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Renal Effects of Celecoxib and Naproxen in Elderly Patients(ผลต่อไตของยาซีลีคอกซิบและยานาพรอกเซนในผู้ป่วยสูงอายุ)

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ผลต่อไตของยาซีลีคอกซิบและยานาพรอกเซนในผู้ป่วยสูงอายุ

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บทคัดย่อ

การศึกษานี้มีวัตถุประสงค์เพื่อเปรียบเทียบผลต่อไตระหว่างยาซีลีคอกซิบและยานาพรอกเซน โดยศึกษาในผู้ป่วยสูงอายุที่มีภาวะโรคข้อและกล้ามเนื้อ 48 ราย ณ แผนกอายุรกรรมโรคข้อ โรงพยาบาลราชวิถี ผู้ป่วยได้รับยานาพรอกเซนขนาด 500 มิลลิกรัมหรือ ซีลีคอกซิบขนาด 200 มิลลิกรัมวันละ 2 ครั้งเป็นเวลา 2 สัปดาห์ ต่อจากนั้นหลังจากหยุดยา 2 สัปดาห์ ผู้ป่วยจะสลับมารับยาอีกชนิดหนึ่งอีก 2 สัปดาห์ ผลการศึกษาพบว่า ซีลีคอกซิบ 200 มิลลิกรัมวันละ 2 ครั้ง มีผลลดการทำงานของไตได้ใกล้เคียงกับนาพรอกเซน 500 มิลลิกรัมวันละ 2 ครั้ง ในผู้ป่วยทุกกลุ่ม รวมทั้งผู้ป่วยความดันโลหิตสูง ผู้ป่วยที่มีไตปกติและผู้ป่วยที่มีการทำงานของไตบกพร่อง โดยการทำงานของไตมีแนวโน้มลดลงในกลุ่มผู้ป่วยที่มีภาวะความดันโลหิตสูง (ทั้งในกลุ่มผู้ป่วยที่ไตปกติหรือไตบกพร่อง) และพบว่านาพรอกเซนเพิ่มความดันโลหิตตัวบนได้อย่างมีนัยสำคัญในผู้ป่วยที่มีความดันโลหิตสูง (ทั้งในผู้ป่วยที่ได้ยาลดความดันโลหิตและผู้ป่วยที่ไม่ได้รับการรักษาด้วยยาลดความดันโลหิต) (p=0.004) ในขณะที่ยาซีลีคอกซิบไม่มีผลเปลี่ยนแปลงความดันโลหิตอย่างมีนัยสำคัญทั้งในผู้ป่วยความดันโลหิตปกติและผู้ป่วยความดันโลหิตสูง เมื่อสิ้นสุดการวิจัยพบว่าการทำงานของไตทั้งหมดในผู้ป่วยสามารถกลับคืนสู่ปกติได้หลังจากหยุดยานาพรอกเซนและซีลีคอกซิบ อุบัติการณ์การเกิดภาวะบวมน้ำจากยานาพรอกเซนมากกว่าซีลีคอกซิบแต่ไม่แตกต่างกันทางสถิติ (p=0.181) นอกจากนี้อุบัติการณ์การเกิดอาการไม่พึงประสงค์อื่นๆจากยานาพรอกเซนมากกว่าซีลีคอกซิบแต่ไม่แตกต่างกันทางสถิติ (p=0.138) และไม่พบอาการไม่พึงประสงค์ที่รุนแรงหรือความผิดปกติของค่าตรวจทางห้องปฏิบัติการแต่อย่างใด จากผลการวิจัยสรุปได้ว่า การใช้กลุ่มยาที่ออกฤทธิ์อย่างเฉพาะเจาะจงในการยับยั้งซัยโคลออกซีจีเนส-2 อาจไม่สำรองการทำงานไตในผู้ป่วยสูงอายุ

กุญแจคำ

ผลต่อไต, ซีลีคอกซิบ, นาพรอกเซน, ภาวะโรคข้อและกล้ามเนื้อ, ผู้ป่วยสูงอายุ, อาการไม่พึงประสงค์ของยา

