CHAPTER II

LITERATURES REVIEW

Arthritis and other chronic musculoskeletal problems such as osteoarthritis (OA), rheumatoid arthritis (RA), tendinitis and muscle pain are the major causes of disability. In US adults, the prevalence rate of OA and RA was 1.2% and 1.0% respectively and increasing with age. More than 50% of persons over 60 years old have radiographic evidence of OA whereas RA and other musculoskeletal problems are also found in the elderly.[23-24]

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for treatment of pain and inflammation from musculoskeletal problems. The approximately 100 million people worldwide use them regularly.[25] They are used for treatment of pain and inflammation in many conditions by reducing swelling, tenderness and stiffness leading to improve physical functions in arthritic patients. In OA and RA, reduction in pain and inflammation are goals of treatment. The American College of Rheumatology has developed guideline for treatment of OA and RA that initial treatments involve in non-selective NSAIDs or highly selective COX-2 inhibitors[16, 26-28]

Mechanism of nonsteroidal anti-inflammatory drugs (NSAIDs) [29]

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase (COX) which is the rate-limiting enzyme for synthesis of prostaglandins (PGs) and thromboxane from arachidonic acid. Arachidonic acid is released from lipid membranes by phospholipase A_2 and converted to the intermediate prostaglandin endoperoxides (PGG_2-PGH_2) by prostaglandin G/H synthase 1 (cyclooxygenase-1) and prostaglandin G/H synthase 2(cyclooxygenase-2) then was rapidly metabolized to more stable prostaglandins and thromboxane by the action of specific enzymes.

NSAIDs that inhibit both COX-1 and COX-2 are called "non-selective NSAIDs or non COX specific NSADs" (Figure 1).

Cyclooxygenase [11-12, 30-32]

A recent discovery found two COX isoforms, COX-1 and COX-2 that variable expressed in different tissues. Both enzymes have approximately 60% identical in their amino acid sequence. As shown in Figure 2, COX-1 has a housekeeping function while COX-2 involved in the inflammatory response. This suggests that the differential inhibition of these isoforms causes variable toxicities of NSAIDs.

Cyclooxygenase-1 (COX-1)

COX-1 is the constitutive form of the enzyme that is expressed in most tissues throughout the body including the gastrointestinal tract (GI tract), kidney and platelet which provide physiologic maintenance e.g., cytoprotection, maintenance of renal functions and haemostasis. Therefore, COX-1 is hypothesized to perform the housekeeping function.

Cyclooxygenase-2 (COX-2)

COX-2 is expressed in low levels in most cells under physiologic conditions. COX-2 is induced by inflammatory stimuli. Expression of COX-2 can be up regulated 10 to 80 fold by cytokines, growth factors and tumor promoters at inflammatory sites and in cancer. It appears that COX-2 expressed during inflammation. The expression of COX-2 plays a major role in inflammation and carcinogenesis.

As displayed in Figure 2, the anti-inflammatory actions of NSAIDs are due to inhibition of COX-2 whereas side effects such as GI complications, decline renal functions and platelet aggregation are due to inhibition of COX-1.

