
$T_{1/2}$ (hr)	50.84±33.06	52.02±25.03	35.73±16.27	Gr.1 vs Gr.2 = 0.932 Gr.1 vs Gr.3 = 0.257 Gr.2 vs Gr.3 = 0.303
Vd (l.)	29.35±13.55	22.61±5.58	22.26±5.39	Gr.1 vs Gr.2 = 0.207 Gr.1 vs Gr.3 = 0.163 Gr.2 vs Gr.3 = 0.954
Clearance(ml/min)	7.33±0.12	5.67±0.13	8.50±0.24	Gr.1 vs Gr.2 = 0.221 Gr.1 vs Gr.3 = 0.360 Gr.2 vs Gr.3 = 0.072

Gr.1 = CrCl changed within 4 ml/min from baseline after treatment (n=14)

Gr.2 = CrCl decreased $\geq$ 4 ml/min from baseline after treatment (n=6)

Gr.3 = CrCl increased $\geq$ 4 ml/min from baseline after treatment (n=7)

p-value = using by ANOVA ; Post Hoc multiple comparison by least-significant different (LSD)

Table 12 showed comparisons of pharmacokinetic parameters among group and found that there were no significant differences in Kd, $T_{1/2}$, Vd, and clearance among the three groups. Although, mean Kd and clearance between group 2 and group 3 showed no statistically significantly different at p=0.05 but showed significantly different at p<0.1 (p=0.095 and 0.072, respectively).

Efficacy of standard dose of allopurinol (300 mg daily) in controlling serum uric acid in gout patients with renal insufficiency.

Efficacy of allopurinol treatment was assessed by using outcomes composed of serum uric acid and uric acid excreted in 24 hour urine output.

Comparison of mean serum uric acid and urate excreted in 24 hour urine collection before and after treatment.

Table 13 : serum uric acid and urate excreted in 24 hour urine collection before and after treatment.

No.	Serum uric acid (mg/dl)		Uric acid excreted 24 hr urine output collection (mg/24 hr)	
	baseline	After Tx.	baseline	After Tx.
1*	11.7	7.7	815	347
2*	14.0	8.9	785	425
3	7.0	5.2	442	242
4	6.6	3.7	400	181
5	7.5	5.0	347	136
6	11.0	7.0	656	490
7	10.5	4.5	371	142
8*	7.5	4.9	963	294
9*	11.9	6.9	719	261
10*	8.6	6.2	432	353
11*	9.0	6.3	752	422
12	13.00	4.6	379	169
13*	13.1	5.6	278	127
14*	14.5	7.8	255	103
15	9.6	3.2	293	64
16*	9.9	5.3	484	164
17*	12.8	6.0	457	138
18	8.5	7.1	284	251
19*	10.1	4.4	445	132
20*	8.9	5.4	282	164
21	11.4	7.2	890	360
22*	10.8	5.1	291	60
23*	14.9	6.2	500	100
24*	9.6	6.2	388	236
25	9.8	6.4	588	468
26	11.4	5.2	309	118
27	9.7	4.7	232	113
Mean (±SD)	10.49 (±2.26)	5.80** (±1.32)	482.85 (±212.24)	224.44** (±127.93)

* = tophi, ** = $p<0.001$

Table 13 showed serum urate level at baseline and after treatment and urate excretion in 24 hr urine collection at baseline and after treatment of each individual patient along with the mean(±SD) and the statistical comparisons.

The results indicated that mean serum urate level after treatment was significantly lower than serum urate level at baseline ($p<0.001$). In addition, mean urate

excretion after treatment was also significantly lower than urate excretion at baseline ($p<0.001$).

The goal of urate-lowering therapy is to reduce the serum urate to less than 6.0 mg/dl or preferably less than 5.0 mg/dl if patients have evidence of tophi. Table 14 showed proportions of patients with and without tophi who could reach the aforementioned goal. The result indicated that with the present standard treatment (300mg daily) with allopurinol, 12 patients (70.59%) with no tophi could reach the therapeutic goal while only one patient (10.0%) with tophi met the goal.