Original Article

Renal Effects of Celecoxib and Naproxen in Elderly Patients

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Abstract

The purpose of this study was to compare renal effects between celecoxib and naproxen. The study was conducted in forty-eight elderly patients with musculoskeletal problems in Rheumatology Clinic at Rajavithi Hospital. Patients were treated with either naproxen 500 mg or celecoxib 200 mg twice daily for 2 weeks. Subsequently, after 2 week washout, patients were switched to the other drug for another 2 weeks. It was found that celecoxib, 200 mg twice daily, and naproxen, 500 mg twice daily, similarly decreased renal functions in all groups of patients including hypertensive patients, normal and renal insufficiency patients. Renal functions had a tendency to decline in hypertensive patients (either normal or renal insufficiency). Naproxen significantly increased systolic blood pressure in hypertensive patients (either treated or untreated) ($p=0.004$) while celecoxib did not significantly affect blood pressure in normal blood pressure patients and hypertensive patients. However, renal functions could return to baseline at the end of the study when the drug was withdrawn. The occurrence of edema from naproxen was higher than that of celecoxib but not statistically significant ($p=0.181$). The occurrence of other adverse drug reactions from naproxen was higher than those of celecoxib but also not statistically significant ($p=0.138$). None of the patients developed serious adverse effects or other vital sign and laboratory abnormalities. The results indicated that selective cyclooxygenase (COX-2) inhibitors might not spare renal functions in elderly patients.

Key words

Renal effect, Celecoxib, Naproxen, Musculoskeletal problem, Adverse drug reaction, Elderly patient

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs), which are widely used for the treatment of pain and inflammation from musculoskeletal problems, reduce prostaglandin synthesis by direct inhibition of cyclooxygenase (COX) enzymes (1). These drugs have some distinctive side effects. Gastrointestinal tract injuries are the most common side effects of NSAID therapy whereas renal complications occur in small proportion of patients treated with NSAIDs (2). Until recently, the development of highly selective COX-2 inhibitors which inhibit COX-2 while sparing COX-1 at therapeutic doses can provide fewer side effects than the non-selective NSAIDs.

Regarding renal effects of the more selective COX-2 inhibitors, these effects have remained unclear. It was hoped that highly selective COX-2 inhibitors might cause fewer side effects than the non-selective NSAIDs (3). Available data on renal effects of highly selective COX-2 inhibitors are conflicting due to differences in the patients' number and characteristics. Results from recent studies support the belief that highly selective COX-2 inhibitors may affect blood pressure, electrolyte excretion while decreasing the glomerular filtration rate (GFR) rather less than non-selective NSAIDs (4).

Recent evidences support a role of COX-1 and COX-2 on renal functions. Electrolyte excretion in healthy human can be regulated by COX-2 while GFR can be regulated by COX-1. Therefore, it was inferred that use of highly selective COX-2 inhibitors might spare the kidneys (5).

A retrospective study at Rajavithi Hospital found that elderly patients were the most common populations received celecoxib for the treatment of osteoarthritis (OA), muscle pain and rheumatoid arthritis (RA). These populations also have many risk factors for renal complications such as hypertension and renal insufficiency (6). However, there are few studies which determine the renal effects of highly selective COX-2 inhibitors in these populations.

Therefore, the purpose of this study was to compare renal effects between celecoxib, which is the first highly selective COX-2 inhibitor, and naproxen, which is a non-selective NSAID. The study was conducted in healthy elderly patients and patients with underlying diseases such as hypertension (HT) and/or renal insufficiency in Rheumatology Clinic at Rajavithi Hospital. This data will help physicians quantify the renal and other adverse drug events associated with the use of highly selective COX-2 inhibitors and non-selective NSAIDs.

Method

The study was double-blind randomized crossover study. Patients were stratified and randomized into two treatment groups: sequences I and II. For each sequence, patients were initially treated with either naproxen 500 mg or celecoxib 200 mg twice daily and then crossover to the second treatment after 2-week washout. Patients were selected for this study if they were elderly (more than 60 years old) men or women with musculoskeletal problems; had never taken any previous medications which can affect renal functions except those received for essential treatments. The patients had to sign the consent form after receiving the information about the study.

Patients were excluded from the study if they had history of hypersensitivity to sulfonamide and/or nonsteroidal anti-inflammatory drugs; had history of gastrointestinal bleeding or peptic ulcer perforation that were confirmed by endoscopy and/or positive stool occult blood, anemia or malnutrition; had serum creatinine level of more than 2 mg/dl or creatinine clearance of less than 25 ml/min/1.73m^2; display evidence of diabetic nephopathy, glomerulonephritis, cirrhosis, congestive heart failure, urinary retention or prostatic hyperplasia, or high blood pressure at the level according to stage III of JNC VI criteria [systolic blood pressure (SBP) more than 180 mmHg and/or diastolic blood pressure (DBP) more than 110 mmHg]; necessarily used angiotensin converting enzyme inhibitors, angiotensin II receptor anta-gonists, flucanazole and diuretics; had serum glutamic oxaloacetic transaminase (SGOT) and/or serum glutamic pyruvic transaminase (SGPT) of more than 80 U/L.

This study was conducted at Rheumatology Clinic , Rajavithi Hospital. The study was approved by the Ethic Committee. Written informed consent was obtained from all patients. Prior to enrollment, patients underwent a screening assessment, which included physical examination and laboratory data.

