CHAPTER IV

RESULTS AND DISCUSSION

1. Patients

Patients who were screened in this study during July 2001 and May 2002 were out-patients of Rheumatology Clinic, Rajavithi Hospital. Figure 10 showed the number of patients up to end of study. Fifty-nine patients entered in the screening of inclusion criteria. Three patients were excluded before initially entered into each sequence treatment group. One of them had creatinine clearance less than 30 ml/min/1.73m^2. One patient received angiotensin II receptor antagonist. The last patient had peptic ulcer history that confirmed by endoscopy. Fifty-six patients were enrolled in this study. The number of patients who were stratified randomization into two treatment groups, sequence I and sequence II, were 27 and 29, respectively. Eight patients were withdrawn during this study. In sequence I treatment group, two patients were unable to collect 24-hour urine while one patient was loss follow up. In sequence II treatment group, one patient had poor compliance. Two patients had creatinine clearance less than 30 ml/min/1.73m^2 and two patients were loss follow up. None of patients were withdrawn from adverse drug reactions, occurred oliguria or changed of serum creatinine more than 0.5 mg/dl from baseline. Finally, only fourty-eight patients completed in this study. The number of patients in each sequence treatment were twenty-four equally.

2. Demographic data

Fourty-eight elderly patients who completed in this study were analyzed. Summary of characteristics of patients was presented in Appendix C_1, C_2. Different characteristics of the patients were present in Table 15. Demographic data of patients

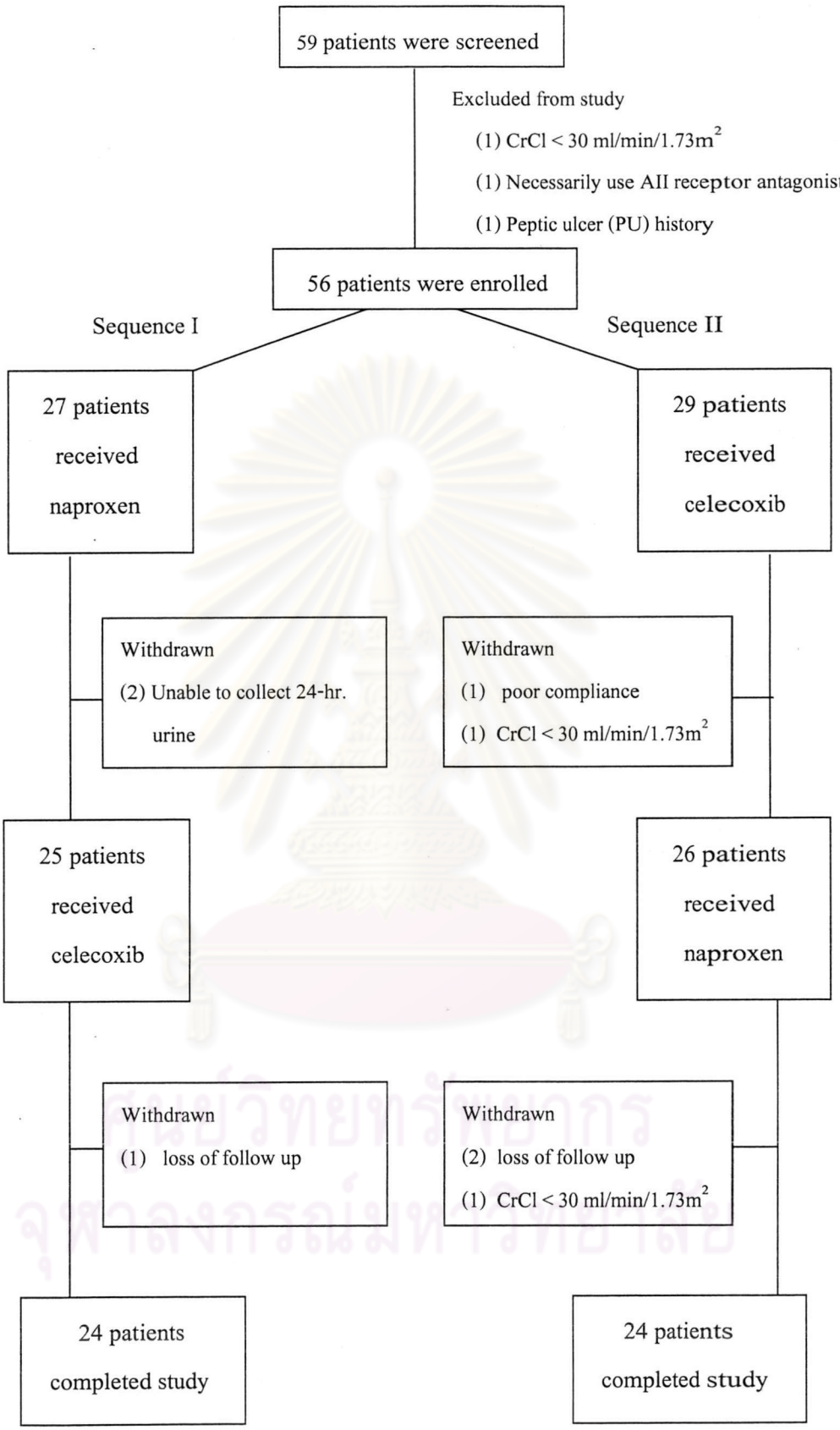


Figure 10: Number of patients up to end of study

Table 15: Demographic data of the patients

Demographic data	Number of patients (%) (N = 48)
Sex	
Male	26 (54.17)
Female	22 (45.83)
Musculoskeletal problems	
Osteoarthritis	27 (56.25)
Gouty arthritis	20 (41.66)
Rheumatoid arthritis	9 (18.75)
Muscle pain	5 (10.41)
Underlying diseases	
Treated hypertension	30 (62.50)
Untreated hypertension	9 (18.75)
Renal insufficiency	22 (45.83)
Diabetic mellitus	5 (10.42)
Coronary artery disease	3 (6.25)
Concomitant medications	
Calcium channel blocker	14 (46.67)
Beta blocker	1 (3.33)
Alpha blocker	1 (3.33)
Combination antihypertensive medications	14 (46.67)
Allopurinol	20 (41.66)
Aspirin (60 mg)	3 (6.25)
Renal functions	
Normal renal function (CrCl $\geq$ 60 ml/min/1.73m^2)	26 (54.16)
Renal insufficiency (CrCl = 30-60 ml/min/1.73m^2)	22 (45.83)

could be classified into five groups according to the sex, musculoskeletal problems, underlying diseases, concomitant medications and renal functions. There were twenty-six males and twenty-two females ranging in age from 60 to 83 years old (Mean±SD = 66.88±13.95). The musculoskeletal problems of all 48 patients were osteoarthritis (56.25%), gouty arthritis (41.66%), rheumatoid arthritis (18.75%) and muscle pain (10.41%). Underlying diseases of all 48 patients were hypertension (81.25%), renal insufficiency (45.83%), diabetic mellitus (10.42%) and coronary artery disease (6.25%). The most antihypertensive medications that the patients consumed were calcium channel blocker (46.67%) and combination antihypertensive medications (46.67%). In addition, twenty patients (41.66%) taking allopurinol and only three patients (6.25%) taking aspirin 60 mg once daily for cardioprotection.

Table 16 presented comparison the laboratory data of all 48 patients at baseline before initially received either naproxen or celecoxib in each sequence treatment group. There were no significant difference between sequence I and sequence II treatment group, except sodium excretion in urine. Sequence I treatment group had 15 males, 9 females ranging in age from 60 to 83 (Mean±SD = 67.88±5.66) while sequence II treatment group consisted of 11 males, 13 females ranging in age from 60 to 75 (Mean±SD = 65.88±4.67). These results implied that there was no sequence effect which preliminary assumption for crossover analysis.

The laboratory data of majority patients were within normal level. However, twelve patients showed high SGOT and/or SGPT level (> 40 U/L) but not more than two times of the normal range while five patients had high level of serum creatinine (>1.5 mg/dl) but not more than 2 mg/dl and 14 patients showed high level of uric acid (>7.0 mg/dl). Laboratory data of each patient at baseline was demonstrated in Appendix D_1, D_2.

Table 16: Comparison the laboratory data of patients at baseline

Laboratory test	SequenceI (N=24) (Mean±SD)	SequenceII (N =24) (Mean±SD)
Cr (0.5-1.5 mg/dl)[a]	1.17±0.28	1.13±0.24[ns]
BUN(5-20 mg/dl) [a]	15.41±4.17	15.08±4.26[ns]
Na (135-155 mEq/L)[a]	143.58±1.89	143.50±2.54[ns]
K (3.5-5.5 mEq/L)[a]	4.20±0.31	4.26±0.35[ns]
Uric acid (2.4-7.0 mg/dl) [a]	6.33±1.92	6.25±2.12[ns]
SBP (mmHg)	142.21±15.87	140.67±14.29[ns]
DBP (mmHg)	79.33±10.42	79.00±11.45[ns]
MAP (mmHg)	100.29±10.96	99.56±11.28[ns]
SGOT (0-40 U/L)[a]	29.29±13.59	28.83±13.37[ns]
SGPT (0-40 U/L)[a]	26.04±13.12	26.92±18.19[ns]
CrCl (ml/min/1.73m^2)	62.92±13.74	62.16±14.44[ns]
Na excrete in urine(10-220 mEq/24hrs)[a]	167.21±69.12	126.63±59.63[*]
K excrete in urine (4-44 mEq/24hrs)[a]	39.46±13.55	36.92±14.67[ns]

[a] = normal range of laboratory data at Rajavithi Hospital

[ns] = no significant versus sequence I

[*] = $p < 0.05$

3. Comparison different methods for predicting creatinine clearance

In this study, creatinine clearance (CrCl) was assessed using 24-hour urine collection in accordance with Cockcroft-Gault equation. As shown in Table 17, we found that CrCl predicted from Cockcroft-Gault equation was significantly different from CrCl measured by 24-hour urine collection. In the study of Rolin et al. found that predicted CrCl using Cockcroft-Gault equation had overestimated GFR as compared to CrCl using iothalamate, which is one of standard method for predicting GFR.[122] It was

possible that there are several factors affecting creatinine generation (e.g., meat intake, muscle wasting) leading to vary predicted CrCl using Cockcroft-Gault equation particularly in patients with renal diseases.

Therefore, CrCl using Cockcroft-Gault equation was not chosen for assessment of renal functions but CrCl using 24-hour urine collection was used in this study. If the error from urine collection occurred, it can be detected by checking creatinine concentration in urine.

Table 17: Comparison of predicted creatinine clearance from two methods

Predicted CrCl by	Mean±SD	P value
Cockcroft-Gault's equation	66.80±25.54	0.001
24-hour urine collection	58.73±14.43	

P value = Statistical significance between CrCl using Cockcroft-Gault's equation and 24-hour urine collection

4. Subgroup of patients

If the subjects were considered along with risk factors which affect renal functions, hypertension and renal insufficiency were found in majority of the patients while diabetic mellitus and coronary artery disease were found in a few patients in this study. To determine renal effects of celecoxib and naproxen, patients were divided into subgroups base on their renal functions and blood pressure level along with their underlying diseases. The results were shown as follows.

4.1 Subgroup of patients based on renal functions

Patients in this study were both normal renal (CrCl $\geq$ 60 ml/min/1.73m^2) and renal insufficiency (CrCl = 30-60 ml/min/1.73m^2) as shown in Table 18, twenty-six patients (54.17%) had normal renal function. Among of 26 patients, there were normal blood pressure (N=5), high blood pressure (N=16), high blood pressure with DM (N=3) and high blood pressure with CAD (N=2).

While renal insufficiency was found in 22 patients (45.83%). Among of 22 patients, there were normal blood pressure (N=4), high blood pressure (N=15), high blood pressure with DM (N=2), high blood pressure with CAD (N=1).

Table 18: Subgroup of patients based on renal functions

Patients	Number of patients
● All patients	48
● Normal renal function	26
- With normal blood pressure level	5
- With high blood pressure level	16
- With high blood pressure level, DM	3
- With high blood pressure level, CAD	2
● Renal insufficiency	22
- With normal blood pressure level	4
- With high blood pressure level	15
- With high blood pressure level, DM	2
- With high blood pressure level, CAD	1

4.2 Subgroup of patients based on blood pressure level

Patients in this study were both normal blood pressure (SBP < 140 and/or DBP < 90 mmHg) and high blood pressure level (SBP ≥ 140 and/or DBP ≥ 90 mmHg). As shown in Table 19. Only nine patients (18.75%) had normal blood pressure level. However, 5 out of them had normal renal function while 4 out them had renal insufficiency.

While, thirty-nine patients (81.25%) had high blood pressure level. Among of 39 patients, there were normal renal function (N=16), with DM (N=3), and with CAD (N=2), with renal insufficiency (N=15), with DM (N=2) and with CAD (N=1).

Table 19: Subgroup of patients based on blood pressure level

Patients	Number of patients
● All patients	48
● Normal blood pressure	9
- With normal renal function	5
- With renal insufficiency	4
● High blood pressure	39
- With normal renal function	16
- With normal renal, DM	3
- With normal renal, CAD	2
- With renal insufficiency	15
- With renal insufficiency, DM	2
- With renal insufficiency, CAD	1

5. Primary outcomes evaluation

In this study, primary outcomes composed of renal haemodynamic (creatinine clearance, serum creatinine, blood urea nitrogen, systolic blood pressure, diastolic blood pressure, mean arterial blood pressure), serum electrolyte, electrolyte excreted in urine and edema. Each outcome except edema was analyzed by pair-T test analysis and crossover analysis. The occurrence of edema was analyzed by Chi-square analysis.