Table 14 : Proportion of patients with or without tophi which their serum urate level could be controlled after allopurinol therapy

Evidence of tophi	number of patients ; n(%) serum urate after allopurinol treatment		
	≤ 5(mg/dl)	5 - 6(mg/dl)	> 6(mg/dl)
No (n=17)	7(41.18%)	5(29.41%)	5(29.41%)
Yes (n=10)	1(10.00%)	2(20.00%)	7(70.00%)
Total (n=27)	8 (29.63%)	7 (25.93%)	12 (44.44%)

Relationship between plasma oxypurinol concentration and the controlling of serum uric acid

Table 15 : Comparison of mean trough and peak plasma oxypurinol concentration between patients with serum urate after treatment ≤ 6 mg/dl (group I) and patients with serum urate after treatment > 6 mg/dl (group II)

plasma oxypurinol concentration (μg/ml)	group I (n=15)	group II (n=12)	p-value
mean trough level ± SD	27.48±16.25	18.43±7.64	0.044*
mean peak level ± SD	35.31±17.07	27.35±8.64	0.078

* significant $p<0.05$ (1-tailed) analyzed by Independent t-test

As presented in table 15, the mean trough plasma oxypurinol concentration of the patients whose serum urate after treatment were ≤ 6 mg/dl, was significant higher than the mean trough level of the patients whose serum urate were >6 mg/dl (p=0.044). However, the mean peak plasma concentration between the two groups showed no statistically significant different at $p < 0.05$ but showed significant different at $p < 0.1$ (p=0.078). Therefore, reducing of serum urate level could be more depended on plasma oxypurinol concentration at the trough level. The optimal trough plasma oxypurinol level to achieve serum urate level less than 6 mg/dl after allopurinol treatment in patients with renal insufficiency should possibly be higher than 15 μg/ml, the upper limit of recommended therapeutic range.

Table 16 : Comparison of mean trough and peak plasma oxypurinol concentration between patients with changes of serum urate ≥5 mg/dl (group I) and patients with change of serum urate < 5 mg/dl (group II).

plasma oxypurinol concentration (μg/ml)	group I (n=13)	group II (n=14)	p-value
mean trough level ± SD	31.20±15.76	16.27±5.56	0.003*
mean peak level ± SD	39.07±17.04	24.99±6.21	0.008*

*significant p<0.05 2-tailed) analyzed by independent t-test

To ensure that plasma oxypurinol concentrations had responsibility on the decreasing of serum urate level, patients were again divided into two groups based on changes of serum urate which were ≥5 mg/dl (group I) or < 5 mg/dl (group II). Both means of trough and peak oxypurinol level in these two groups were significantly different (p=0.003, p=0.008; respectively), as shown in table 16.

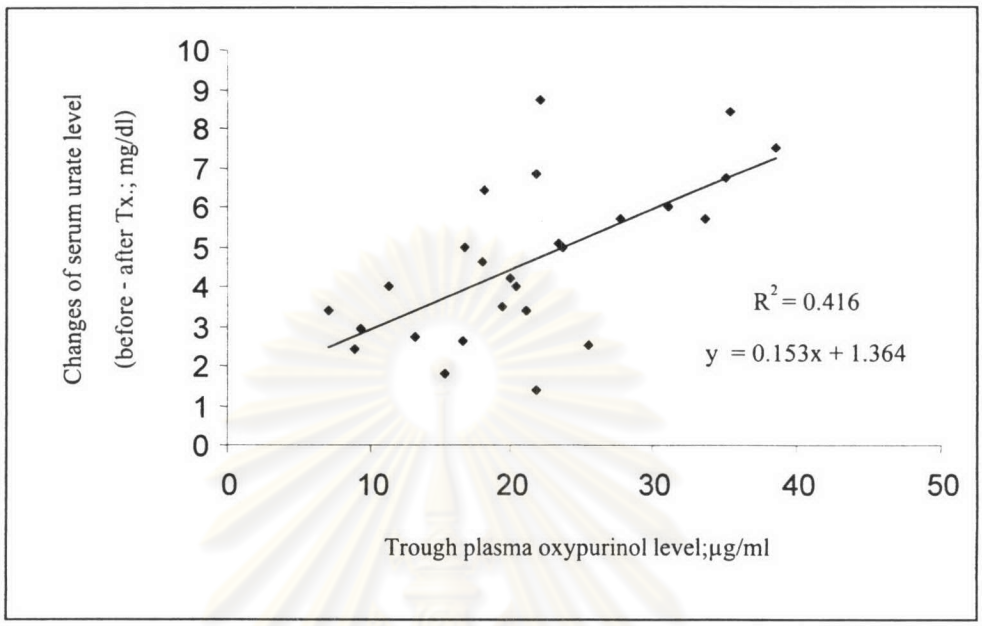
Table 17 : Proportion of patients with serum urate level ≤ 6 mg/dl and with change of serum urate level ≥ 5 mg/dl after allopurinol treatment at various levels of trough plasma oxypurinol concentration