Clinical assessment

Endpoints of this study were primary outcomes (renal haemodynamic and electrolyte homeostasis). Renal haemodynamic in this study included creatinine clearance in accordance with

serum creatinine and blood urea nitrogen, systolic blood pressure, diastolic blood pressure and mean arterial blood pressure. Electrolyte homeostasis included sodium excretion in the urine in accordance with serum sodium and edema, and potassium excretion in the urine in accordance with serum potassium.

Secondary outcomes included any adverse drug reactions except renal adverse events that occurred during the study.

Procedure of primary/secondary outcomes

Creatinine clearance in this study was assessed by 24-hour urine collection. Compliance was checked by monitoring creatinine in 24-hour urine which was kept at 15-20 mg/LBW/day. Creatinine in the serum and urine were measured by Jaffe's reaction. Serum creatinine was measured at the last point of 24-hour urine collection. Sodium and potassium in the serum and urine were measured by Direct Ion Selective Electrode method.

Systolic blood pressure and diastolic blood pressure were measured by a mercury sphygmo-manometer on the arm after fifteen minutes of rest in the sitting position. Two consecutive blood pressure were measured five minutes apart. Conditions that might affect blood pressure were excluded by using the same material, observer and conditions (e.g., maintaining visit time, location and temperature).

Edema was evaluated using four levels of Likert's scale (0 to 3) in accordance with the body weight of the patients assessed by the same physician. Criteria for significant edema were at least one of these: (1) increased scale from baseline at least of 1 grade in edema in accordance with 2% weight gain; (2) increased scale from baseline of more than or equal to 2 grades in accordance with or without weight gain.

Statistical analysis

Analysis was conducted by using data analysis softwares (SPSS for Windows version 10.07 and Number Cruncher Statistical System, NCSS 2002). Change of primary outcomes before and after receiving naproxen and celecoxib was analyzed by paired student *t*-test. Primary outcomes between celecoxib and naproxen from crossover design were analyzed by crossover analysis. The occurrence of edema and secondary outcomes between celecoxib and naproxen were analyzed by using chi-Square test. All significant levels were set at p value < 0.05.

Results and Discussion

Demographic and baseline patient characteristics

Patients who were screened in this study during July 2001 and May 2002 were out-patients of Rheumatology Clinic at Rajavithi Hospital. Fifty-six patients were enrolled in this study. Eight patients were withdrawn during the study due to loss of follow-up and inability to collect 24-hour urine sample. None of the patients were withdrawn due to adverse drug reactions. Finally, forty-eight patients completed this study. The number of patients in each sequence treatment was twenty-four. There were 26 males and 22 females, ranging in age from 60-83 years old (mean $\pm$ SD = 66.88 $\pm$ 13.95). Demo-graphic data of all patients were presented in Table 1. 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%), diabetes mellitus (10.42%) and coronary artery disease (6.25%). The main antihypertensive medica-tions that the patients consumed were calcium channel blocker (46.67%) and combination of antihypertensive medications (46.7%). In addition, twenty patients (41.66%) were taking allopurinol and three patients (6.25%) were taking aspirin 60 mg once daily for cardioprotection.

There was no significant difference between sequence I (naproxen treatment group) and sequence II (celecoxib treatment group). The laboratory data at baseline of most patients were within the normal level. However, 12 patients showed high SGOT and/or SGPT level, but not more than twice the normal range, while 5 patients

Table 1. 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)
Diabetes 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 of antihypertensive medications	14 (46.67)
Allopurinol	20 (41.66)
Aspirin (60 mg)	3 (6.25)
Renal functions	
Normal renal function (CrCl > 60 ml/min/1.73m^2)	26 (54.16)
Renal insufficiency (CrCl = 30-60 ml/min/1.73m^2)	22 (45.83)

Table 2. Mean change from baseline of creatinine clearance, serum creatinine and blood urea nitrogen

Patients	CrCl (mean±SD)		Scr (mean±SD)		BUN (mean±SD)	
	Naproxen	Celecoxib	Naproxen	Celecoxib	Naproxen	Celecoxib
All patients (N = 48)	-6.39±7.39***	-5.64±6.79***	0.02±0.09^{ns}	0.03±0.104*	2.15±3.86***	1.52±2.83**
Normal renal (N = 26)	-6.06±7.63***	-6.69±7.29***	0.046±0.08**	0.027±1.00^{ns}	2.04±3.26**	0.38±2.23^{ns}
With normal BP (N = 5)	-2.11±2.14^{ns}	-5.04±8.74^{ns}	0.00±0.07^{ns}	0.08±0.19^{ns}	2.80±1.30**	0.20±2.39^{ns}
With high BP (N = 16)	-5.92±8.54*	-6.85±6.27**	0.05±0.08*	0.00±0.05^{ns}	1.38±3.40^{ns}	0.81±2.37^{ns}
Renal insufficiency(N =22)	-6.79±7.25***	-4.39±6.08*	0.045±0.11^{ns}	0.05±0.11*	2.27±4.54*	2.86±2.92***
With normal BP (N = 4)	-7.32±6.33^{ns}	-6.37±4.39^{ns}	0.05±0.10^{ns}	0.07±0.17^{ns}	2.75±3.95^{ns}	3.00±3.16^{ns}
With high BP (N = 15)	-7.45±7.48*	-4.14±7.11*	0.02±0.11^{ns}	0.04±0.09^{ns}	3.20±4.81*	2.53±3.31*

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

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).