5.1 Creatinine clearance (CrCl), serum creatinine (Scr) and blood urea nitrogen (BUN)

Appendix E_1 showed urine creatinine, urine volume and body surface area of each patient before and after naproxen and celecoxib treatment. These data were calculated CrCl using 24-hour urine collection by equation 1-2. Change of CrCl, Scr, BUN before and after celecoxib and naproxen treatment were presented in Appendix E_2. Overall statistical levels of significant (P value) were displayed in Appendix J-O.

5.1.1 Comparison mean of CrCl, Scr, BUN before and after receiving naproxen and celecoxib (using pair T test analysis)

The results of all patients and each subgroup were presented in Table 20-27 as follows.

A. All patients

As results of naproxen treatment group in Table 20-21, CrCl was significantly decreased from baseline ($p<0.001$) but BUN was significantly increased ($p< 0.001$) while Scr not significantly increased from baseline. As compare to celecoxib treatment group in Table 22-23, CrCl was significantly decreased ($p<0.001$) but BUN were significantly increased from baseline ($p< 0.01$). Scr was significantly increased from baseline 0.03 ± 0.10 mg/dl. It implied that the increment of Scr was not meaningful

clinical implication (Scr increase from baseline equal or more than 0.5 mg/dl is meaningful clinical implication)

Since variation in underlying diseases might have influence on this finding. The results from concerning underlying diseases were also presented according to subgroup of patients based on renal functions.

B. Normal renal and renal insufficiency patients

Regarding renal functions, naproxen group (Table 20, 21) had CrCl decreasing in both normal renal (N=26) and renal insufficiency patients (N=22) but serum creatinine significantly increased in normal renal patients ($p< 0.01$) but the increasing of Scr was not meaningful clinical implication. BUN showed increase in both normal renal and renal insufficiency significantly.

While results from celecoxib group (Table 22, 23), CrCl also significantly decreased in normal renal (N=26) and renal insufficiency patients (N=22) but Scr and BUN significantly increased in only renal insufficiency patients.

For patient whose normal renal with normal blood pressure (N=5), CrCl, Scr did not change in naproxen and celecoxib group but BUN increased in naproxen group significantly. However, the number of subjects in this normalized group was so small. Further studies with more sample size are required.

While patient whose normal renal with high blood pressure (N=16), in contrast to previous subgroup, CrCl significantly decreased in naproxen and celecoxib group while Scr significantly increased in only naproxen treatment group and BUN did not significantly change in both treatment groups.

In patient whose normal renal with high blood pressure level and other underlying diseases (e.g., DM, CAD) (N= 5), CrCl significantly decreased in only naproxen treatment group while BUN and Scr did not change significantly in both treatment groups. However, the number of patients was so small, the further studies with more sample size are required.

Table 20 : CrCl, Scr, BUN before and after receiving naproxen (all patients and subgroup of patients based on renal function)

Patients	CrCl (mean ± SD)		Scr (mean±SD)		BUN (mean±SD)	
	before	after[a]	before	after[a]	before	after[a]
All patients (N =48)	62.18±14.22	55.79±14.93***	1.15±0.27	1.17±0.27ns	15.35±4.26	17.50±4.55***
Normal renal (N = 26)	71.83±11.79	65.77±12.08***	1.03±0.25	1.08±0.27**	14.42±3.49	16.46±3.55**
with normal BP (N = 5)	68.13±9.98	66.02±9.35ns	1.00±0.24	1.00±0.23ns	12.60±1.95	15.40±3.13**
with high BP (N =16)	72.59±13.85	66.68±13.55*	1.05±0.24	1.10±0.27*	15.38±3.54	16.75±3.86ns
with high BP, other risk factors(e.g.,DM, CAD) (N = 5)	73.10±5.73	62.64±11.02*	1.00±0.32	1.08±0.32ns	13.20±3.96	16.60±3.36ns
Renal insufficiency (N =22)	50.77±5.96	43.99±7.44***	1.28±0.24	1.29±0.23ns	16.45±4.88	18.73±5.33*
with normal blood pressure (N =4)	54.47±3.74	47.15±4.77ns	1.10±0.14	1.15±0.17ns	11.00±0.82	13.75±4.65ns
with high BP (N = 15)	49.95±6.44	42.50±7.32*	1.32±0.22	1.34±0.21ns	17.07±5.26	20.27±5.06*
with high BP, other risk factors(e.g.,DM, CAD) (N =3)	49.58±4.49	45.51±8.44ns	1.47±0.06	1.40±0.20ns	18.33±1.15	19.00±2.00ns

*** p< 0.001, **p<0.01, *p<0.05, ns = no significant versus baseline

CrCl = creatinine clearance (ml/min1.73m^2), Scr = serum creatinine (mg/dl), BUN = blood urea nitrogen (mg/dl)

[a] = naproxen versus baseline (before treatment)

before = before receiving naproxen in sequence I, II

after = after receiving naproxen in sequence I, II

Table 21: Mean change of CrCl, Scr, BUN after receiving naproxen (all patients and subgroup of patients based on renal function)

Patients	CrCl (mean±SD)	Scr (mean±SD)	BUN (mean±SD)
All patients (N =48)	−6.39±7.39***	0.02±0.09ns	2.15±3.86***
Normal renal (N = 26)	−6.06±7.63***	0.046±0.08**	2.04±3.26**
with normal BP (N = 5)	−2.11±2.14ns	0.00±0.07ns	2.80±1.30**
with high BP (N =16)	−5.92±8.54*	0.05±0.08*	1.38±3.40ns
with high BP, other risk factors(e.g.,DM, CAD) (N = 5)	−10.46±6.51*	0.08±0.08ns	3.40±4.04ns
Renal insufficiency (N =22)	−6.79±7.25***	0.045±0.11ns	2.27±4.54*
with normal blood pressure (N =4)	−7.32±6.33ns	0.05±0.10ns	2.75±3.95ns
with high BP (N = 15)	−7.45±7.48*	0.02±0.11ns	3.20±4.81*
with high BP, other risk factors(e.g.,DM, CAD) (N =3)	−4.07±7.59ns	−0.06±0.15ns	0.67±1.15ns

*** p< 0.001, **p<0.01, *p<0.05, ns = no significant versus baseline

CrCl = creatinine clearance (ml/min1.73m^2), Scr = serum creatinine (mg/dl), BUN = blood urea nitrogen (mg/dl)

Table 22: CrCl, Scr, BUN before and after receiving celecoxib (all patients and subgroup of patients based on renal function)

Patients	CrCl (mean ± SD)		Scr (mean±SD)		BUN (mean±SD)	
	before	after[b, c]	before	after[b, c]	baseline	after[b, c]
All patients (N =48)	61.30±13.94	55.56±13.77[***, ns]	1.16±0.28	1.19±0.31[*, ns]	15.35±3.77	16.88±4.14[**, ns]
Normal renal (N = 26)	70.69±11.71	63.99±12.39[***, ns]	1.05±0.28	1.07±0.29[ns, ns]	15.31±3.21	15.69±4.12[ns, *]
with normal BP (N = 5)	67.61±4.93	62.57±10.20[ns, ns]	1.00±0.27	1.08±0.41[ns, ns]	13.80±1.64	14.00±2.92[ns, ns]
with high BP (N =16)	71.43±14.41	64.58±13.39[**, ns]	1.08±0.27	1.08±0.27[ns, ns]	16.06±3.66	16.88±4.38[ns, ns]
with high BP, other risk factors(e.g.,DM, CAD) (N = 5)	71.39±6.25	63.55±13.37[ns, $]	1.02±0.35	1.08±0.31[ns, $]	14.40±2.30	13.60±3.29[ns, $]
Patients with renal insufficiency (N=22)	50.21±5.84	45.82±7.36[*, ns]	1.28±0.22	1.33±0.26[*, ns]	15.41±4.43	18.27±3.79[***, ns]
with normal blood pressure (N =4)	54.47±3.74	47.15±4.77[ns, ns]	1.10±0.14	1.15±0.17[ns, ns]	11.00±0.82	13.75±4.65[ns, ns]
with high BP (N = 15)	49.61±5.97	45.47±7.34[*, ns]	1.32±0.19	1.36±0.23[ns, ns]	15.60±4.69	18.13±3.79[*, ns]
with high BP, other risk factors(e.g.,DM, CAD) (N =3)	49.20±6.58	42.88±10.04[ns, $]	1.47±0.15	1.57±0.23[ns, $]	18.67±3.06	21.67±3.06[ns, $]

*** p< 0.001, **p<0.01, *p<0.05, ns = no significant versus baseline

CrCl = creatinine clearance (ml/min1.73m^2), Scr = serum creatinine (mg/dl), BUN = blood urea nitrogen (mg/dl)

[b] = celecoxib versus baseline (before treatment)

[c] = celecoxib versus naproxen

before = before receiving celecoxib in sequence I, II

after = after receiving celecoxib in sequence I, II

$ = not enough sample size to compare celecoxib with naproxen

Table 23: Mean change of CrCl, Scr, BUN after receiving celecoxib (all patients and subgroup of patients based on renal function)

Patients	CrCl (mean±SD)	Scr (mean±SD)	BUN (mean±SD)
All patients (N =48)	−5.64±6.79***	0.03±0.104*	1.52±2.83**
Normal renal (N = 26)	−6.69±7.29***	0.027±1.00ns	0.38±2.23ns
with normal BP (N = 5)	−5.04±8.74ns	0.08±0.19ns	0.20±2.39ns
with high BP (N =16)	−6.85±6.27**	0.00±0.05ns	0.81±2.37ns
with high BP, other risk factors(e.g.,DM, CAD) (N = 5)	−7.84±0.19ns	0.06±0.08ns	−0.08±1.30ns
Renal insufficiency (N =22)	−4.39±6.08*	0.05±0.11*	2.86±2.92***
with normal blood pressure (N =4)	−6.37±4.39ns	0.07±0.17ns	3.00±3.16ns
with high BP (N = 15)	−4.14±7.11*	0.04±0.09ns	2.53±3.31*
with high BP, other risk factors(e.g.,DM, CAD) (N =3)	−6.32±4.32ns	0.01±0.01ns	3.00±2.00ns

*** p< 0.001, **p<0.01, *p<0.05, ns = no significant versus baseline

CrCl = creatinine clearance (ml/min1.73m^2), Scr = serum creatinine (mg/dl), BUN = blood urea nitrogen (mg/dl)

In patient whose renal insufficiency with normal blood pressure (N=4), CrCl , Scr, BUN were not significantly different in both treatment groups. While patient whose renal insufficiency with high blood pressure (N=15), CrCl significantly increased in either naproxen or celecoxib group and BUN significantly increased in both treatment groups but Scr was not significantly different. Patient whose renal insufficiency with high blood pressure and concomitant underlying diseases (e.g., DM, CAD) (N=3), CrCl, Scr, BUN did not change significantly in both treatment groups. There may be small subjects participated in this group. Further studies with more sample size are required.

As these results, naproxen and celecoxib declined renal functions in normal renal (N=26), renal insufficiency (N=22) and high blood pressure patients (N=39) but not observed in normal blood pressure patients (N=9). It was implied that there were not enough normal blood pressure patients in this study or high blood pressure level seems to associate with decline renal functions after naproxen or celecoxib treatment. Therefore, we would analyze in subgroup of patients based on blood pressure level.

C. Normal blood pressure and high blood pressure patients

Blood pressure level was one of risk factors that can affect decline renal function in patients receiving NSAIDs. Table 24-27 showed CrCl, Scr, BUN in naproxen and celecoxib treatment. Naproxen and celecoxib was not significantly decreased CrCl from baseline in patients with normal blood pressure (N=9) but significantly decreased in patients with high blood pressure level (N= 39). The results of Scr and BUN similar to those of CrCl, there were significantly increased in only high blood pressure patients.

As shown in Table 24-27, it could be seen obviously that high blood pressure patients (either normal or renal insufficiency) had a tendency to decline renal function in this study. Although there was no significant difference between normal blood pressure and high blood pressure patients, it is possible that hypertensive patients were

found in the majority of the patients in this study while other populations were found in a few of patients in this study. Thus, we could not observe the decrement of renal function in other populations. Apart from this, it is probable that hypertensive patients appear to be potential renal risk factor of COX-2 inhibitors as a result of discovery by Khan et al., who found that hypertension associated with increased renal COX-2 expression particularly in macula densa[102] while expression of COX-1 in hypertensive patients should be investigated in the future. Interestingly, additional underlying diseases (e.g., DM, CAD) were not affected renal functions in this study because it might be not enough patients in this group. Further studies with more sample size of each underlying disease are necessary to conclude in this group of patients.