Levels of trough plasma oxypurinol concentration (μg/ml)	Number of patients (n)	No. of patients with the change of serum urate level ≥ 5 mg/dl ; n(%)	No. of patients with serum urate level ≤ 6 mg/dl : n(%)
<5	0	0	0
5 – 15*	5	0	1(20.0%)
15 – 25	14	6(42.9%)	7(50.0%)
25 – 35	4	3(75.0%)	4(100%)
>35	4	4(100%)	3(75.0%)
total	27	13(48.1%)	15(55.6%)

* = proposed therapeutic range of oxypurinol concentration

Previous studies have suggested that plasma oxypurinol concentration in the range of 5 – 15 μg/ml was the optimal therapeutic range for effectively decrease serum uric acid to the target level and reduce risk of serious adverse events[9,42-43]. In order to find the optimum plasma concentration ranges, the patients were stratified into 5 groups according to their trough plasma levels as shown in table 17. The percentages of patients with change of serum uric acid ≥ 5 mg/dl, were increasing with increased plasma oxypurinol concentrations. The proportions of patient with the change of serum urate level ≥ 5 mg/dl were significantly different among groups of different trough levels (using Pearson Chi square analysis ; p=0.016). The percentages of patients with serum urate level ≤ 6 mg/dl after treatment were also tended to increase with increasing plasma oxypurinol concentrations except for one patient in the last group (trough plasma concentration > 35 μg/ml) which his or her serum uric acid had not met the target level of ≤ 6 mg/dl since his or her baseline serum uric acid was as high as 14.5 mg/dl. The proportions of patient with serum urate level ≤ 6 mg/dl after therapy among groups of different plasma trough levels were significantly different at p=0.088.

Figure 4 : Relationship between trough plasma oxypurinol concentration (μg/ml) and the change of serum urate level (mg/dl) after allopurinol treatment.



Moreover, figure 4 demonstrated that there were significantly linear correlation between trough plasma levels and changes in serum urate levels after therapy (R^2=0.42, r= 0.64 , p=0.002, n=26 when patient no. 26 was excluded because of outlier data, or R^2= 0.256 , r= 0.506, p= 0.007, n=27).

The relationship between plasma oxypurinol concentrations and the changes in serum urate level were further observed with peak plasma concentrations.