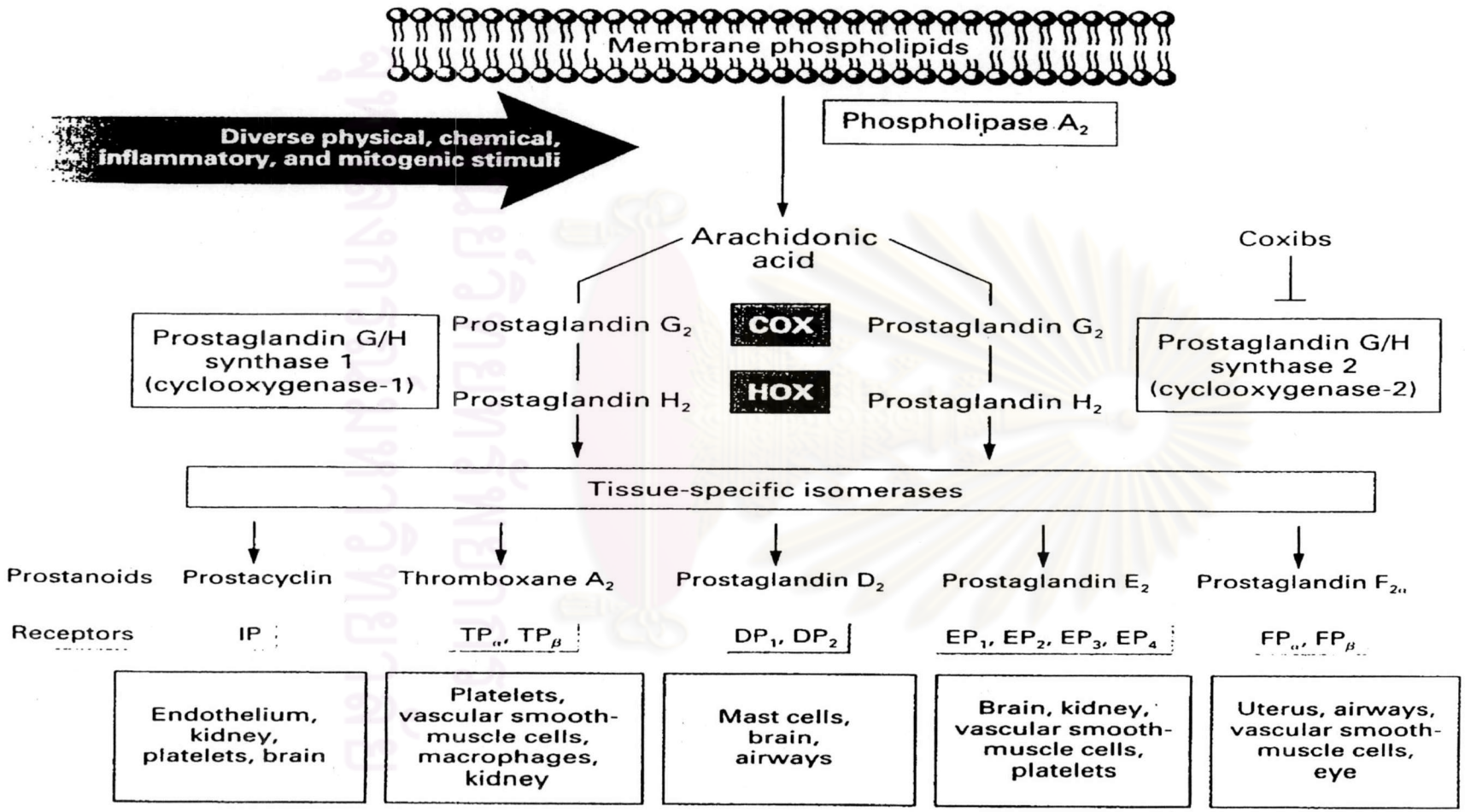

Figure 1: Synthesis pathway and physiologic functions of prostaglandins and thromboxane.[5]