Table 24: CrCl, Scr, BUN before and after receiving naproxen (subgroup of patients based on blood pressure level)

Patients	CrCl (mean ± SD)		Scr (mean±SD)		BUN (mean±SD)	
	before	after[a]	before	after[a]	before	after[a]
Normal blood pressure patients (N=9)	62.19±10.25	58.19±12.20^{ns}	1.00±0.18	1.00±0.18^{ns}	12.66±2.59	14.22±3.63^{ns}
with normal renal (N = 5)	68.13±9.98	66.02±9.35^{ns}	1.00±0.24	1.00±0.23^{ns}	12.60±1.95	15.40±3.13**
with renal insufficiency (N =4)	54.47±3.74	47.15±4.77^{ns}	1.10±0.14	1.15±0.17^{ns}	11.00±0.82	13.75±4.65^{ns}
High blood pressure patients (N=39)	62.18±15.10	55.23±15.57***	1.18±0.28	1.21±0.27*	15.97±4.35	18.26±4.44**
with normal renal (N =16)	72.59±13.85	66.68±13.55*	1.05±0.24	1.10±0.27*	15.38±3.54	16.75±3.86^{ns}
with normal renal, other risk factors(e.g.,DM, CAD) (N = 5)	73.10±5.73	62.64±11.02*	1.00±0.32	1.08±0.32^{ns}	13.20±3.96	16.60±3.36^{ns}
with renal insufficiency (N = 15)	49.95±6.44	42.50±7.32*	1.32±0.22	1.34±0.21^{ns}	17.07±5.26	20.27±5.06*
with renal insufficiency, other risk factors(e.g.,DM, CAD) (N =3)	49.58±4.49	45.51±8.44^{ns}	1.47±0.06	1.40±0.20^{ns}	18.33±1.15	19.00±2.00^{ns}

*** p< 0.001, **p<0.01, *p<0.05, ns = no significant versus baseline

CrCl = creatinine clearance (ml/min1.73m^2), Scr = serum creatinine (mg/dl), BUN = blood urea nitrogen (mg/dl)

[a] = naproxen versus baseline (before treatment)

before = before receiving naproxen in sequence I, II

after = after receiving naproxen in sequence I, II

Table 25: Mean change of CrCl, Scr, BUN after receiving naproxen (subgroup of patients based on blood pressure level)

Patients	CrCl (mean±SD)	Scr (mean±SD)	BUN (mean±SD)
Normal blood pressure patients (N=9)	−3.99±5.38^{ns}	0.00±0.087^{ns}	1.56±3.36^{ns}
with normal renal (N = 5)	−2.11±2.14^{ns}	0.00±0.07^{ns}	2.80±1.30**
with renal insufficiency (N =4)	−7.32±6.33^{ns}	0.05±0.10^{ns}	2.75±3.95^{ns}
High blood pressure patients (N=39)	−6.95±7.73***	0.03±0.101*	2.28±3.99**
with normal renal (N =16)	−5.92±8.54*	0.05±0.08*	1.38±3.40^{ns}
with normal renal, other risk factors(e.g.,DM, CAD) (N = 5)	−10.46±6.51*	0.08±0.08^{ns}	3.40±4.04^{ns}
with renal insufficiency (N = 15)	−7.45±7.48*	0.02±0.11^{ns}	3.20±4.81*
with renal insufficiency, other risk factors(e.g.,DM, CAD) (N =3)	−4.07±7.59^{ns}	−0.06±0.15^{ns}	0.67±1.15^{ns}

*** p< 0.001, **p<0.01, *p<0.05, ns = no significant versus baseline

CrCl = creatinine clearance (ml/min1.73m^2), Scr = serum creatinine (mg/dl), BUN = blood urea nitrogen (mg/dl)

Table 26: CrCl, Scr, BUN before and after receiving celecoxib (subgroup of patients based on blood pressure level)

Patients	CrCl (mean ± SD)		Scr (mean±SD)		BUN (mean±SD)	
	before	after [b, c]	before	after [b, c]	before	after [b, c]
Normal blood pressure patients (N=9)	61.22±8.96	56.67±10.68 [ns, ns]	1.00±0.20	1.07±0.31 [ns, ns]	13.11±1.90	15.00±3.08 [ns, ns]
with normal renal (N = 5)	67.61±4.93	62.57±10.20 [ns, ns]	1.00±0.27	1.08±0.41 [ns, ns]	13.80±1.64	14.00±2.92 [ns, ns]
with renal insufficiency (N =4)	54.47±3.74	47.15±4.77 [ns, ns]	1.10±0.14	1.15±0.17 [ns, ns]	11.00±0.82	13.75±4.65 [ns, ns]
High blood pressure patients (N=39)	61.32±14.95	55.43±14.50 [***, ns]	1.19±0.28	1.22±0.30 [*, ns]	15.87±3.92	17.31±4.26 [**,ns]
with normal renal (N =16)	71.43±14.41	64.58±13.39 [**, ns]	1.08±0.27	1.08±0.27 [ns, ns]	16.06±3.66	16.88±4.38 [ns, ns]
with normal renal, other risk factors(e.g.,DM, CAD) (N = 5)	71.39±6.25	63.55±13.37 [ns, $]	1.02±0.35	1.08±0.31 [ns, $]	14.40±2.30	13.60±3.29 [ns, $]
with renal insufficiency (N = 15)	49.61±5.97	45.47±7.34 [*, ns]	1.32±0.19	1.36±0.23 [ns, ns]	15.60±4.69	18.13±3.79 [*, ns]
with renal insufficiency, other risk factors(e.g.,DM, CAD) (N =3)	49.20±6.58	42.88±10.04 [ns, $]	1.47±0.15	1.57±0.23 [ns, $]	18.67±3.06	21.67±3.06 [ns, $]

*** p< 0.001, **p<0.01, *p<0.05, ns = no significant versus baseline

CrCl = creatinine clearance (ml/min1.73m^2), Scr = serum creatinine (mg/dl), BUN = blood urea nitrogen (mg/dl)

[b] = celecoxib versus baseline (before treatment)

[c] = celecoxib versus naproxen

before= before receiving celecoxib in sequence I, II

after = after receiving celecoxib in sequence I, II

$ = not enough sample size to compare celecoxib with naproxen

Table 27: Mean change of CrCl, Scr, BUN after receiving celecoxib (subgroup of patients based on blood pressure level)

Patients	CrCl (mean±SD)	Scr (mean±SD)	BUN (mean±SD)
Normal blood pressure patients (N=9)	-4.55 ± 6.37^{ns}	0.06 ± 0.17^{ns}	1.89 ± 2.85^{ns}
with normal renal (N = 5)	-5.04 ± 8.74^{ns}	0.08 ± 0.19^{ns}	0.20 ± 2.39^{ns}
with renal insufficiency (N =4)	-6.37 ± 4.39^{ns}	0.07 ± 0.17^{ns}	3.00 ± 3.16^{ns}
High blood pressure patients (N=39)	$-5.89\pm6.94^{***}$	$0.03\pm0.08^{*}$	$1.44\pm2.85^{**}$
with normal renal (N =16)	$-6.85\pm6.27^{**}$	0.00 ± 0.05^{ns}	0.81 ± 2.37^{ns}
with normal renal, other risk factors(e.g.,DM, CAD) (N = 5)	-7.84 ± 0.19^{ns}	0.06 ± 0.08^{ns}	-0.08 ± 1.30^{ns}
with renal insufficiency (N = 15)	$-4.14\pm7.11^{*}$	0.04 ± 0.09^{ns}	$2.53\pm3.31^{*}$
with renal insufficiency, other risk factors(e.g.,DM, CAD) (N =3)	-6.32 ± 4.32^{ns}	0.01 ± 0.01^{ns}	3.00 ± 2.00^{ns}

*** p< 0.001, **p<0.01, *p<0.05, ns = no significant versus baseline

CrCl = creatinine clearance (ml/min1.73m^2), Scr = serum creatinine (mg/dl), BUN = blood urea nitrogen (mg/dl)

Regarding other factors that can affect renal functions e.g., sex, uric acid level or concomitant antihypertensive medications, allopurinol. These factors were considered along with high blood pressure and normal renal group (N=16). This group was chosen to assess other factors, which might affect renal functions after naproxen and celecoxib treatment because patients had enough and none of them had renal insufficiency, DM and CAD. Table 28 showed characteristics of this group as follow.

Table 28: Characteristics of hypertensive patients with normal renal functions

Hypertensive patients with normal renal functions	Number (N =16)
Sex	
Male	8
Female	8
Uric acid	
High uric acid	6
Normal uric acid	10
Antihypertensive medications	
Patients who had been treated with antihypertensive medications	13
Patients who had never been treated with antihypertensive medications	3
Allopurinol	
Patients received allopurinol	7
Patients not received allopurinol	9

Results were shown in Table 29, overall statistical levels of significant (P value) were shown in Appendix V. CrCl of the patients with high blood pressure level in celecoxib treatment group decreased higher than those of naproxen treatment group although from a statistical point of view, there was no difference between naproxen and celecoxib.

Table 29: Mean change of creatinine clearance obserbved in hypertensive patients with normal renal functions

Patients	Naproxen (mean+SD)[a]	Celecoxib (mean+SD)[b, c]
All hypertensive patients with normal renal function (N=16)	$-5.92\pm8.54^{*}$	$-6.85\pm6.27^{**, ns}$
Sex		
Male (N = 8)	-4.43 ± 6.83^{ns}	$-5.26\pm5.59^{*, ns}$
Female (N = 8)	-7.41 ± 10.21^{ns}	$-8.44\pm6.88^{*, ns}$
Uric acid level		
Patients with high uric acid level(uric acid > 7 mg/dl) (N = 6)	-6.86 ± 6.65^{ns}	$-8.21\pm5.32^{*, ns}$
Patients with normal uric acid level(uric acid ≤ 7 mg/dl) (N = 10)	-5.35 ± 9.79^{ns}	$-6.04\pm6.92^{*, ns}$
Concomitant antihypertensive medications		
Treated hypertension (N=13)	$-5.02\pm6.28^{*}$	$-7.55\pm6.37^{**, ns}$
Untreated hypertension (N=3)	-9.80 ± 16.78^{ns}	$-3.84\pm5.94^{ns, \$}$
Allopurinol use		
Patients taking allopurinol (N = 7)	$-7.13\pm6.11^{*}$	$-6.22\pm6.36^{*, ns}$
Patients not taking allopurinol (N = 9)	-4.98 ± 10.31^{ns}	$-7.34\pm6.55^{*, ns}$

*** p <0.001, **p <0.01, *p < 0.05, ns = no significance versus baseline

[a] = naproxen versus baseline (before treatment)

[b] = celecoxib versus baseline (before treatment)

[c] = celecoxib versus naproxen

$ = not enough sample size to compare celecoxib with naproxen

As shown in Table 29, there was no significant difference between male and female gender, high and low uric acid level. This result disagrees with a previous study by Gutthann SP et al., who found that incidence rate of acute renal failure from NSAIDs related to male gender[9] and Perez-Ruiz et al. found that decreasing of CrCl had occurred in patients who could not control of uric acid and taking NSAIDs.[118] Moreover, concomitant with allopurinol in this study could not be seen significant difference as compared to patients without receiving allopurinol.

One other interesting observation from this study was concomitant with antihypertensive medications could be seen significantly different from baseline after naproxen and celecoxib treatment while patients without taking antihypertensive medications were not observed. It was possible that the number of treated hypertensive patients higher than untreated hypertensive patients or antihypertensive medications might also decline renal function. Further studies should investigate this assumption.

5.1.2. Comparison mean change of creatinine clearance (CrCl), serum creatinine (Scr) and blood urea nitrogen (BUN) between naproxen and celecoxib (using crossover analysis)

Crossover analysis was conducted for comparison renal effects between naproxen and celecoxib. After crossover study of both sequences, the two treatments in 2 x 2 crossover design with 24 subjects in sequence I and 24 subjects in sequence II. All subgroup analysis had preliminary test assumption of equal period effect and carry over effect at the 0.05 significance level.

Figure11-13 showed mean change of CrCl, Scr, BUN in all patients and subgroup of patients. Figure 14-16 showed change of CrCl, Scr and BUN after treatment of naproxen and celecoxib in each patient respectively. The mean change of CrCl, Scr and BUN was shown along the vertical axis. The two sequences were shown

along the horizontal axis. The change of CrCl, Scr and BUN for each subject is directed by two points connected by a line. There were some patients different from the others.

In crossover analysis showed that there were no significant difference in CrCl, Scr, BUN between naproxen and celecoxib in all patients. When patients were divided into each subgroup, the results as same to all patients that there were no significant difference in both normal renal and renal insufficiency patients and also no significant difference between naproxen and celecoxib in either normal blood pressure or high blood pressure patients. These results were also shown in Table 22, 26. Overall statistical levels of significant (P value) were presented in Appendix J-O.