Table 18 : Proportion of patients with serum urate level ≤ 6 mg/dl and with change of serum urate level ≥ 5 mg/dl after allopurinol treatment at various levels of peak plasma oxypurinol concentration

Levels of peak plasma oxypurinol concentration (µg/ml)	Number of patients (n)	No. of patients with decreased serum urate level ≥ 5 mg/dl ; n(%)	No. of patients with serum urate level $\leq$ 6 mg/dl : n(%)
0	0	0	0
5 – 15*	0	0	0
15 – 25	7	1(14.3%)	3(42.9%)
25 – 35	13	6(46.2%)	6(46.2%)
35 – 45	4	3(75.0%)	4(100%)
> 45	3	3(100%)	2(66.7%)
total	27	13(48.1%)	15(55.6%)

* = proposed therapeutic range of oxypurinol concentration

Table 18 showed the percentages of patients whose serum urate levels met the recommended targets when the patients were stratified into six groups based on their peak plasma oxypurinol concentrations. Same as trough plasma concentrations, the percentages of patients whose plasma uric acid levels met the proposed targets were increased with increasing peak plasma oxypurinol concentrations. Using Pearson Chi Square analysis, the percentages of patients which met the target of changing serum uric acid level ≥ 5 mg/dl were significantly different among groups of different peak plasma concentrations at $p = 0.055$. When the target was changed to serum urate level of ≤ 6 mg/dl, the significant difference was found at $p = 0.234$.

Figure 5 : Relationship between peak plasma oxypurinol concentration (μg/ml) and the change of serum urate level (mg/dl) after allopurinol treatment.

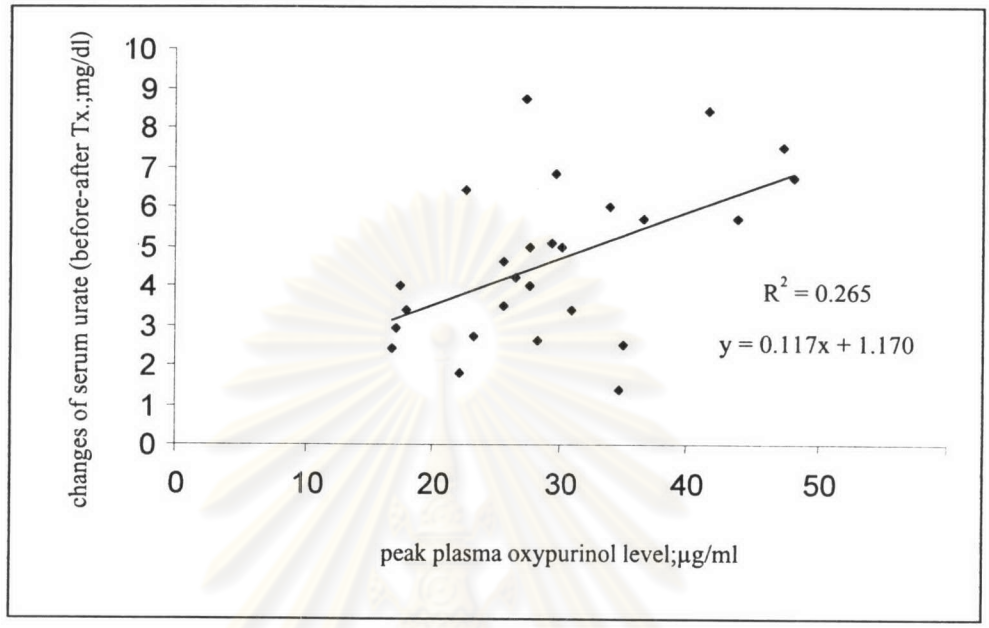


Figure 5 showed that there were significantly linear correlation between peak plasma levels and the changes in serum urate levels after therapy (R^2= 0.27, r=0.52 , p=0.007, n=26 when patient no. 26 was excluded because of outlier data; or R^2= 0.18 , r= 0.43, p= 0.026, n= 27)

Relationship between plasma oxypurinol concentration and the changes in the amount of urate excreted in 24 hour urine collection

Since there was significantly lower amount of urate excreted in 24 hour urine collection after allopurinol treatment, allopurinol should efficiently reduce serum urate production.

