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APPENDICES

Appendix

Appendix A : Demographic data of the individual subjects

Subject number	age	sex	tophi	Duration of gout (months)	Height (cm)	Cr/LBW (mg/kg)	BMI (kg/m^2)	Undeerlying diseases					Concomitant medications				
								HTN	Dyslipid-emia	CRF	DM	CAD	HCTZ	ACEI	ASA	prednisolone	NSAIDs
1	43	Male	Yes	96	174	24.6	26.2		/	/							
2	59	Male	Yes	96	170	22.7	30	/	/					/			
3	70	Male	No	12	161	23.7	25										
4	49	Male	No	3	173	15.0	18										
5	73	Female	No	12	161	17.0	27	/									
6	49	Male	No	1	171	25.7	31.1	/			/		/	/			
7	73	Male	No	1	171	24.5	20.5	/									
8	70	Male	No	48	161	27.0	26.2	/	/								
9	62	Male	yes	36	154	19.3	27.4			/							
10	59	Male	no	36	160	23.4	28	/	/								

Subject number	age	sex	tophi	Duration of gout (months)	Height (cm)	Cr/LBW 9mg/kg0	BMI (kg/cm^2)	Undeerlying diseases					Concomitance medications				
								HTN	Dyslipid-emia	CRF	DM	CAD	HCTZ	ACEI	ASA	prednisolone	NSAIDs
11	47	Male	Yes	96	167	23.8	25.1	/	/		/			/	/		/
12	51	Female	No	60	155	18.8	29.6	/	/								
13	59	Female	No	1	157	16.0	30	/	/		/		/	/	/		
14	42	Male	Yes	12	172	20.4	25.5		/	/		/		/	/	/	
15	73	Male	No	3	158	16.1	17.2	/									
16	49	Male	No	60	145	20.0	29.5		/								
17	65	Male	Yes	36	165	21.9	20.9	/	/								
18	69	Male	No	240	167	16.0	17.9	/	/								
19	73	Male	No	120	154	19.2	28.3	/	/			/			/		
20	69	Male	Yes	24	166	18.0	23.6	/				/			/		
21	57	Male	No	108	181	22.5	24.1	/	/	/							

Subject number	age	sex	tophi	Duration of gout (months)	Height (cm)	Cr/LBW (mg/kg)	BMI (kg/cm^2)	Undeerlying diseases					Concomitance medications				
								HTN	Dyslipid-emia	CRF	DM	CAD	HCTZ	ACEI	ASA	prednisolone	NSAIDs
22	68	Male	No	36	158	21.2	26	/	/								
23	48	Male	Yes	48	160	18.0	22.3	/	/	/				/	/		
24	50	Male	Yes	60	170	24.2	22.5		/							/	
25	66	Male	No	36	164	23.0	24.2	/					/				
26	58	Male	No	3	166	19.0	17.1	/	/	/							
27	79	Male	yes	60	166	13.5	25.4	/	/					/			

Appendix B : Laboratory data at baseline of all 27 patients.

Subject no.	SBP (mmHg)	DBP (mmHg)	WBC (cell/mm^3)	K (mmol/l)	Na (mmol/l)
1	125	75	7,370	4.47	142
2	125	85	5,140	4.60	143
3	130	80	5,950	4.33	141
4	90	60	11,300	5.03	141
5	120	70	7,900	4.10	146
6	105	85	8,00	4.12	143
7	120	80	4,590	3.62	141
8	145	90	5,700	4.00	141
9	170	100	8,050	5.67	140
10	120	75	9,500	3.59	137
11	165	100	5,900	4.37	143
12	125	80	5,500	4.63	142
13	110	75	4,420	4.71	142
14	100	80	7,100	3.81	145
15	130	80	6,500	4.60	139
16	105	75	3,500	4.15	138
17	160	90	7,060	4.70	142
18	130	85	5,900	4.46	140
19	130	70	7,500	5.60	141
20	125	85	7,100	4.59	142
21	155	100	3,880	3.70	141
22	160	80	5,300	4.41	149
23	120	80	7,900	4.15	145
24	120	80	13,480	4.30	147
25	165	95	8,400	3.75	140
26	137	100	11,300	5.55	139
27	125	85	4,400	4.19	142
mean±SD	130.07±21.05	82.96±10.03	6,986.67±2,374.38	142.67±2.50	4.41±0.56