Figure 11: Mean change of creatinine clearance (CrCl) in the patients

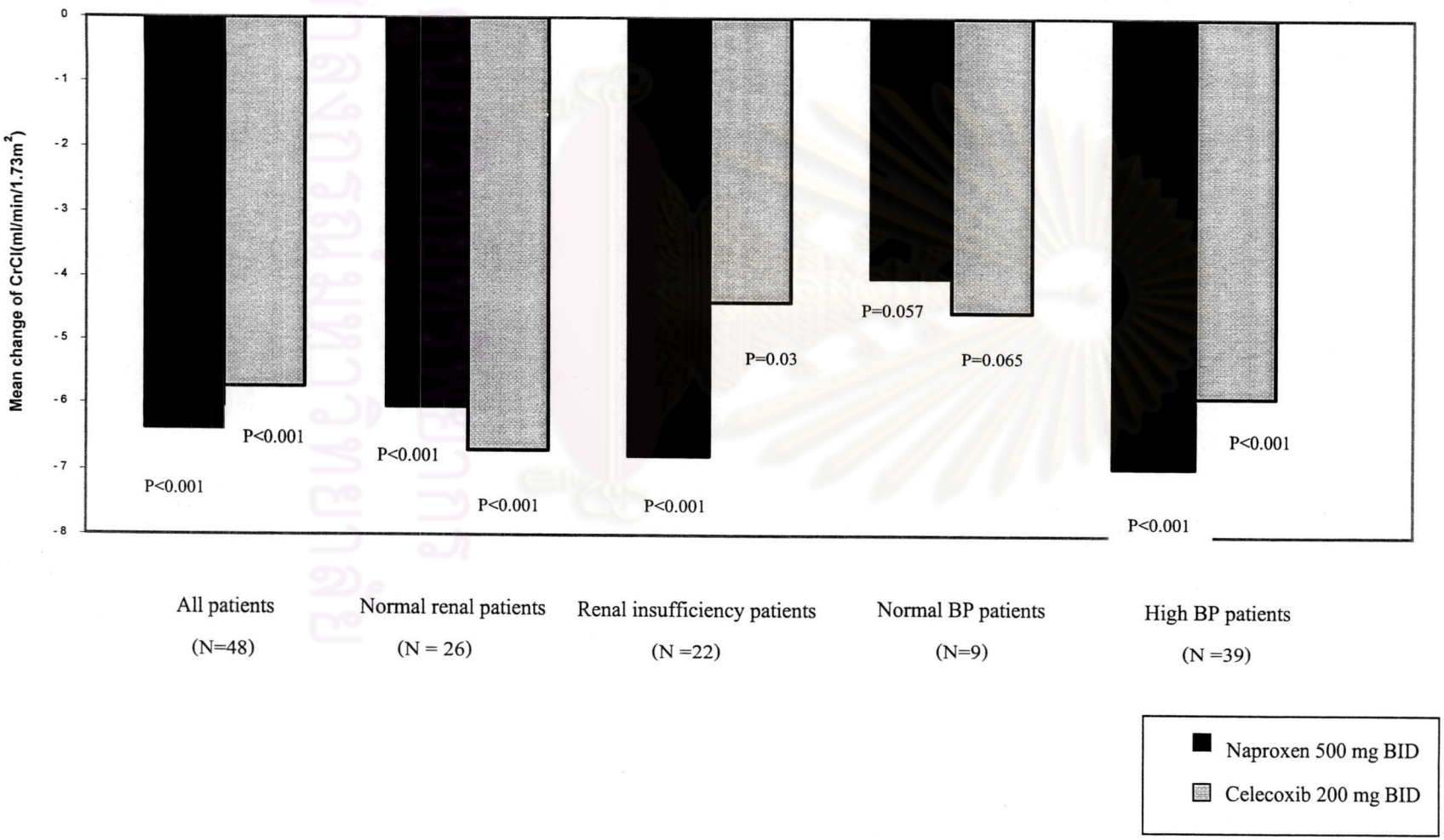


Figure 12: Mean change of serum creatinine (Scr) in the patients

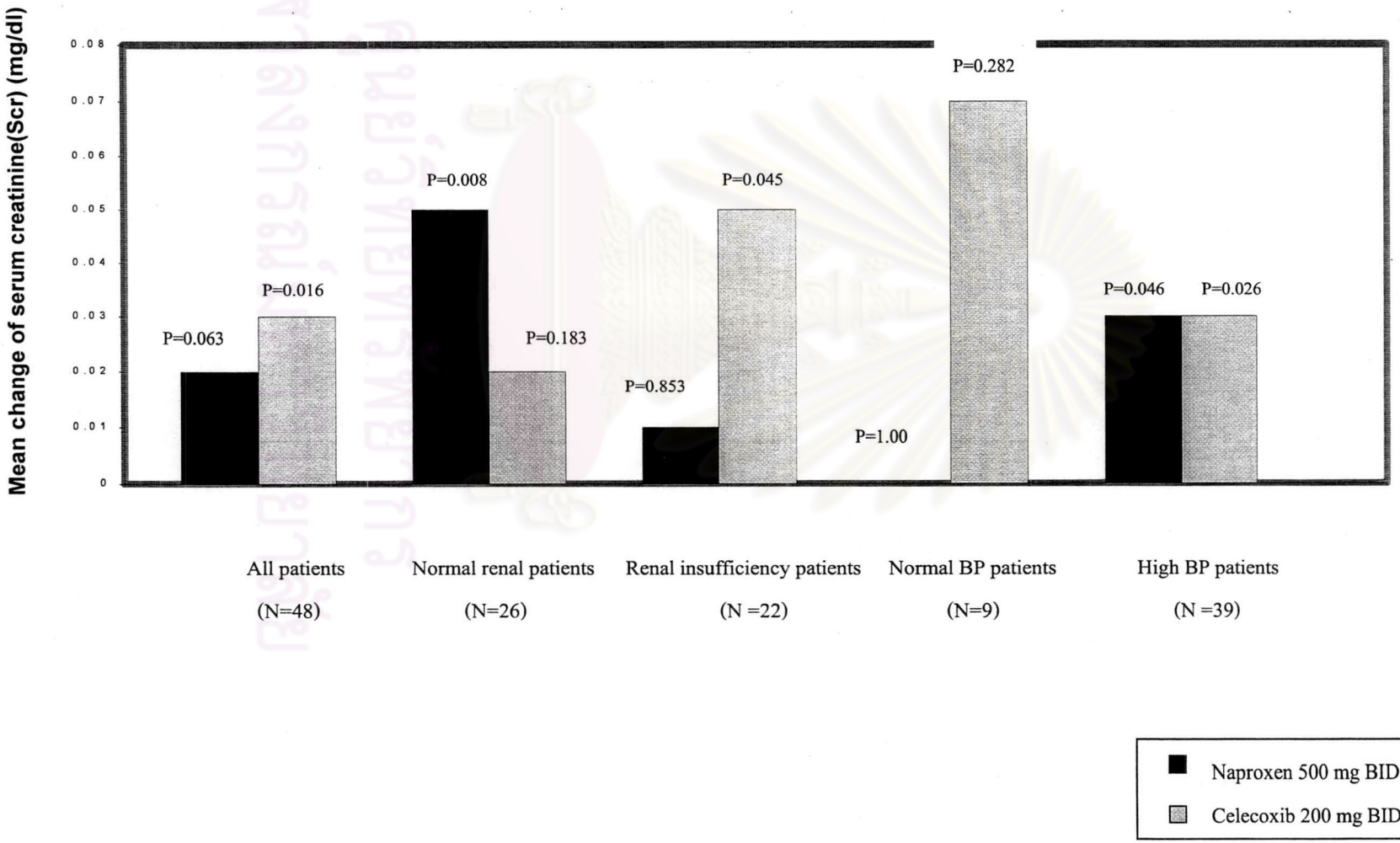


Figure 13: Mean change of blood urea nitrogen (BUN) in the patients

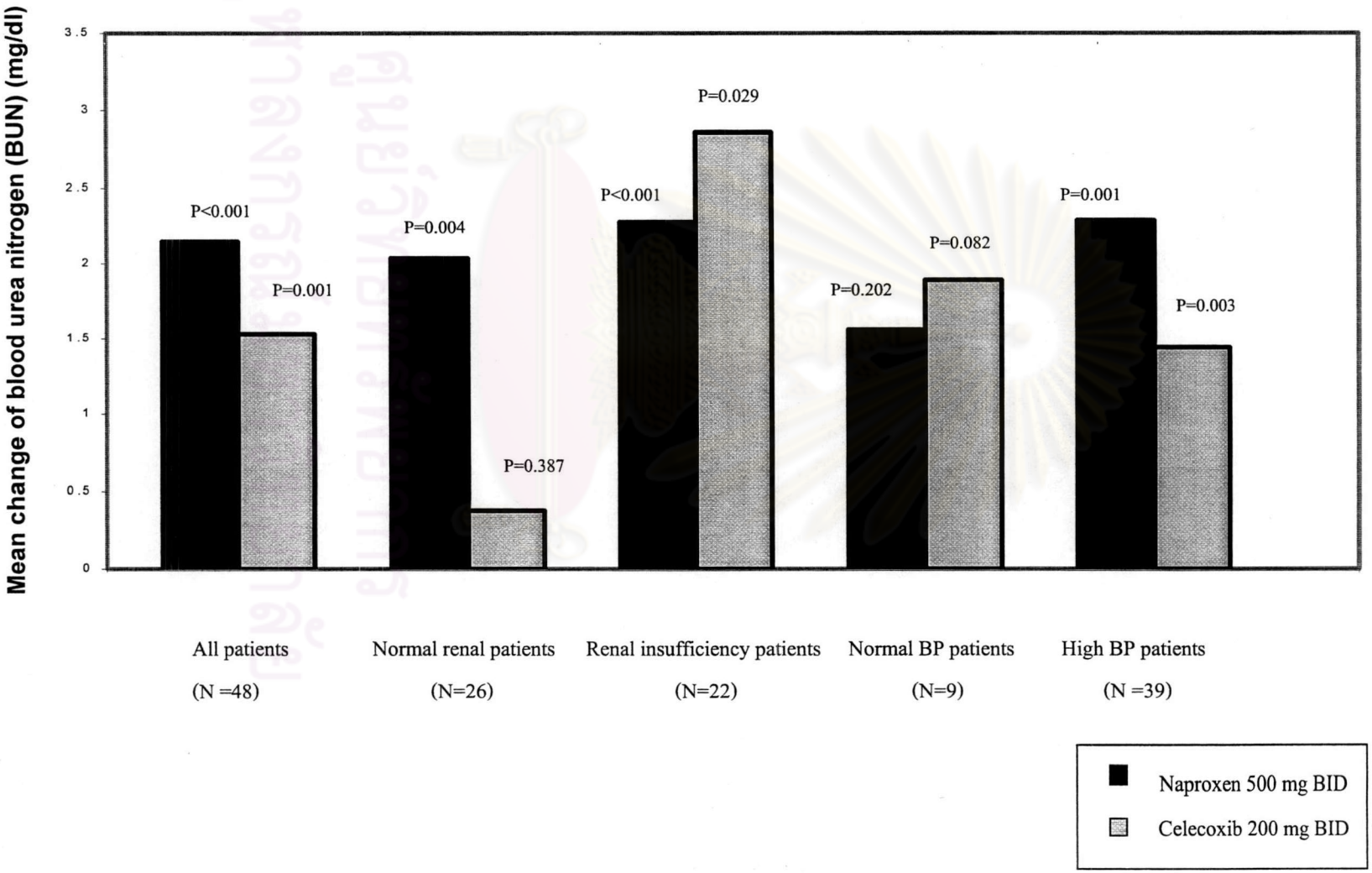
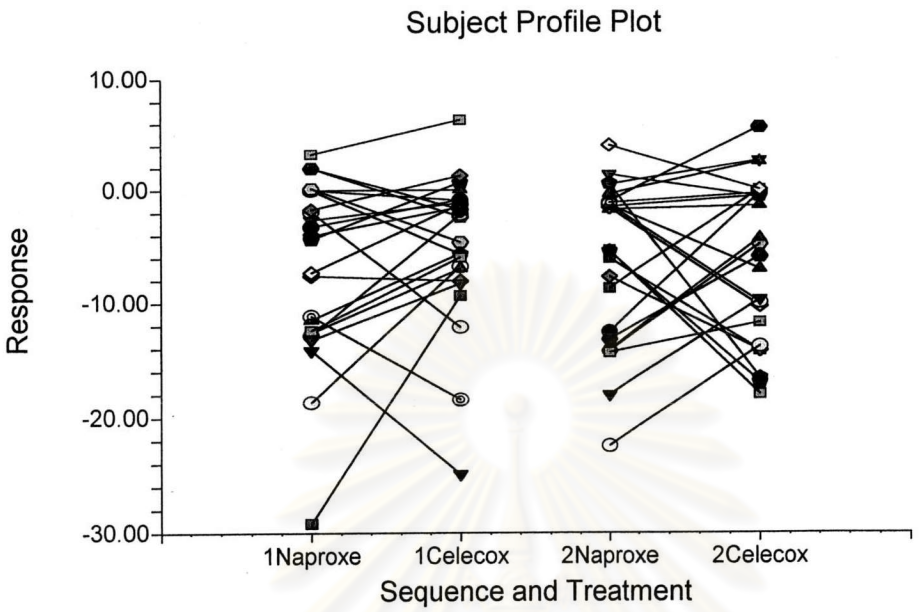
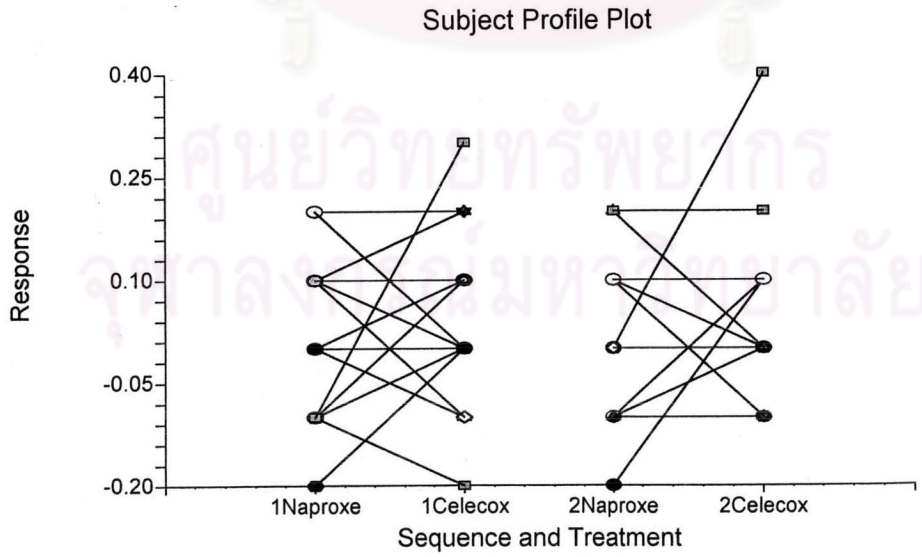