Table 19 : Proportions of patients whose urate excretions in 24 hr urine collection were decreased ≥100 mg/24hr and ≥200 mg/24hr from baseline at various levels of trough plasma oxypurinol concentration

Trough oxypurinol concentration (μg/ml)	Number of patients (n)	Number of patients ; n(%) Decreasing in urate excretion in 24 hour urine collection	
		≥ 100 (mg/24hr)	≥ 200 (mg/24hr)
<5	0	0	0
5 – 15*	5	4 (80.0%)	2 (40.0%)
15 – 25	14	13 (92.9%)	10 (66.7%)
25 – 35	4	4 (100%)	4 (100%)
>35	4	4 (100%)	1 (25.0%)
total	27	25(92.6%)	17(63.0%)

* = proposed therapeutic range of oxypurinol concentration

Table 19 demonstrated that proportion of patients whose urate excretion were decreased for more than 100 mg/24hr, tended to be increased at higher trough levels. However, there were no significant differences of those proportions among different trough level groups (p=0.615, using Pearson chi-square analysis). Similarly, the proportions of patient with urate excretion decrement of more than 200 mg/24hr were mostly increased with increasing trough levels. Again, the difference in these proportions were not statistically significant among different trough level groups (p=0.791, using Pearson chi-square analysis).

Table 20 : Proportion of patients whose urate excretion in 24 hr urine collection were decreased ≥100 mg/24hr and ≥200 mg/24hr from baseline at various levels of peak plasma oxypurinol concentration

peak oxypurinol concentration (μg/ml)	Number of patients (n)	Number of patients ; n(%) Decreasing in urate excretion in 24 hour urine collection	
		≥ 100 (mg/24hr)	≥ 200 (mg/24hr)
<5	0	0	0
5 – 15*	0	0	0
15 – 25	7	6 (85.7%)	4 (57.1%)
25 – 35	13	12 (92.3%)	9 (69.2%)
35-45	4	4 (100%)	4 (100%)
> 45	3	3(100%)	0
total	27	25(92.6%)	17(63.0%)

* = therapeutic range of oxypurinol concentration

Same as those found with trough concentrations, table 20 showed that proportions of patients with decreasing in urate excretion more than 100 mg/24hr tended to be increased at higher peak level. However, there were no significantly different in those proportions among different peak level groups (p=0.940, using Pearson chi-square analysis). Similarly, there were increment in proportions of patients with urate excretion more than 200 mg/24hr, in the groups whose peak level were higher, except for the group with peak level ranged >45 μg/ml which the proportion was reduced to 0% which might due to the amounts of uric acid excreted in the urine of the patients in this group were already low at baseline. Using Pearson Chi-Square analysis , the differences in proportions among different peak level groups were significant at p = 0.051.

figure 6 : Relationship between trough plasma oxypurinol concentration (μg/ml) and percent change of uric acid excreted in 24 hour urine collection (mg/day); before-after allopurinol treatment