Appendix C : The standard curve of oxypurinol in plasma

After the steps of extraction according to the modified method of Kramer WG et al.. As mentioned in detail in chapter III, the samples were injected in to HPLC column. The retention time of oxypurinol and 8-methylxanthine (IS) were approximate 9.6 and 16.8 minutes respectively. The chromatograms were shown in figure 1, 2, 3, 4

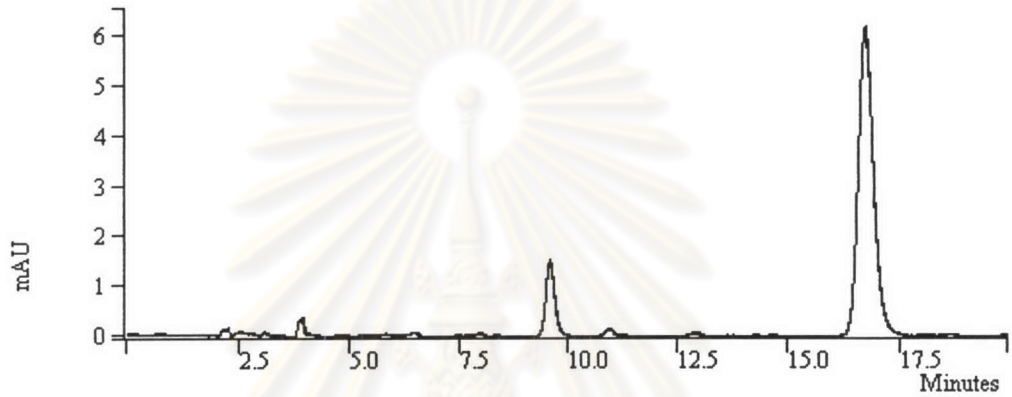

Figure1 : Chromatogram of oxypurinol 1 μg/ml and internal standard from standard solution.

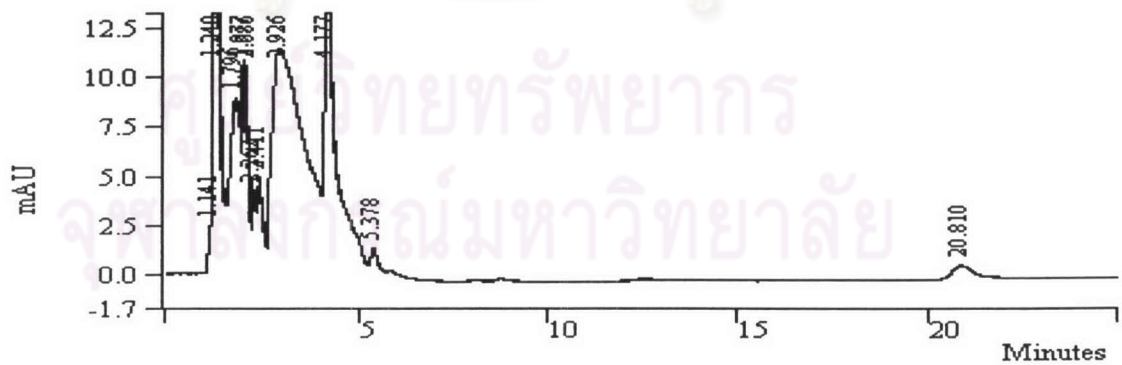

Figure 2 : Chromatogram of blank plasma

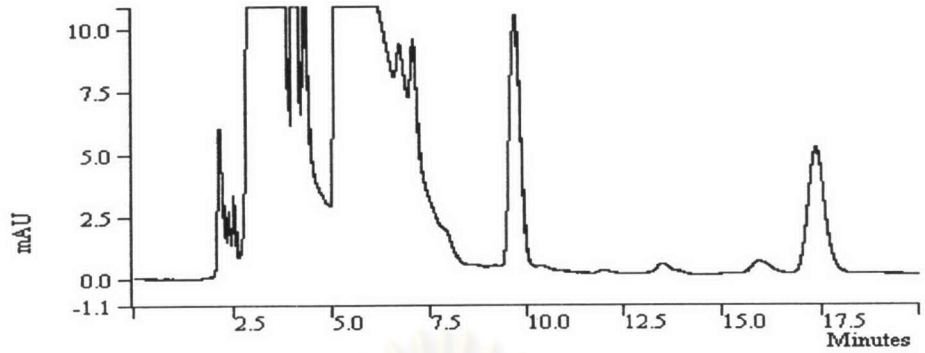

Figure 3 : Chromatogram of oxypurinol 10 μg/ml and internal standard in plasma sample.