Primary outcomes evaluation

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

As shown in Table 2, in all groups of patients, CrCl was significantly decreased from baseline ($p<0.001$), BUN was significantly increased ($p<0.001$), while Scr was not significantly increased from baseline in naproxen treatment group ($p=0.063$). CrCl was significantly decreased ($p<0.001$), BUN and Scr were significantly

increased from baseline ($p<0.01$) in celecoxib treatment group ($p=0.001$, $p=0.016$).

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

Regarding renal functions, naproxen group displayed CrCl decreasing in both normal (N=26) ($p<0.001$) and renal insufficiency patients (N=22) ($p<0.001$). Serum creatinine was significantly increased in patients with normal renal functions ($p=0.008$), but the increasing Scr had no meaningful clinical implication. BUN was significantly increased in both normal ($p=0.004$) and renal insufficiency patients ($p=0.029$).

In the celecoxib group, CrCl was also significantly decreased in normal (N=26) ($p<0.001$) and renal insufficiency patients (N=22) ($p<0.001$), but Scr and BUN were significantly increased in renal insufficiency patients only.

For patient who had normal renal functions and normal blood pressure (N=5), CrCl and Scr were not changed in both naproxen and celecoxib groups, but BUN was increased in naproxen group significantly. However, the number of subjects in this normalized group was so small that further studies with larger sample size are required.

As for the patients who had normal renal functions but had high blood pressure (N=16), CrCl was significantly decreased in both naproxen and celecoxib groups while Scr significantly increased in only the naproxen treatment group. BUN was not significantly changed in both treatment groups.

In renal insufficiency patients with normal blood pressure (N=4), CrCl , Scr and BUN were not significantly different in both treatment groups, whereas in renal insufficiency patients with high blood pressure (N=15) CrCl and BUN were significantly increased in both treatment groups while Scr was not significantly different.

These results showed that naproxen and celecoxib decreased renal functions in normal (N=26), renal insufficiency (N=22) and high blood pressure patients (N=39), although no change was observed in normal blood pressure patients (N=9). The implication was that either there were not enough normal blood pressure patients in this study or high blood pressure level seems to associate with decreased renal functions after naproxen or celecoxib treatment. It is possible that hypertensive patients were the majority of the patients in this study while only a few other populations were included and the decrement of renal functions in these populations could not be observed. In addition, it is probable that hypertension might be potential renal risk factor of COX-2 inhibitors as reported by Khan *et al.*, who found that hypertension was associated with increased renal COX-2 expression particularly in macula densa (7). Expression of COX-1 in hypertensive patients should also be further investigated.

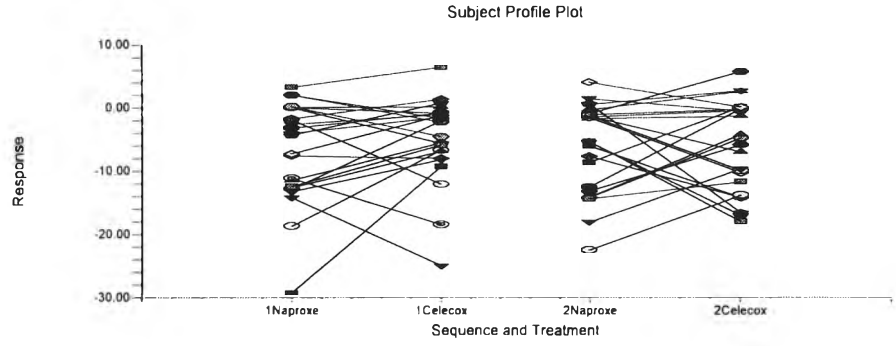
Crossover analysis was conducted to compare the renal effects of naproxen and celecoxib in crossover study of both sequences, with the two treatments in 2 x 2 crossover design employing 24 subjects in each sequence. All subgroup analysis had preliminary test assumption of equal period effect and carry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

Figures 1-3 showed change of CrCl, Scr and BUN, respectively, in each patient after treatment with naproxen and celecoxib. The mean changes of CrCl, Scr and BUN were shown along the vertical axis. The two sequences were shown along the horizontal axis. The changes in CrCl, Scr and BUN for each subject are shown as two points connected by a line. In some patients these changes were remarkably different from others.