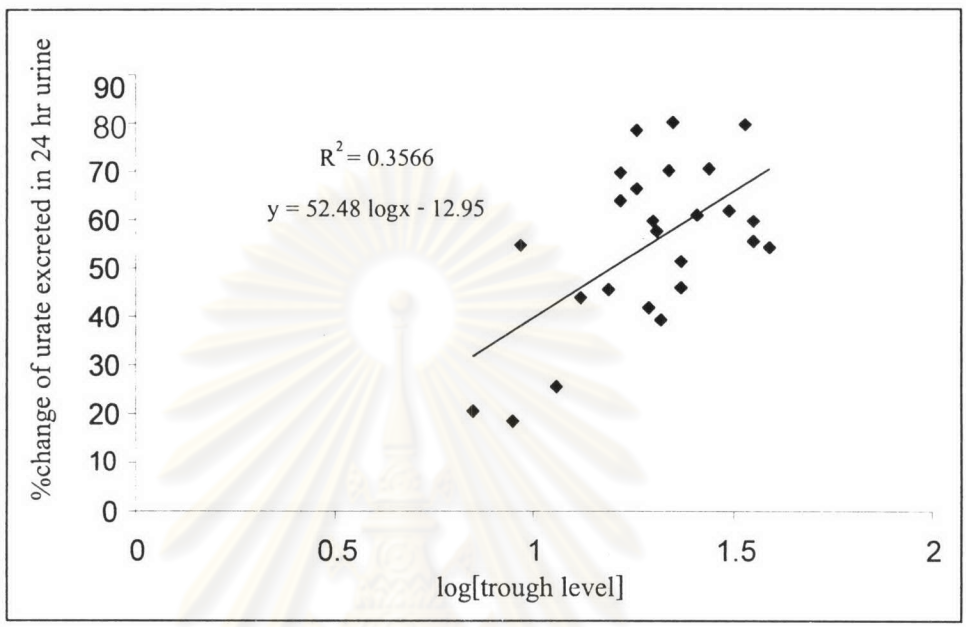
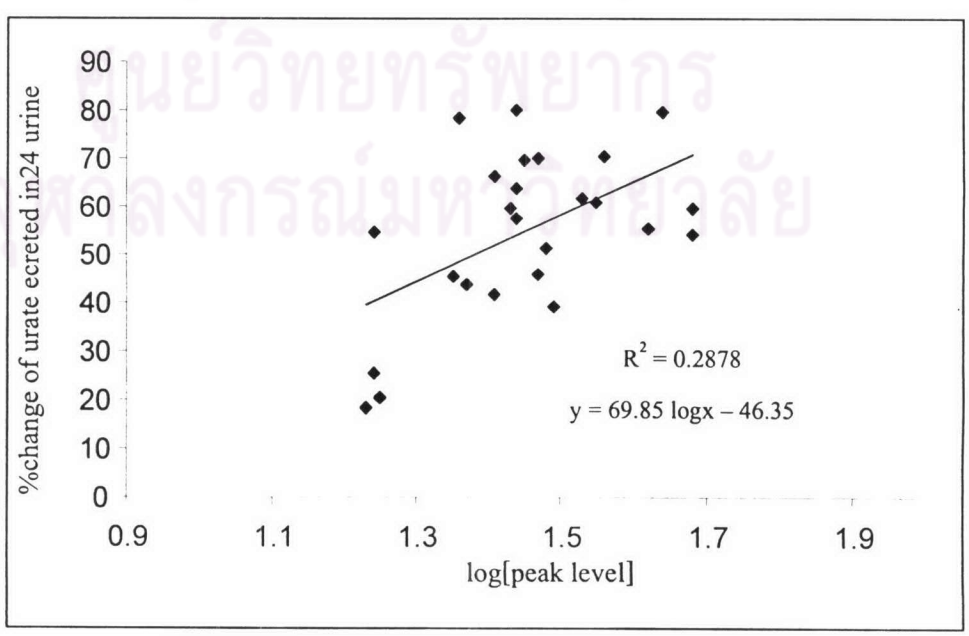


figure 7 : Relationship between peak plasma oxypurinol concentration (μg/ml) and percent change of uric acid excreted in 24 hour urine collection (mg/day); before-after allopurinol treatment



From these results, it was quite possible that higher plasma oxypurinol concentrations should be related to higher decrement in urate excretion. Figure 6 and 7 showed that there were significantly relationship between trough and peak oxypurinol levels and percentage of decreasing in urate excretion from 24 hr urine output, respectively. For trough concentration, R^2=0.36, r=0.60, p=0.002, n=25 when excluded 2 outlier data, patient no.18, 26; if included R^2=0.23, r=0.48, p=0.01, n=27. For peak concentration, R^2=0.29, r=0.54, p=0.006, n=25 when excluded 2 outlier data, patient no.18, 26; if included R^2=0.14, r=0.38, p=0.05, n=27.

Adverse Drug Reactions (ADRs)

Any ADRs that could happen after receiving allopurinol treatment for 6 weeks were monitored. None of the patients developed any skin rash, serious adverse events or AHS. However, two patients had minor clinical symptoms of adverse reactions after allopurinol treatment, consisting of nausea and vomiting in one case (patient no.8), also malaise, headached and dizziness in another case (patient no. 1).