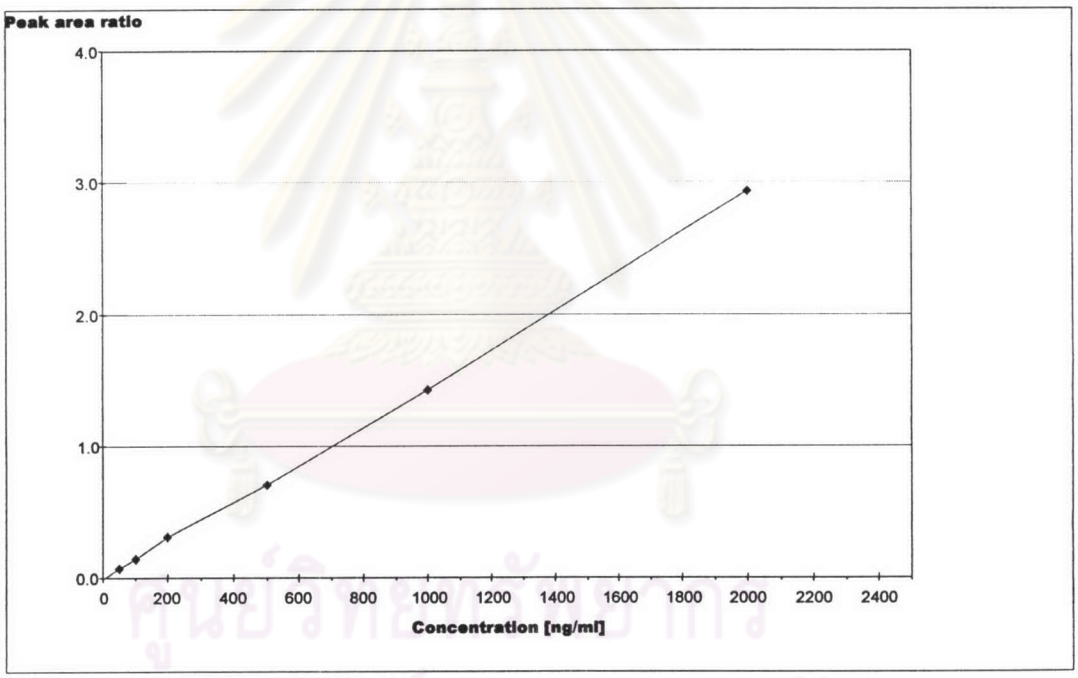

Figure 4 : The standard curve of different concentrations of oxypurinol versus peak area ratio

The chromatographic conditions proved to be acceptable since a good separation of oxypurinol and 8-methylxanthine was obtained as shown in figure 2 and 3. Increased concentrations of oxypurinol resulted in a linearly increase in peak area ratio of

oxypurinol to 8-methylxanthine (r^2= 0.9987). The standard curve of oxypurinol is thus plotted as a line of best fit (figure 4). The concentration of oxypurinol in each plasma sample was calculated from this standard curve by using the following equation:

Peak area ratio = 0.00015(concentration) -0.00584.....equation 1

As displayed in table 12, the average percentage of recovery of the analysis was 98.95%. The precision and accuracy of the mentioned procedure[1] was satisfactory since the coefficient of variation (%CV) were found to be 3.01% for within-run and 4.34% for between run.

Table 1 : Coefficient of variation (%CV) and % recovery of plasma oxypurinol concentration analysis

Oxypurinol concentration (μg/ml)	Within-run %CV	Between-run %CV	% recovery
1	5.06	5.73	101.16
7.5	2.61	3.30	97.95
15	1.36	3.98	97.79
Mean	3.01	4.34	98.95

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1. U.S. Department of Health and Human Services. Guidance for industry bioanalytical method validation: MD: 2001.