Figure 14: Change of creatinine clearance(CrCl) after treatment of naproxen and celecoxib in each patient



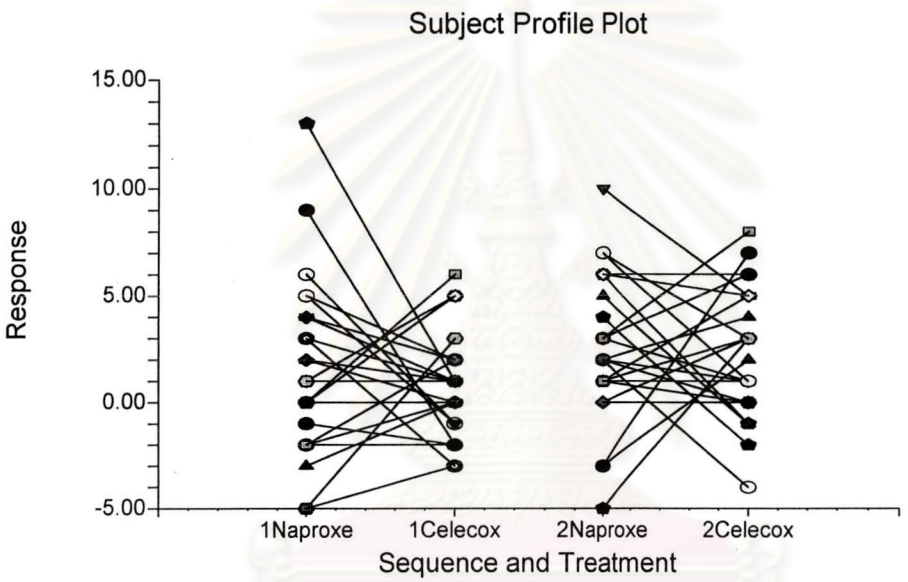
Response = Change of creatinine clearance (CrCl) after treatment of naproxen and celecoxib in each patient

Figure 15: Change of serum creatinine (Scr) after treatment of naproxen and celecoxib in each patient



Response = Change of serum crearinine (Scr) after treatment of naproxen and celecoxib in each patient

Figure 16 : Change of blood urea nitrogen (BUN) after treatment of naproxen and celecoxib in each patient



Response = Change of blood urea nitrogen (BUN) after treatment of naproxen and celecoxib in each patient

5.2 Blood pressure

Mean of systolic blood pressure (SBP) and diastolic blood pressure (DBP) from two times measurement before and after treatment with naproxen and celecoxib were shown in Appendix F_1. Mean arterial blood pressure (MAP) was calculated by equation11 and was presented in Appendix F_2. Analyzed data were presented in all patients and subgroup of patients based on blood pressure level after treatment with celecoxib 200 mg twice daily and naproxen 500 mg twice daily. Overall statistical levels of significant (P value) were displayed in Appendix P-R.

5.2.1 Comparison mean of SBP, DBP, MAP before and after receiving naproxen and celecoxib (using pair T test analysis)

The results of all patients and each subgroup were presented in Table 30-33 as follow.

A. All patients

As results of naproxen group in Table 30-31, after naproxen treatment, SBP significantly increased ($p<0.001$) but DBP, MAP did not significantly change from baseline.

While celecoxib group in Table 32-33, SBP, DBP and MAP small increased but not significantly difference from baseline.

B. Normal blood pressure patients

Regarding normal blood pressure patients (N=9), SBP, DBP and MAP were not significantly increased in naproxen and celecoxib group.

C. High blood pressure patients

In high blood pressure patients (N=39) (include treated hypertension and untreated hypertension), naproxen significantly increased SBP from baseline ($p<0.01$)

Table 30: SBP, DBP and MAP before and after receiving naproxen

Patients	SBP (mean±SD)		DBP (mean±SD)		MAP (mean±SD)	
	before	after[a]	before	after[a]	before	after[a]
All patients (N=48)	141.42±17.29	146.54±14.87**	80.69±10.95	79.65±11.89^{ns}	100.93±11.57	101.94±10.87^{ns}
- Normal blood pressure patients (N=9)	124.00±19.09	126.55±10.19^{ns}	73.00±8.11	73.33+10.06^{ns}	90.00±9.51	91.07±8.00^{ns}
- High blood pressure patients (N=39)	145.44±14.29	151.15±11.63**	82.46±10.83	81.10±11.92^{ns}	103.45±10.55	104.45±9.91^{ns}
Treated hypertension (N=30)	144.97±14.96	150.47±11.17*	82.80±11.57	81.53±12.04^{ns}	103.52±11.44	104.51±10.35^{ns}
Untreated hypertension (N=9)	147.00±12.51	153.44±13.53*	81.33±8.37	79.67±12.07^{ns}	103.22±7.39	104.26±8.86^{ns}

*** p <0.001, **p <0.01, *p < 0.05, ns = no significant versus baseline

SBP = systolic blood pressure DBP = diastolic blood pressure MAP = mean arterial blood pressure

[a] = naproxen versus baseline (before treatment)

before = before receiving naproxen in sequence I, II

after = after receiving naproxen in sequence I, II

Table 31: Mean change of SBP, DBP and MAP after receiving naproxen

Patients	SBP (mean±SD)	DBP (mean±SD)	MAP (mean±SD)
All patients (N=48)	5.13±12.66**	−1.04±9.34ns	1.01±9.56ns
- Normal blood pressure patients (N=9)	2.56±16.96ns	0.33+8.35ns	1.07±9.98ns
- High blood pressure patients (N=39)	5.72±11.66**	−1.36±9.63ns	1.00±9.59ns
Treated hypertension(N=30)	6.44±6.71*	−1.67±7.09ns	0.98±10.45ns
Untreated hypertension (N=9)	5.50±12.86*	−1.27±10.38ns	1.04±6.48ns

*** p <0.001, **p <0.01, *p < 0.05, ns = no significant versus baseline

SBP = systolic blood pressure DBP = diastolic blood pressure MAP = mean arterial blood pressure

Table 32: SBP, DBP, MAP before and after receiving celecoxib

Patients	SBP (mean±SD)		DBP (mean±SD)		MAP (mean±SD)	
	before	after[b, c]	before	after[b, c]	before	after[b, c]
All patients (N=48)	143.25±14.13	146.27±16.67[ns, ns]	78.44±10.42	79.04±10.81[ns, ns]	100.04±9.96	101.45±10.55[ns, ns]
- Normal blood pressure patients (N=9)	125.78±9.32	126.33±21.24[ns, ns]	75.22±10.17	76.11±9.48[ns, ns]	92.07±9.02	92.85±11.83[ns, ns]
- High blood pressure patients (N=39)	147.28±11.82	150.87±11.53[ns, ns]	79.18±10.47	80.21±11.22[ns, ns]	101.88±9.33	103.44±9.31[ns, ns]
Treated hypertension (N=30)	147.10±11.48	150.77±10.61[ns, ns]	80.27±10.52	80.57±11.31[ns, ns]	102.54±9.59	103.97±9.34[ns, ns]
Untreated hypertension (N=9)	147.89±13.61	151.22±14.92[ns, ns]	75.56±10.23	76.89±10.44[ns, ns]	99.67±8.51	101.67±9.52[ns, ns]

*** p <0.001, **p <0.01, *p < 0.05, ns = no significant versus baseline

SBP = systolic blood pressure DBP = diastolic blood pressure MAP = mean arterial blood pressure

[b] = celecoxib versus baseline (before treatment)

[c] = celecoxib versus naproxen

before = before receiving celecoxib in sequence I, II

after = after receiving celecoxib in sequence I, II

Table 33: Mean change of SBP, DBP and MAP after receiving celecoxib

Patients	SBP (mean±SD)	DBP (mean±SD)	MAP (mean±SD)
All patients (N=48)	3.02 ± 13.17^{ns}	0.60 ± 7.74^{ns}	1.41 ± 8.48^{ns}
- Normal blood pressure patients (N=9)	0.57 ± 20.00^{ns}	$0.89+9.41^{ns}$	0.78 ± 12.64^{ns}
- High blood pressure patients (N=39)	3.59 ± 11.33^{ns}	0.54 ± 7.74^{ns}	1.56 ± 7.43^{ns}
Treated hypertension(N=30)	3.33 ± 8.83^{ns}	1.33 ± 1.80^{ns}	1.42 ± 8.29^{ns}
Untreated hypertension (N=9)	3.67 ± 12.12^{ns}	0.30 ± 8.45^{ns}	2.00 ± 3.49^{ns}

*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$, ns = no significant versus baseline

SBP = systolic blood pressure DBP = diastolic blood pressure MAP = mean arterial blood pressure

and also significantly increased in both treated and untreated hypertension while DBP, MAP was not significantly increased in any group. In contrast to naproxen, celecoxib was not significantly increased SBP, DBP and MAP in either treated or untreated hypertension.

5.2.2. Comparison mean change of SBP, DBP and MAP between naproxen and celecoxib (using crossover analysis)

After crossover study of both sequence, the two treatment used 2 x 2 crossover design with 24 subjects in sequence I and 24 subjects in sequence II. All subgroup analysis had preliminary test assumption of equal period effect and carry over effect at the 0.05 significance level. In Figure 17-19 showed mean change of SBP, DBP and MAP after naproxen and celecoxib treatment. Figure 20-21 presented change of SBP, DBP after both treatments in each patient.

Crossover analysis showed that there were not significantly difference in SBP, DBP and MAP between naproxen and celecoxib in all patients, normal blood pressure and hypertensive patients. The results were presented in Table 32. Overall statistical level of significant (P value) were presented in Appendix P-R.

Since hypertension is a common comorbidity in elderly patients with using NSAIDs[119] therefore management of these comorbidity should be concerned. In large clinical trials, if sustained increase in SBP 3 mmHg could explain 10 to 20% increase in CHF [120], 15% to 20% increase in stroke risk[57] and 12% increase in angina risk.[121] These results were implied for the maintenance of adequate blood pressure control among NSAIDs treated and comorbid hypertension.

In this study, only naproxen significantly increased in SBP but not DBP, MAP while celecoxib did not affect SBP, DBP and MAP in all patients. In normal blood pressure patients, both naproxen and celecoxib did not significantly affect SBP, DBP