Crossover analysis showed no significant difference in CrCl, Scr and BUN between treatments with naproxen and celecoxib in all patients. When the patients were divided into subgroups, there was also no significant difference between normal and renal insufficiency patients and between naproxen and celecoxib in either normal blood pressure or high blood pressure patients.

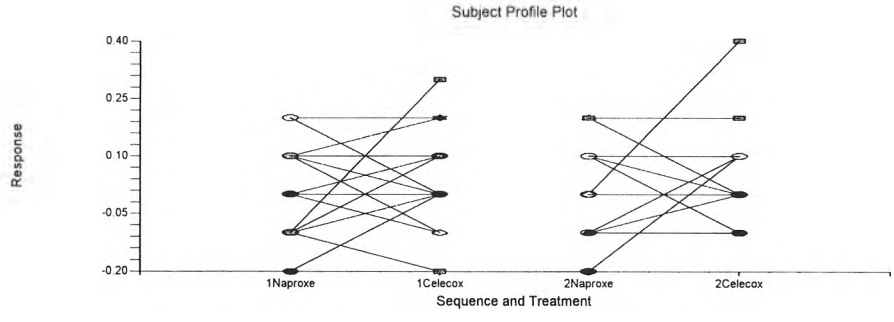
Blood pressure

As shown in Figure 4, systolic blood pressure significantly increased ($p<0.001$) whereas diastolic blood pressure and mean arterial blood pressure (MAP) did not significantly change from baseline



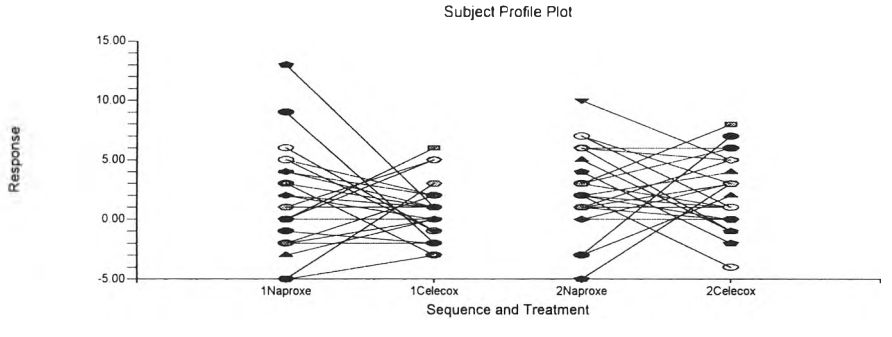
Response = Change of creatinine clearance (CrCl) after treatment with naproxen and celecoxib in each patient

Figure 1. Change of CrCl after treatment with naproxen and celecoxib in each patient



Response = Change of Scr after treatment with naproxen and celecoxib in each patient

Figure 2. Change of Scr after treatment with naproxen and celecoxib in each patient



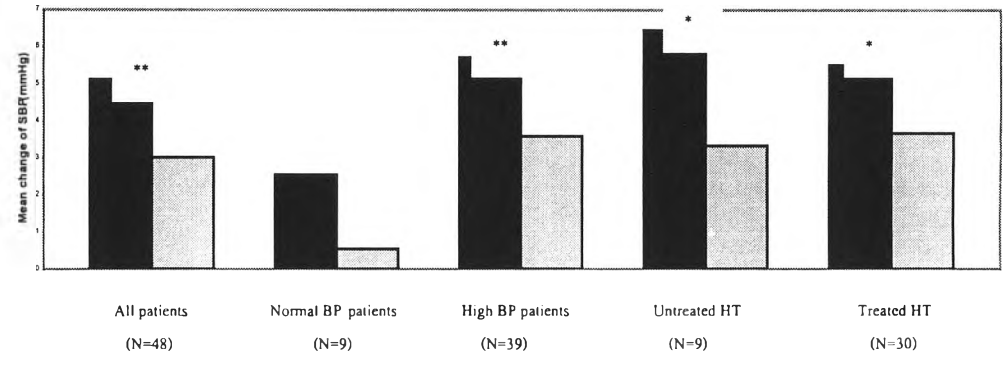
Response = Change of BUN after treatment with naproxen and celecoxib in each patient

Figure 3. Change of BUN after treatment with naproxen and celecoxib in each patient