Table 21 : Comparision of SGOT, SGPT, eosinophil, Hct, Hgb, Plt at baseline and after treatment.

patient no.	SGOT (U/L) (0-40 U/L)		SGPT(U/L) (0-40 U/L)		Eosinophil (%) (0-75%)		Hct. (%) (M,40-52 %) (F,37-47 %)		Hgb. (g/dl) (M,14-18 g/dl) (F,12-16 g/dl)		Plt. (/mm^3) (130,000-400,000/mm^3)	
	BL	after tx	BL	after tx	BL	after tx	BL	After tx	BL	after tx	BL	after tx
1.	31	29	35	30	4	7	41	38	13	13	172,000	164,000
2.	32	29	41	41	7	2	41	36	13	12	260,000	279,000
3.	16	18	14	14	5	2	38	36	12	12	190,000	202,000
4.	21	24	19	19	6	5	36	41	12	13	397,000	269,000
5.[f]	25	25	19	21	4	4	33	32	11	11	212,000	263,000
6.	30	38	49	55	4	1	40	37	13	12	177,000	172,000
7.	32	42	28	40	2	2	42	40	14	13	108,000	180,000
8.	37	62	46	91	2	4	39	39	13	13	197,000	227,000
9.	34	45	28	73	5	3	39	38	12	12	424,000	458,000
10.	17	53	22	130	3	4	39	37	13	12	277,000	242,000
11.	27	38	18	20	3	1	38	42	12	14	251,000	257,000
12.[f]	43	57	56	64	3	2	38	37	13	12	285,000	252,000
13.[f]	79	72	72	80	3	5	33	32	11	10	228,000	296,000
14.	20	21	10	16	3	6	37	34	12	12	350,000	331,000
15.	74	38	31	15	2	0	34	39	11	13	416,000	370,000
16.	28	30	25	34	0	0	49	47	17	15	279,000	244,000
17.	23	22	23	19	4	5	47	43	16	15	239,000	305,000
18.	17	25	10	16	8	6	39	41	13	14	231,000	190,000
19.	23	31	24	26	0	3	39	41	13	14	305,000	246,000
20.	20	27	20	31	5	6	39	41	13	14	213,000	178,000
21	23	22	31	27	2	3	39	37	13	12	265,000	343,000
22.	28	22	35	28	4	4	46	45	15	15	177,000	169,000
23.	23	26	26	33	4	3	46	45	16	15	165,000	161,000
24.	37	29	48	26	0	0	41	40	13	13	233,000	211,000
25.	31	20	47	28	6	1	43	42	14	13	203,000	246,000
26.	28	26	28	21	0	0	29	29	10	10	319,000	264,000
27.	21	31	21	32	1	6	36	37	12	12	186,000	168,000
Mean (SD)	30.37 (14.89)	33.41 (13.79)	30.59 (14.75)	38.15 (27.55)	3.33 (2.13)	3.15 (2.14)	39.21 (4.38)	38.63 (4.18)	12.96 (1.50)	12.79 (1.46)	250,333 (78,754)	247,667 (71,345)
p-value	0.093[a]		0.130[b]		0.692[b]		0.249[b]		0.281[b]		0.775[b]	

[a] = analyzed by Wilcoxon signed rangs test, [b] = analyzed by Pair t-test, [f] = female patient

Table 21, compared several laboratory data at baseline with those after treatment. All patients had Eosinophil, hematocrit(Hct), hemoblobin(Hgb), Platelet (plt) within normal ranges in both periods, however, eight patients showed slightly high SGOT and/or SGPT level (>40 U/L) at baseline, but not more than two times of the normal range (patient no. 2, 6, 8, 12, 13, 15, 24, and 25). Overall, there were no significant differences in these data between before and after treatment.

Two patients had their SGPT level increased more than 2 times of its upper limit after treatment (patient no. 8 and 10). However, both patient did not show any clinical sign of adverse events and were still continued on allopurinol therapy.