Figure17: Mean change of systolic blood pressure(SBP) in the patients

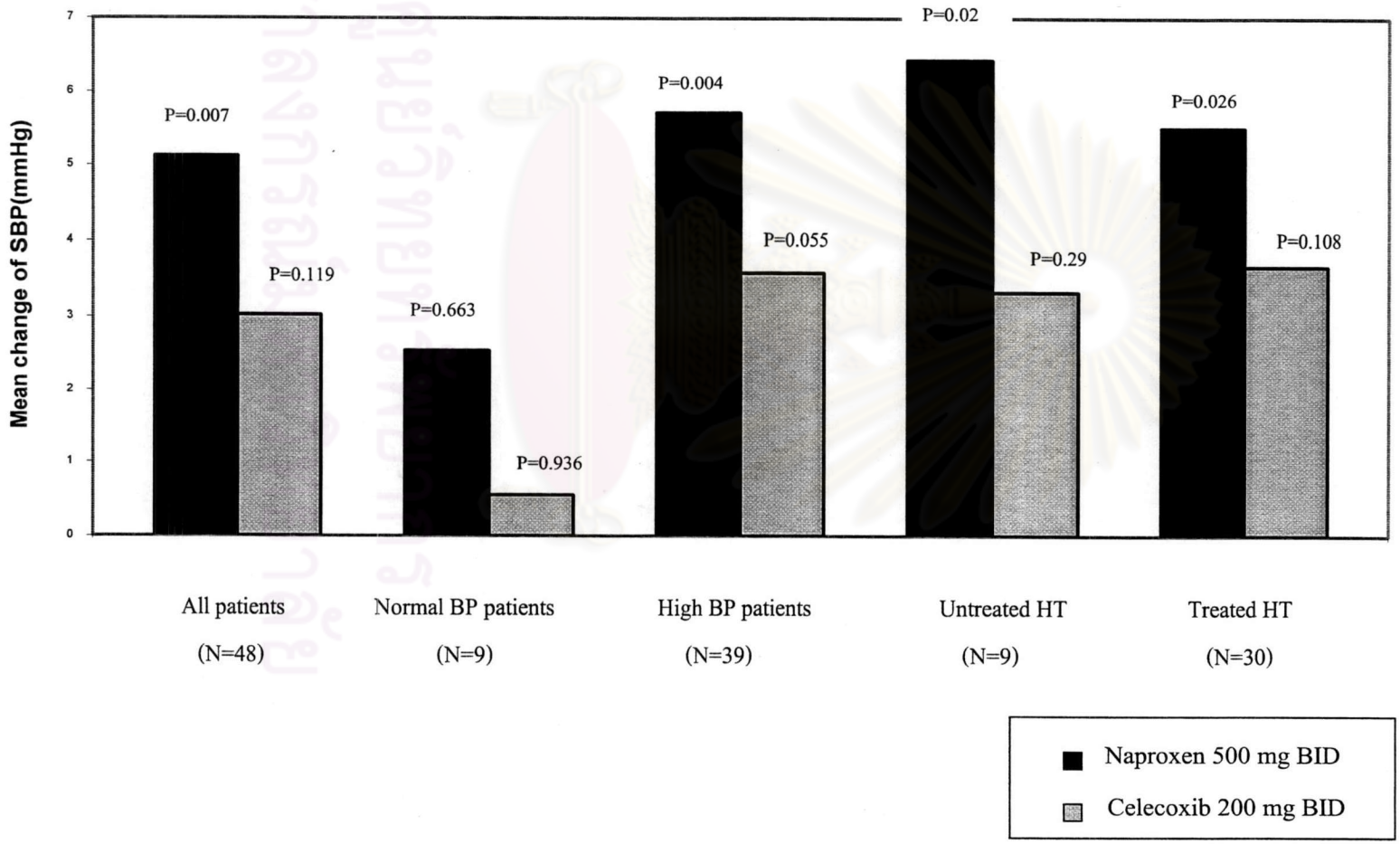


Figure18: Mean change of diastolic blood pressure (DBP) in the patients

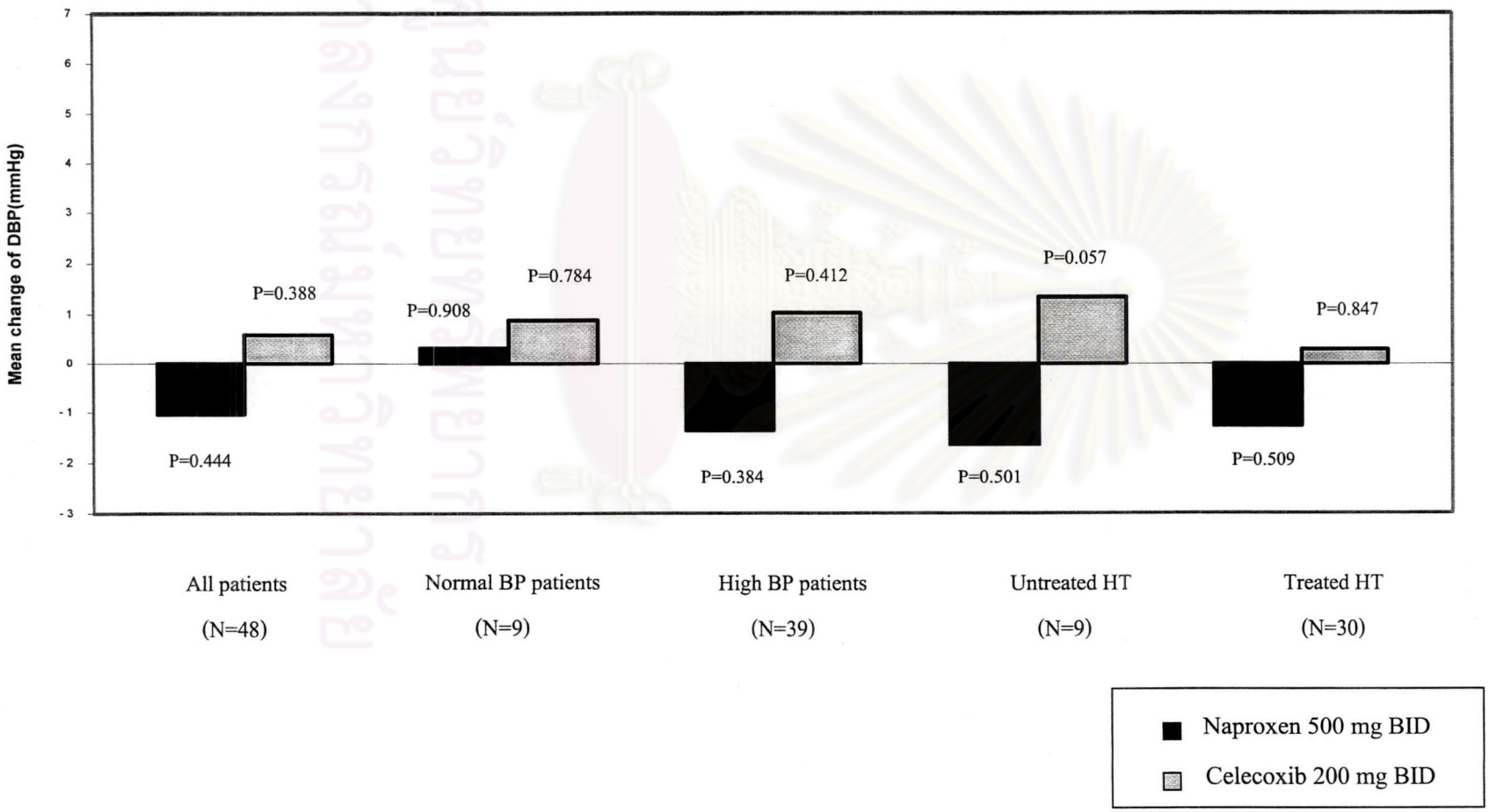


Figure19: Mean change of mean blood pressure (MAP) in the patients

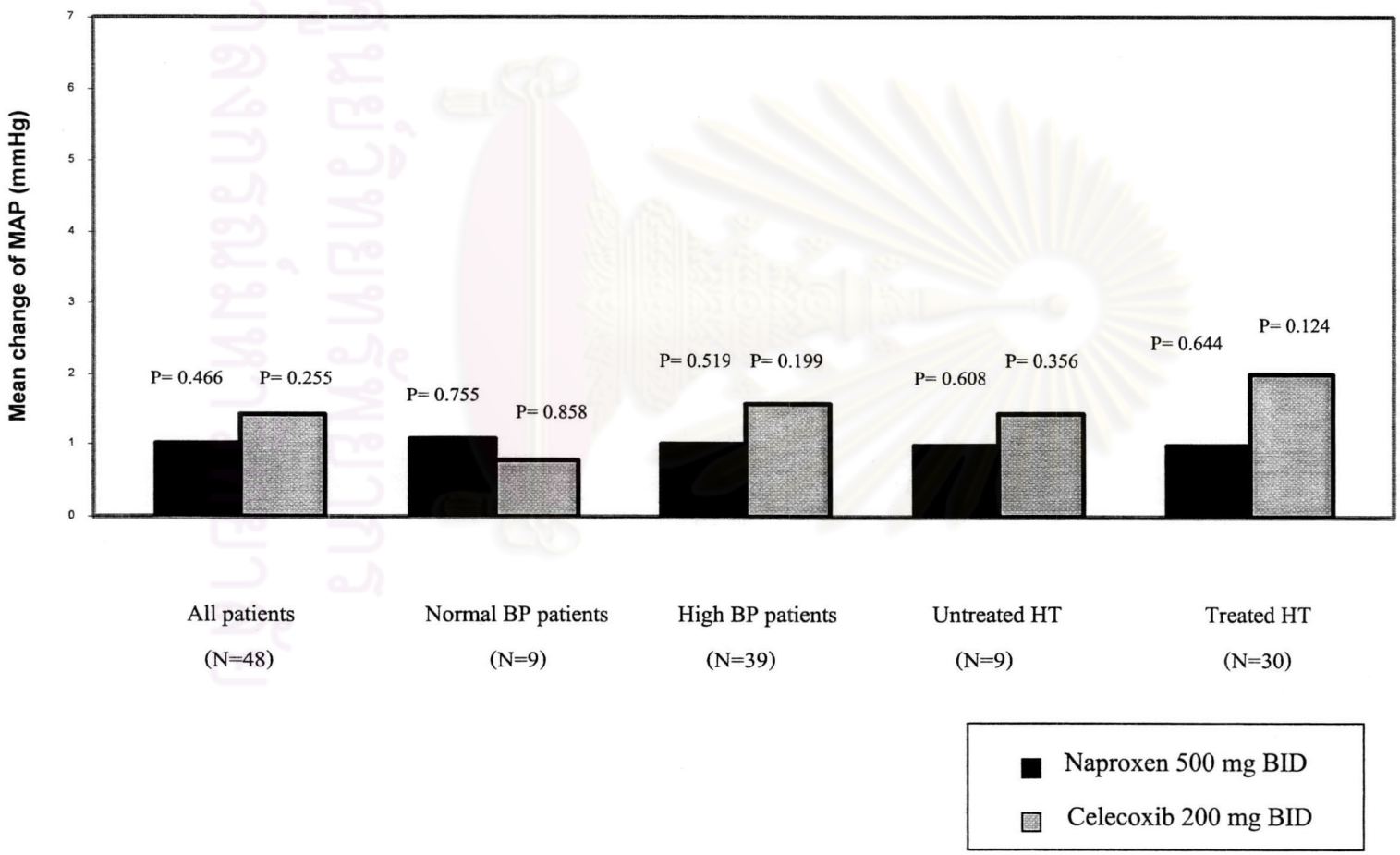
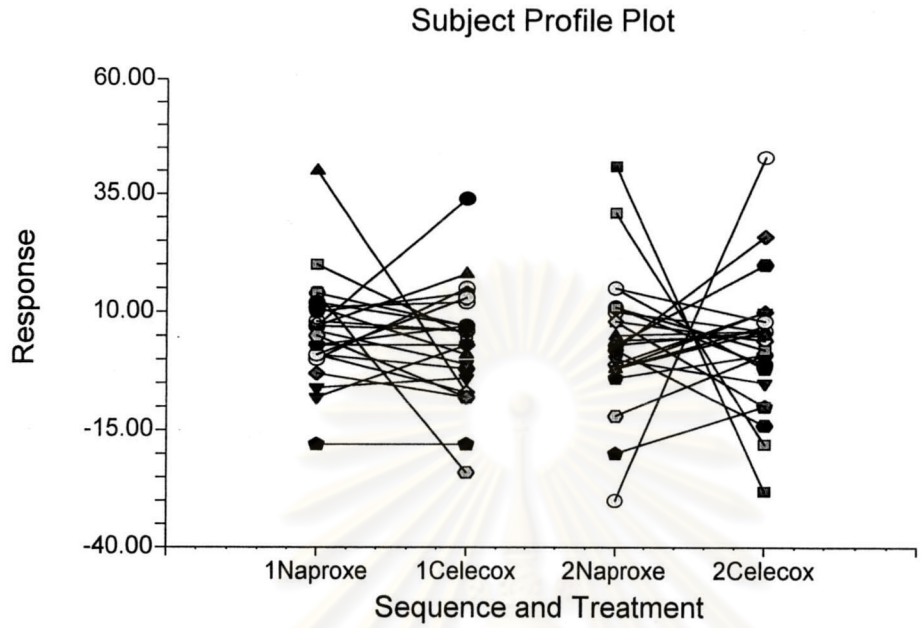
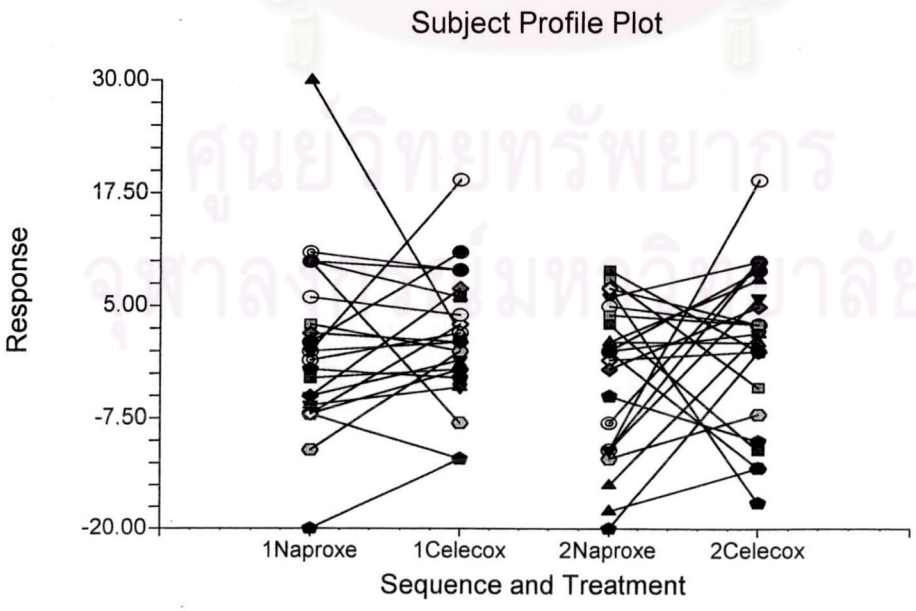


Figure 20: Change of systolic blood pressure (SBP) after treatment of naproxen and celecoxib in each patient



Response = Change of systolic blood pressure (SBP) after treatment of naproxen and celecoxib in each patient

Figure 21: Change of diastolic blood pressure (DBP) after treatment of naproxen and celecoxib in each patient



Response = Change of diastolic blood pressure (DBP) after treatment of naproxen and celecoxib in each patient

and MAP. However, there were only nine patients had normal blood pressure. Further studies with more sample size are required.