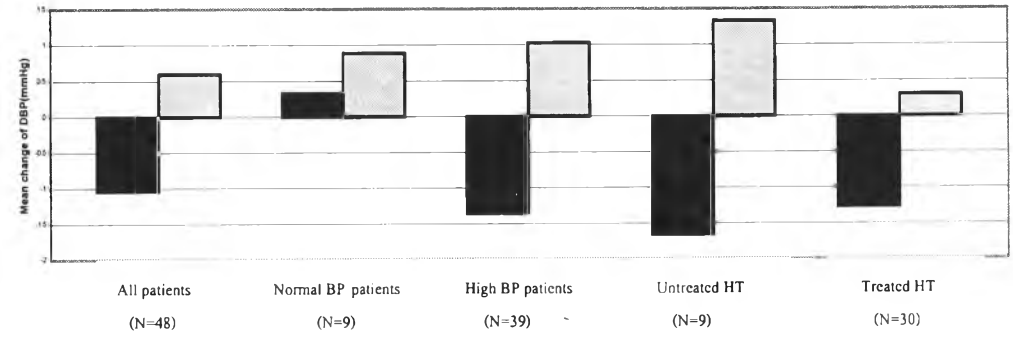
in the naproxen group. In the celecoxib group, SBP, DBP and MAP were slightly increased although not significantly different from baseline. As for the normal blood pressure patients (N=9), SBP, DBP and MAP were not significantly increased in both naproxen and celecoxib group. In high blood pressure patients (N=39) (including treated hypertension and untreated hypertension), naproxen significantly increased SBP from baseline ($p<0.01$) while DBP and MAP were not significantly increased in any group. In contrast to naproxen, celecoxib did not significantly increase SBP, DBP and MAP in either treated or untreated hypertensive patients.

Crossover analysis showed that there were no significant difference in SBP, DBP and MAP

Systolic blood pressure



Diastolic blood pressure



Mean change of mean blood pressure

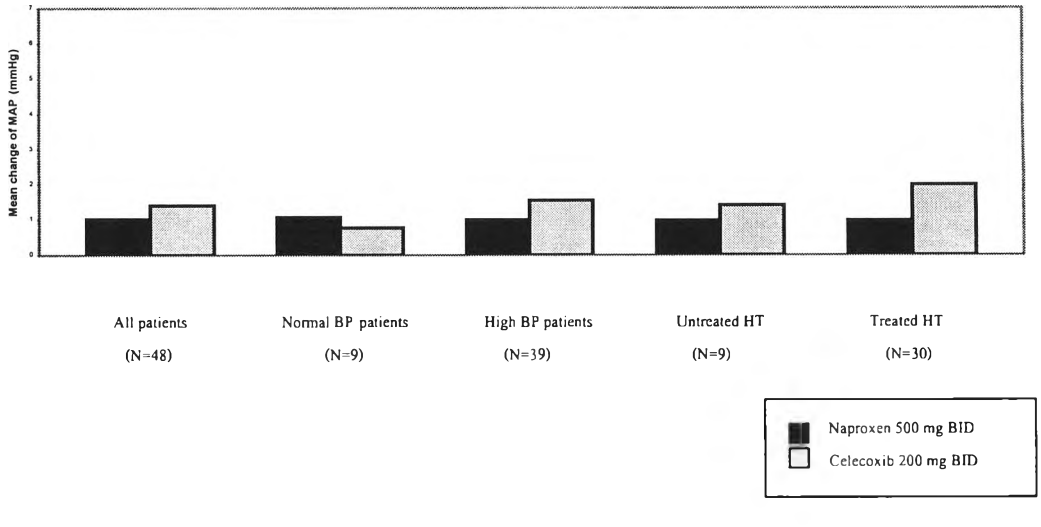


Figure 4. Mean changes in SBP, DBP and MAP in the patients

between the treatments with naproxen and celecoxib in both normal blood pressure and hypertensive patients.

Since hypertension is a common comorbidity in elderly patients using NSAIDs (8), therefore management of these comorbidity should be considered. Extensive clinical trials have shown that sustained increase in SBP of 3 mmHg is related to 10 to 20% increase in congestive heart failure (9), 15% to 20% increase in stroke risk (10) and 12% increase in angina risk (11). These results are implicated in the maintenance of adequate blood pressure control among NSAID treated and comorbid hypertensive patients.

In this study, only naproxen significantly increased SBP but not DBP and 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 and MAP. However, there were only nine patients with normal blood pressure. Further studies with larger sample size are required.

For hypertensive patients, SBP was not significantly increased in celecoxib treatment group (both treated and untreated hypertension). This result is similar to that of the SUCCESS VI study by Whelton *et al.*, which found that celecoxib 200 mg once daily did not affect blood pressure in older hypertensive osteoarthritic patients (12). As for the results of naproxen, it is possible that different types of NSAIDs might affect blood pressure to different degrees. Pope *et al.* have determined that NSAIDs, such as indometacin and naproxen, appeared to greater increase in SBP in treated hypertension than other NSAIDs (13).