Appendix D : Calculation for pharmacokinetic parameters in plasma of individual patient

Following oral administration, plasma allopurinol and oxypurinol concentration decline in an exponential fashion consistent with a first-order profile. Thus,

1. Kd can be calculated by

$$Kd = \frac{\ln(Cp_1 / Cp_2)}{t} \quad \text{.....equaltion 2}$$

Cp_1 is the peak plasma concentration

Cp_2 is the trough plasma concentration

t is the time interval between trough and peak plasma samples

2. $t_{1/2}$ can be calculated by

$$t_{1/2} = \frac{0.693}{Kd} \quad \text{.....equation 3}$$

In this study, allopurinol was given 300 mg daily for 6 weeks, oxypurinol concentration had been already achieved to steady state and 6-folds of absorption time less than $t_{1/2}$. Therefore, the appropriate model to calculate drug concentration is bolus model, thus

3. Vd can be calculated by

$$Vd = \frac{(S)(F)(Dose)(e^{-Kd*t})}{C_t} \quad \text{.....equation 4}$$

S is fraction of administered salt form (S =1.0)

F is the bioavailability factor (F =0.85)

C_t is oxypurinol concentration at any time

t is the time interval between beginning of administration and plasma sample

4. Clearance (Cl) of this drug can be calculated by

$$Cl = Kd*Vd \quad \text{.....equation 5}$$

Appendix E : Definitions

Gout patients : patients who present with gouty arthritis or tophi as clinical picture

Renal insufficiency : CrCl = 30-60 ml/min/1.73m^2

Maintenance dose of allopurinol : the initial maintenance dose of allopurinol

Primary outcomes : effect of allopurinol on renal functions

Glomerular filtration rate (GFR) : assessed creatinine clearance (CrCl) from 24-hour urine collection in accordance with serum creatinine and blood urea nitrogen.

Urine output (ml/day) : assessed as volume of urine excretion (ml.) in 24-hours.

Secondary outcomes : any adverse drug reaction except renal adverse events that occur during the study (each adverse event was assessed by using Naranjo's Algorithm).

Wash out period : the period that patients discontinued allopurinol. Only colchincine (0.6mg) tablet was used for relieving or prevention gouty attack.

Appendix F : Equations used for calculation of the creatinine clearance :

Equation 1:

$$CrCl\ (ml/min/1.72m^2) = \frac{Ucr \times V \times 1.73\ (m^2)}{Scr \times 1440 \times BSA\ (m^2)}$$

where

V = urine volume (ml/day)

Ucr = urine creatinine (mg/dl)

Scr = serum creatinine (mg/dl)

BSA = body surface area (m^2)

Equation 2:

$$BSA\ (m^2) = W^{0.425} \times H^{0.725} \times 0.007184$$

where

W = body weight (kg.) : H = height (cm.)

Cockcroft-Gault's equation

Equation 3:

$$CrCl\ (ml/min)(male) = \frac{(140 - age) \times BW}{72 \times Scr}$$

Equation 4:

$$CrCl\ (ml/min)(female) = \frac{(140 - age) \times BW}{72 \times Scr} \times 0.85$$

where

W = body weight(kg) : Scr = serum creatinine(mg/dl)

If body mass index (BMI) $\geq$ 27 kg/m^2 and/or % indeal body weight (%IBW) $\geq$ 120 used ideal body weight (IBW) instead of actual of actual body weight.

Equation 5:

$$IBW(kg)(male) = 50 + 2.3 \text{ (height in inches - 60)}$$

Equation 6:

$$IBW(kg)(female) = 45.5 + 2.3 \text{ (height in inches - 60)}$$

Equation 7:

$$\% IBW = \frac{\text{actual BW}}{\text{IBW}} \times 100$$

Equation 8:

$$BMI = W/H^2$$

Where

W = body weight (kg) : H = height (cm.)

Equations used for calculation of lean body weight (LBW) :

Equation 9:

$$LBW (kg)(male) = 0.3821W + 0.33929H - 29.5336$$

Equation 10:

$$LBW (kg)(female) = 0.2957W + 0.41813H - 43.2933$$

where

W = body weight (kg) : H = height (cm.)

BIOGRAPHY

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