For high blood pressure patients, SBP was not significantly increased in celecoxib treatment group (including treated and untreated hypertension). This results similar to SUCCESS VI study by Whelton et al., who found that celecoxib 200 mg once daily did not affect blood pressure in older hypertensive osteoarthritis patients.[104] In contrast to results of naproxen, it is possible that different types of NSAIDs might affect different degrees of blood pressure. Pope et al. determined that NSAIDs e.g., indometacin and naproxen appeared to greater increase in SBP in treated hypertension than other NSAIDs.[60]

Apart from this, Johnson AG et al. investigated that destabilized of blood pressure control by NSAIDs was the greatest in treated hypertensive patients because in addition to physiologic mechanism, NSAIDs can interaction with antihypertensive medications. Beta-blocker, calcium channel blockers and ACE inhibitors are the most common antihypertensive agents affected by NSAIDs.[59]

From this study, mean change of systolic blood pressure between treated and untreated hypertension was not significantly difference in both naproxen and celecoxib treatment groups (Table 34). These results were noted that the number of untreated hypertensive patients was lower than the number of treated hypertensive patients. Thus further studies are needed to investigate this point.

Concerning NSAIDs - antihypertensive interactions, this finding was not determined in this study because of majority of patients taking combination antihypertensive medications. Moreover, ACE inhibitors were prohibited in this study.

Table 34: Mean change of SBP after naproxen and celecoxib treatment between treated and untreated hypertension

Hypertension	Naproxen (Mean±SD)	Celecoxib (Mean±SD)
Untreated hypertension (N=9)	6.44±6.71	3.33±8.83
Treated hypertension (N=30)	5.37±12.79	3.67±12.12
P-value	0.811	0.940

P value = Statistical significance between treated and untreated hypertension

5.3 Electrolyte

Sodium, potassium in serum and urine before and after treatment with naproxen and celecoxib were shown in Appendix G. Analyzed data were presented in all patients after treatment with celecoxib 200 mg twice daily and naproxen 500 mg twice daily. Overall statistical levels of significant (P value) were displayed in Appendix S.

5.3.1 Comparison of electrolyte before and after receiving naproxen and celecoxib (using pair T test analysis)

Serum sodium, serum potassium, sodium excreted in urine and potassium excreted in urine did not significantly change in all patients as shown in Table 35.

5.3.2. Comparison mean change of electrolyte between naproxen and celecoxib (using crossover analysis)

After crossover study of both sequence, the two treatment in 2 x 2 crossover design with 24 subjects in sequence I and 24 subjects in sequence II. All subgroup analysis had preliminary test assumption of equal period effect and carry over effect at the 0.05 significance level. In Figure 22, showed mean change of serum sodium, potassium after naproxen and clecoxib treatment. Figure 23 showed mean change of sodium and potassium excretion in urine. Figure 24-27 presented change of electrolyte after both treatments in each patient.

Results from crossover analysis showed that change of electrolyte was not significantly difference between naproxen and celecoxib treatment group (Table 35).

This finding is inconsistent with previous study by Rossat et al., who found that both celecoxib 400 mg twice daily and naproxen 500 mg twice daily significantly decreased sodium excretion in urine and promote sodium and potassium retention in

salt deplete subjects.[105] Different findings possible that we conducted this study in out-patients department, thus could not regulate electrolyte intake which might be the weak point of this study.

5.4 Primary outcomes after wash out naproxen and celecoxib

All of primary outcomes (CrCl, Scr, BUN, SBP, DBP, sodium and potassium in serum and urine) before receiving naproxen were compared with primary outcomes after washout naproxen in both sequence treatment group. In sequence II, only 6 out of 24 patients participated until the last visit (visit 6). Thus, the results of 30 patients were assessed primary outcomes after washout naproxen in naproxen group.

In sequence I, only 8 out of 24 patients participated until the last visit (visit 6). Therefore, the results of 32 patients were assessed primary outcomes after washout celecoxib in celecoxib group.

The results were illustrated in Table 36, all laboratory data for primary outcomes can return to baseline after 14 days wash out period. It indicated that renal functions of patients could reverse after discontinue naproxen 500 mg twice daily for 14 days and celecoxib 200 mg twice daily for 14 days. Overall statistical levels of significant (P value) were presented in Appendix U.

Table 35: Sodium, potassium in serum and urine before and after receiving naproxen and celecoxib

Electrolyte	Naproxen (mean±SD)		Celecoxib (mean±SD)	
	before	after[a]	before	after[b, c]
Serum sodium	143.71±2.19	143.44±3.42[ns]	143.44±2.24	142.83±2.36[ns, ns]
Serum potassium	4.21±0.29	4.36±0.76[ns]	4.27±0.33	4.37±0.38[ns, ns]
Sodium excrete in urine	156.88±63.16	139.50±73.82[ns]	137.04±64.93	139.52±65.15[ns, ns]
Potassium excrete in urine	40.10±14.69	34.58±17.87[ns]	38.04±15.43	34.96±11.86[ns, ns]

*** p <0.001, **p <0.01, *p < 0.05, ns = no significant versus baseline

[a] = naproxen versus baseline (before treatment)

[b] = celecoxib versus baseline (before treatment)

[c] = celecoxib versus naproxen

before = before receiving naproxen, celecoxib in sequence I, II

after = after receiving naproxen and celecoxib in sequence I, II

Figure 22: Mean change of serum sodium and potassium in all patients (N=48)

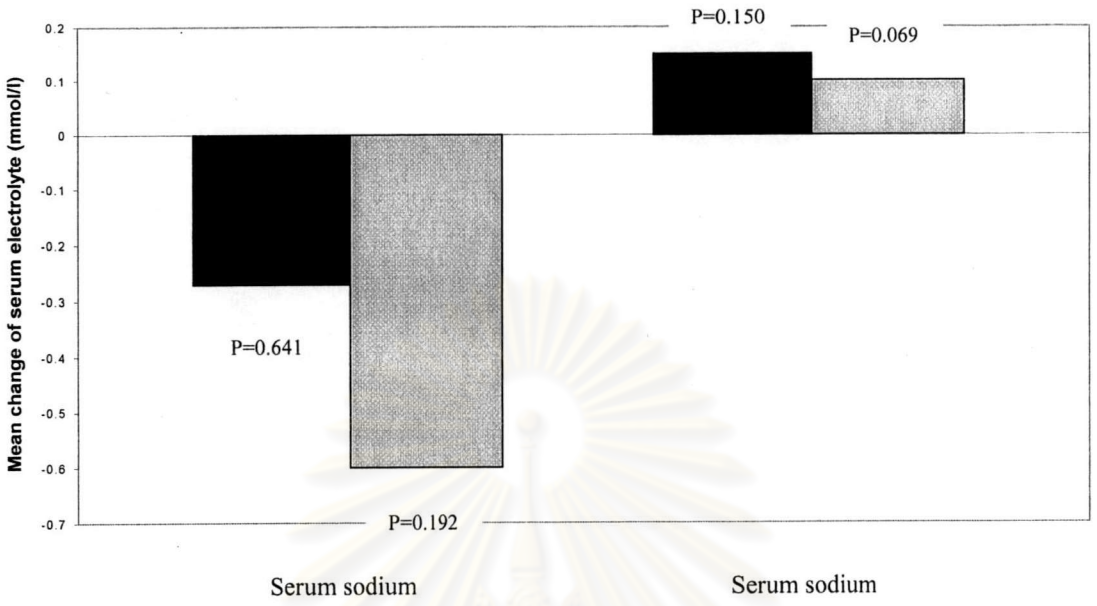


Figure 23: Mean change of sodium and potassium excretion in urine in all patients (N=48)

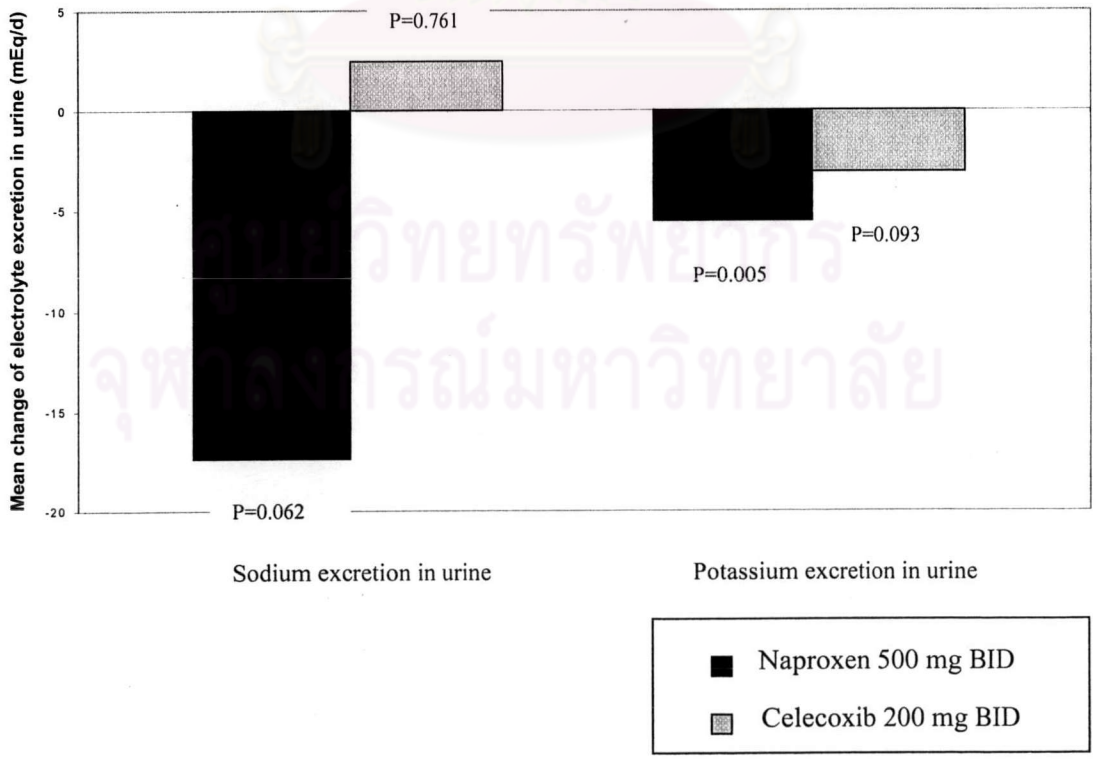
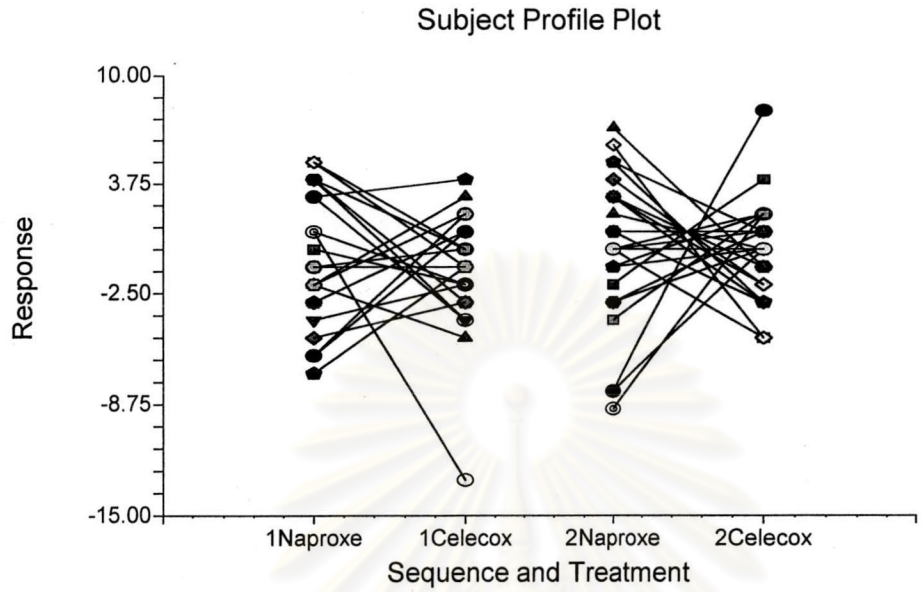
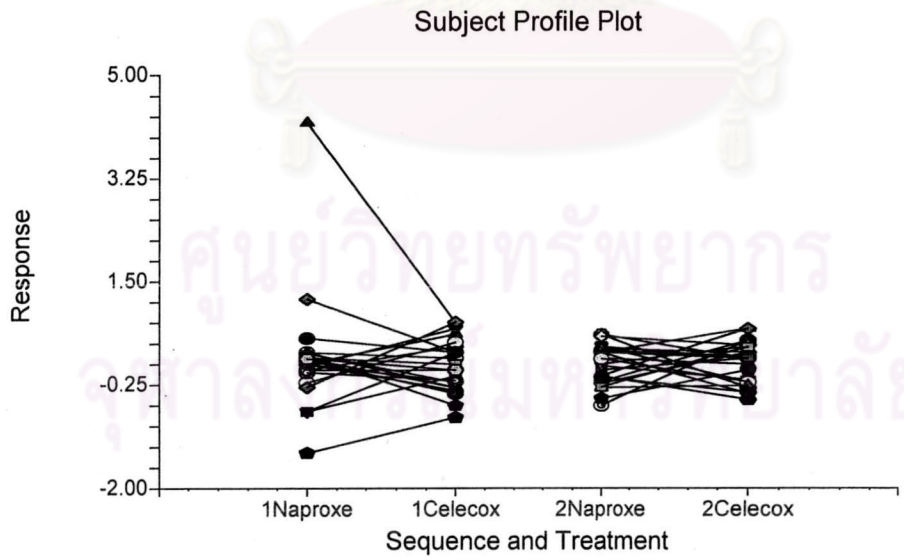