In addition, Johnson *et al.* demonstrated that destabilization of blood pressure control by NSAIDs was the greatest in treated hypertensive patients since NSAIDs can interaction with antihypertensive medications. Beta-blocker, calcium channel blockers and ACE inhibitors are the most common antihypertensive agents affected by NSAIDs (14).

From this study, mean change of systolic blood pressure between treated and untreated hypertension was not significantly different in both naproxen and celecoxib treatment groups (Table 3). The number of untreated hypertensive patients in this study was much lower than the number of treated hypertensive patients. Thus, further studies are needed to inves-tigate this point.

NSAIDs-antihypertensive interactions was not determined in this study because most of the patients were taking combination of antihypertensive medica-tions. Moreover, ACE inhibitors were prohibited in this study.

Electrolyte

Sodium and potassium in the serum and urine were not significantly affected in all patients, as shown in Figures 5-6. Results from crossover analysis showed that the change in electrolyte was not significantly different between naproxen and celecoxib treatment group.

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 depleted subjects (15).

Table 3. Mean changes in systolic blood pressure after naproxen and celecoxib treatments in the treated and untreated hypertensive patients

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

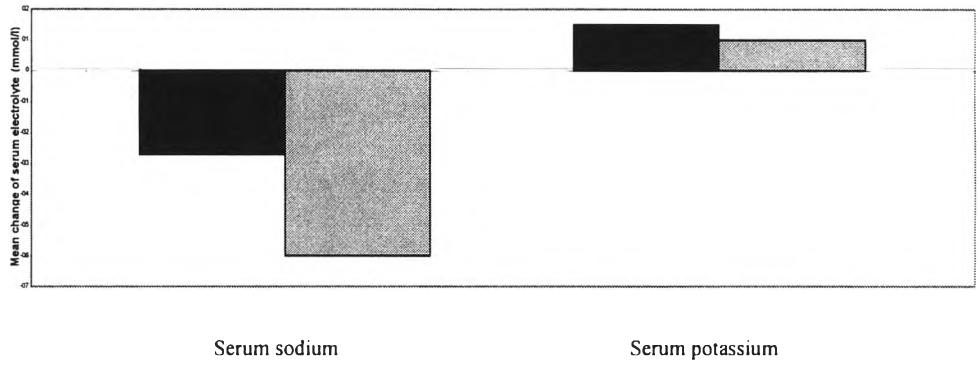


Figure 5. Mean changes in serum sodium and potassium in all patients

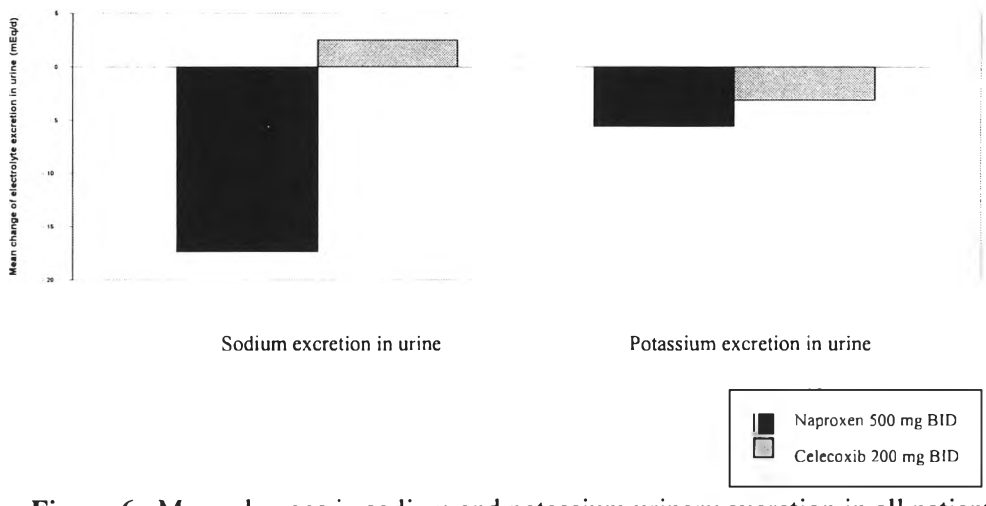


Figure 6. Mean changes in sodium and potassium urinary excretion in all patients

Difference in the findings might result from our conducting of this study in out-patient department, and thus could not regulate electrolyte intake of the patients. This might be a weak point of this study.

Edema

Incidence of edema after celecoxib and naproxen treatment was assessed by the same physician. The criteria indicating edema was an increase of at least 1 grade in edema scale from baseline in accordance with 2% weight gain at least 2 grades in accordance with or without weight gain. In this study, edema occurred in 7 out of all 48 patients (14.58%) after naproxen treatment and 3 (6.25%) after celecoxib treatment.