Figure 24: Change of serum sodium after treatment of naproxen and celecoxib in each patient



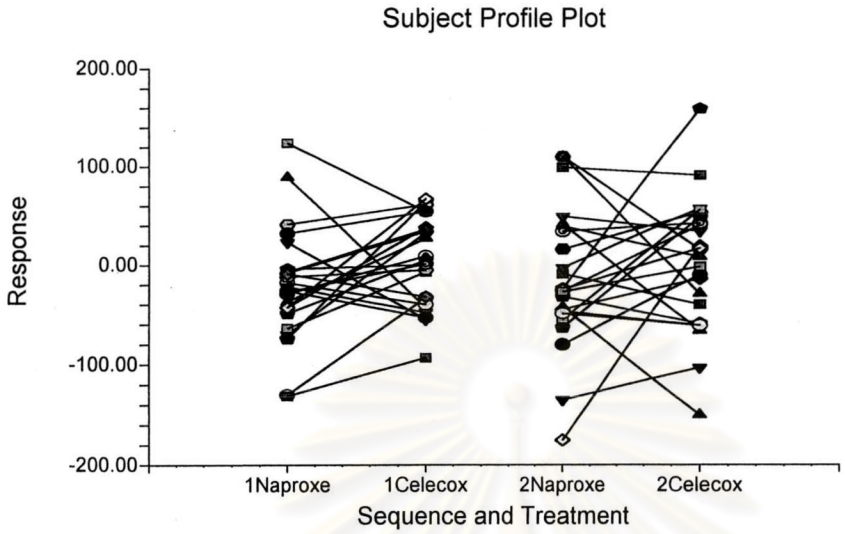
Response = Change of serum sodium after treatment of naproxen and celecoxib in each patient

Figure 25: Change of serum potassium after treatment of naproxen and celecoxib in each patient



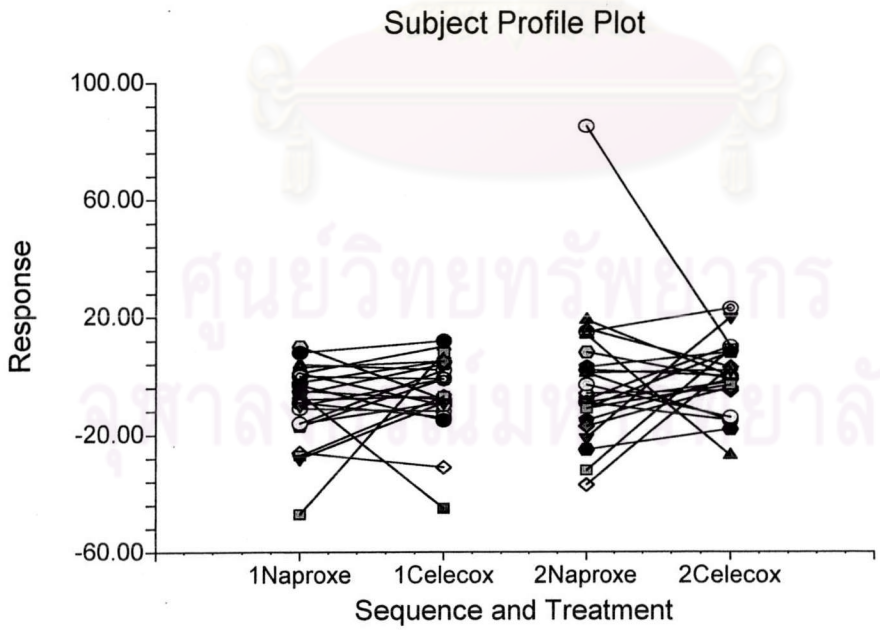
Response = Change of serum potassium after treatment of naproxen and celecoxib in each patient

Figure 26: Change of sodium excretion in urine after treatment of naproxen and celecoxib in each patient



Response = Change of sodium excretion in urine after treatment of naproxen and celecoxib in each patient

Figure 27: Change of potassium excretion in urine after treatment of naproxen and celecoxib in each patient



Response = Change of potassium excretion in urine after treatment of naproxen and celecoxib in each patient

Table 36: Primary outcomes before and after washout naproxen and celecoxib

Primary outcomes	Naproxen (N=30) (mean±SD)		Celecoxib (N=32) (mean±SD)	
	before	after washout[a]	before	after wash out[b]
Creatinine clearance	60.47±13.50	58.29±13.37[ns]	60.33+13.56	59.73±14.49[ns]
Serum creatinine	1.20±0.27	1.20±0.29[ns]	1.17±0.26	1.14±0.27[ns]
Blood urea nitrogen	15.97±4.72	15.53±3.39[ns]	15.31±4.35	15.47±4.73[ns]
Systolic blood pressure	143.57±14.81	144.60±13.35[ns]	141.63±13.37	141.28±16.97[ns]
Diastolic blood pressure	80.47±10.56	77.97±9.75[ns]	78.75±10.36	81.13±11.35[ns]
Serum sodium	143.83±2.12	143.28±1.96[ns]	143.34±2.54	143.56+2.54[ns]
Serum potassium	4.23±0.32	4.25±0.38[ns]	4.27±0.34	4.18±0.38[ns]
Sodium excrete in urine	163.13±73.07	146.03±65.15[ns]	137.00±66.39	147.91±64.58[ns]
Potassium excrete in urine	37.70±13.14	38.00±15.19[ns]	37.78±14.96	39.03±15.94[ns]

ns = no significant versus baseline

[a] = naproxen versus baseline (before treatment)

[b] = celecoxib versus baseline (before treatment)

before = before receiving naproxen, celecoxib in sequence I, II

after washout = after 14-day washout naproxen, celecoxib in sequence I, II

5.5 Edema

Incidence of edema after celecoxib and naproxen treatment was assessed by the same physician. The criteria indicated edema was increase at least 1 grade in edema scale from baseline in accordance with 2% weight gain or increase of edema scale from baseline of more than or equal to 2 grades in accordance with or without weight gain. Edema scale and body weight before and after receiving naproxen and celecoxib in each treatment group were presented in Appendix H_1. In this study, 7 out of all 48 patients (14.58%) occurred edema after naproxen treatment and 3 out of them (6.25%) occurred edema after celecoxib treatment (Table37). Chi-Square table for the assessment of edema was presented in Appendix H_2.

Table 37: Patients who were identified edema according to edema criteria.

Patient number.	Treatment	Sequence	edema scale change	weight change (%)
3	naproxen	I	+ 2	5.56
8	naproxen	I	+ 1	3.17
14	naproxen	I	+ 1	2.65
18	naproxen	I	+ 1	2.70
29	naproxen	II	+ 2	0.64
40	naproxen	II	+ 2	1.67
47	naproxen	II	+ 2	1.55
24	celecoxib	I	+ 1	2.46
31	celecoxib	II	+ 1	5.33
41	celecoxib	II	+ 2	1.88

Although incidence of edema in naproxen treatment group was higher than that of celecoxib treatment group, Chi-square analysis showed that there was no significant difference in edema between naproxen and celecoxib (p=0.181). This finding is consistent with previous study by Silverstein et al., who found that celecoxib

occurred edema similar to naproxen but the occurrence of edema from CLASS study was lower than the occurrence of edema in this study.[18] This possibly that we used the different edema criteria.

In addition, previous study also found that edema was frequently seen in hypertensive patients. This effect due to increase blood pressure will lead to greater loss of fluid to the extravascular space and renal factors such as sodium retention may also lead to peripheral edema.[44]

As shown in Table 38, regarding patients who developed edema in this study, naproxen significantly increased SBP and serum sodium while did not observed in celecoxib. This result implied that the induction of edema from non-selective NSAIDs was associated with destabilization of SBP and sodium retention.

Table 38: Blood pressure, electrolyte in patients developed edema from naproxen and celecoxib

Blood pressure and electrolyte	Naproxen (N =7)(mean±SD)		Celecoxib (N = 3)(mean±SD)	
	before	after	before	after
Systolic blood pressure	143.14±11.84	150.57±10.15*	145.00± 16.09	158.33±12.74ns
Diastolic blood pressure	82.57±12.07	85.14±11.35ns	76.33±17.04	82.67±3.51ns
Serum sodium	142.71±1.89	147.71±1.70***	142.67±1.53	145.00±2.65ns
Sodium excretion in urine	135.14±57.52	129.86±64.69ns	131.00±46.76	157.00±113.06ns

*** p <0.001, *p < 0.05, ns = no significant versus baseline

before = before receiving naproxen, celecoxib in sequence I, II

after = after receiving naproxen, celecoxib in sequence I, II

6. Secondary outcomes evaluation

Secondary outcomes in this study were any adverse drug reactions that collected by open-ended question after each treatment. Adverse effects that constituting renal endpoints were excluded from this part analysis. The adverse effects that received score 1-9 points of Naranjo's algorithm were presented and used for statistical analysis. Naranjo's algorithm was shown in Appendix B. Adverse drug reaction of each patient was presented in Appendix I_1-I_2. Chi-Square table for the assessment of secondary outcomes was presented in Appendix I_3. Overall statistical levels of significant (P value) were shown in Appendix T.

The adverse drug reactions of naproxen and celecoxib were reported in Table 39. The percentage of patients who experienced at least one adverse event was 43.75% in the naproxen group and 29.17% in the celecoxib group ($p = 0.138$). The most commonly reported adverse effects in the naproxen group were gastrointestinal complications e.g., abdominal pain, dyspepsia and heart burn respectively. Dizziness, diarrhea and dyspepsia mostly occurred in the celecoxib group. In addition, one patient developed constipation from naproxen and one patient occurred nausea from celecoxib.

Concerning other laboratory findings [e.g., SGOT, SGPT, hemoglobin (Hgb), hematocrit (Hct)], none of the patients increased SGOT and/or SGPT more than two times of normal level. The number of patients who decreased in Hgb and Hct were greater in naproxen than those of celecoxib (Table 39). It suggested that naproxen might cause ulcer complications more than celecoxib, although there were no significant difference between naproxen and celecoxib in the decrement of Hgb, Hct (Table 40). Statistical levels of significant when comparing the mean Hgb, Hct were shown in Appendix W.

In this study some patients who had history of gastrointestinal complications from NSAIDs received omeprazole (O-Sid®) for preventing ulcer complications. None of the patients in this study received H_2-blocker antagonists. Therefore, patients

were divided into two groups (20 patients taking omeprazole and 28 patients not taking omeprazole). In patients not taking omeprazole, naproxen treated patients occurred abdominal pain and heart burn more than celecoxib treated patients. While patients taking omeprazole, secondary outcomes were not significantly difference between naproxen and celecoxib. Overall statistical levels of significant (P value) were also shown in Appendix T.

Table 39: Secondary outcomes in naproxen and celecoxib treatment

Secondary outcomes	All patients (N=48) Number (%)		Patients not taking omeprazole (N=28) Number (%)		Patients taking omeprazole (N=20) Number (%)	
	Naproxen	Celecoxib[a]	Naproxen	Celecoxib[b]	Naproxen	Celecoxib[c]
Abdominal pain	7(14.58)	1(2.08)*	7(25)	1(3.57)*	0	0
Dyspepsia	6(12.5)	3(6.25)ns	4(14.29)	2(7.14)ns	2(10)	1(5)ns
Heart burn	6(12.5)	0*	5(17.86)	0*	1(5)	0
Diarrhea	1(2.08)	3(6.25)ns	1(3.57)	1(3.57)	0	2(10)ns
Headache	1(2.08)	1(2.08)	0	1(3.57)	1(5)	0
Dizziness	0	4(8.33)*	0	1(3.57)	0	3(15)ns
Back pain	0	2(4.17)ns	0	0	0	2(10)ns
Rash	2(4.17)	1(2.08)ns	1(3.57)	1(3.57)	1(5)	0
Ecchymosis	1(2.08)	1(2.08)	0	0	1(5)	1(5)
Shortness of breath	1(2.08)	1(2.08)	1(3.57)	1(3.57)	0	0
Decreased from baseline in Hct of ≥ 5%	13(27.08)	7(14.58)ns	6(21.43)	5(17.86)ns	7(35)	2(10)ns
Decreased from baseline in Hgb of ≥ 1.5 g/dl	2(4.17)	0ns	1(3.57)	0	1(5)	0

* $p < 0.05$, ns = not significance

[a] = versus naproxen in all patients

[b] = versus naproxen (not taking omeprazole)

[c] = versus naproxen (taking omeprazole)

Table 40: Mean change of Hgb and Hct obserbved in all patients (N=48)

Other laboratory data	Naproxen (mean±SD)[a]	Celecoxib (mean±SD)[b, c]
Hemoglobin (Hgb)	−0.21±0.75[ns]	−0.01±0.57[ns, ns]
Hematocrit (Hct)	−1.22±4.91[ns]	−0.33±1.77[ns, ns]

ns = no significant versus baseline

[a] = naproxen versus baseline (before treatment)

[b] = celecoxib versus baseline (before treatment)

[c] = celecoxib versus naproxen