Although incidence of edema in naproxen treatment group was higher than in celecoxib treatment group, Chi-square analysis showed that there was no significant difference in edema between both groups (p=0.181). This finding is consistent with previous study by Silverstein *et al.*, although the occurrence of edema from CLASS study was lower than in this study (16). This might be due to different edema criteria used.

Secondary outcomes evaluation

For this study, secondary outcomes were any adverse drug reactions that were recorded by open-ended question at the end of each treatment. Adverse effects constituting renal endpoints were excluded from this analysis. The adverse effects that received score 1-9 points of Naranjo's algorithm were presented and used for statistical analysis.

The adverse drug reactions of naproxen and celecoxib were reported in Table 4. 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

Table 4. Secondary outcomes in naproxen and celecoxib treatments

Secondary outcomes	All patients (N=48)		Patients not taking omeprazole (N=28)		Patients taking omeprazole (N=20)	
	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]
Heartburn	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 > 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)	0[ns]	1(3.57)	0	1(5)	0

Data are given as number (%) of patients
* $p < 0.05$, ns = not significant
[a] = versus naproxen in all patients
[b] = versus naproxen (not taking omeprazole)
[c] = versus naproxen (taking omeprazole)

Table 5. Mean changes in Hgb and Hct observed in all patients

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

[ns] = no significant versus baseline
[a] = naproxen versus baseline
[b] = celecoxib versus baseline
[c] = celecoxib versus naproxen

most commonly reported adverse effects in the naproxen group were gastrointestinal complications e.g. abdominal pain, dyspepsia and heartburn, respectively, while dizziness, diarrhea and dyspepsia mostly occurred in the celecoxib group. In addition, one patient developed constipation from naproxen and one developed nausea from celecoxib.

As for other laboratory findings [e.g., SGOT, SGPT, hemoglobin (Hgb), hematocrit (Hct)], in none of the patients were SGOT and/or SGPT increased more than twice the normal level. The number of patients with decreased Hgb and Hct from naproxen were greater than those of celecoxib. This suggested that naproxen might cause ulcer complications more than celecoxib, although no significant difference in the decrement of Hgb and Hct was detected between both groups (Table 5).

Some patients who enrolled in this study history of gastrointestinal complications from NSAIDs were receiving omeprazole (O-Sid®) to prevent ulcer complications. None of the patients in this study received H_2-antagonists. Therefore, patients were divided into two groups (20 patients taking and 28 patients not taking omeprazole). In patients not taking omeprazole, abdominal pain and heartburn occurred in the naproxen more than celecoxib group, while in patients taking omeprazole, the secondary outcomes were not significantly different between both groups.

Conclusion

In this study, celecoxib 200 mg twice daily and naproxen 500 mg twice daily similarly

decreased creatinine clearance in elderly patients (hypertensive patients, patients with normal renal functions and renal insufficiency patients). Hypertensive patients (either with or without insufficiency) had a tendency to suffer decreased renal function from naproxen and celecoxib. In hypertensive patients with normal renal functions, celecoxib caused greater decrease in CrCl than naproxen. However, creatinine clearance was not significantly decreased after treatment with naproxen and celecoxib in normal blood pressure patients. Since this study employed only a small number of these patients, further studies in larger group of patients are required to confirm this conclusion. In the case of serum creatinine, the increment of serum creatinine in this study had no meaningful clinical implications.

Naproxen had a tendency to increase systolic blood pressure, particularly in high blood pressure patients (either treated or untreated), while celecoxib did not significantly affect blood pressure in both normal and high blood pressure patients. Although the effect of celecoxib on blood pressure was less than that of naproxen, patients with risk of hypertension should be monitored closely during administration of non-selective NSAIDs or highly selective COX-2 inhibitors. In the elderly, an increase in SBP should be closely monitored since this was recognized as the important predictor of cerebrovascular and cardiovascular disease. Naproxen and celecoxib did not significantly alter sodium and potassium in the serum and urine. It was noted that electrolyte intakes were not regulated in this study, which might be a weak point of the study.

The occurrence of edema from naproxen was higher than that of celecoxib but not statistical significant. Among patients who developed edema from naproxen, there was significant increase in serum sodium and destabilization of systolic blood pressure. Other adverse drug reactions occurred more frequently when naproxen was used, although there was no significant difference. However, celecoxib caused less symptomatic gastrointestinal complications than naproxen. For long term treatment, physicians should monitor more serious gastrointestinal complications, such as perforation, obstruction and bleeding.

Although renal functions (creatinine clearance, serum creatinine, blood pressure) and electrolyte values could return to baseline after the drug had been withdrawn and there was no vital sign and other laboratory abnormalities during the study, non-selective NSAIDs or highly selective COX-2 inhibitors should be used with caution especially when use in long term period.

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