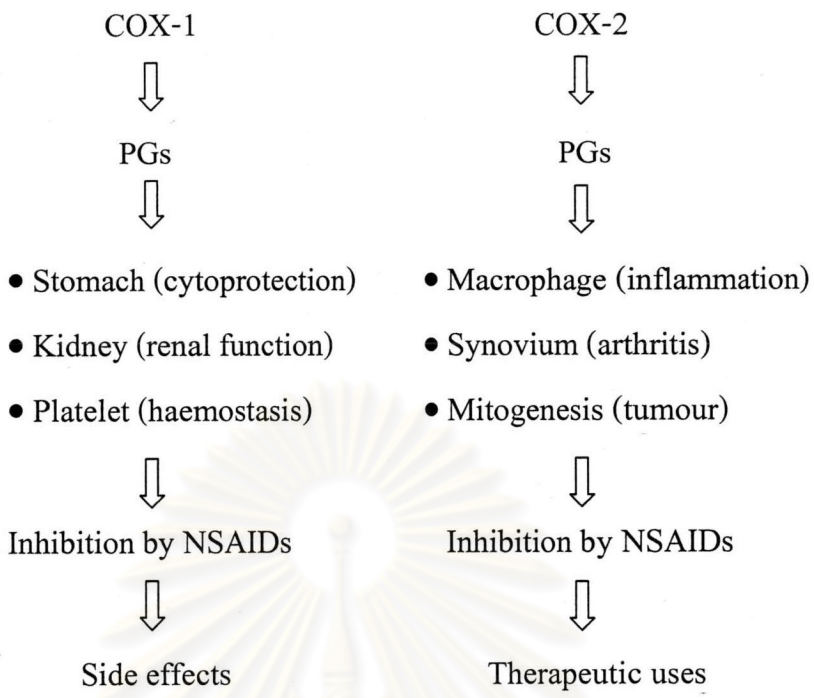

Figure 2: Efficacy and side effects of NSAIDs due to mechanism of actions[32]

Prostaglandins and thromboxane[31]

Prostaglandins (PGs) and thromboxane (TXA) are local mediators of inflammation and modulators of physiologic function. PGs are potent vasodilators and act synergistically with other inflammatory mediators in producing pain and inflammation. Some physiologic responses such as GI mucosal protection, vascular tone and renal blood flow can be regulated by PGs whereas platelet aggregation can be regulated by TXA (Table 1).

The three important roles of PGs involve in gastrointestinal mucosa, platelet aggregation and renal functions. The scope of this review is prostaglandin and renal functions.

Table 1: Physiologic functions of prostaglandins and thromboxane[15, 31]

Physiologic functions	PGs and TxA involved
Relax vascular smooth muscle	PGE_2, $PGF_{2\alpha}$, PGI_2
Promote platelet aggregation	TxA_2
Inhibit platelet aggregation	PGI_2
Relax bronchial smooth muscle	PGE_2, PGI_2
Contract bronchial smooth muscle	$PGF_{2\alpha}$
Increase renal blood flow	PGE_2, PGI_2
Protect gastric mucosa	PGE_2, PGI_2
Contract uterine smooth muscle	PGE_2, $PGF_{2\alpha}$
Relax uterine smooth muscle	PGI_2

1. Prostaglandins and gastrointestinal mucosa

PGE_2, PGI_2 are essential compounds of gastroprotective process. They stimulate mucous and bicarbonate secretion, increase mucosal blood flow, increase mucosal cell restitution and inhibit acid secretion. The inhibition of PGs in gastrointestinal mucosa often results in gastric and intestinal ulcers.[33-34]

2. Prostaglandins, thromboxane and platelet

COX-1 and COX-2 synthesize TxA_2, PGI_2 from arachidonic acid. TxA_2 functions as prothrombotic by promoting platelet aggregation while PGI_2 functions as an antithrombotic by inhibiting platelet aggregation. At low doses of NSAIDs, TxA_2 synthesis is first inhibited but PGI_2 formation continues leading to the antiplatelet aggregating state.[31, 36]

3. Prostaglandins and renal functions

PGs such as PGE_2, PGI_2 (prostacycline) and $PGF_{2\alpha}$ are generated at various intrarenal sites and modulate a variety aspects of renal physiology. PGE_2 and PGI_2 play a major role in the modulation of renal hemodynamics, renin release and tubular salt and water reabsorption.[4, 37-38] Renal actions of PGs were shown in table 2 and Figure 3-4

Table 2 : Renal actions of prostaglandins[39]

1. Act on renal blood flow and maintain renal perfusion when systemic circulation is compromised
2. Excrete renal sodium
3. Antagonize to the action of antidiuretic hormone (ADH) on water permeability
4. Stimulate renin release
5. Modulate vasoconstriction due to sympathetic nerve stimulation , catecholamines and angiotensin

As shown in Figure 3, PGs function as modulators of renal blood flow. Under normal conditions, PGs play a minor role in maintaining renal and glomerular blood flow but in decrease renal perfusion conditions (e.g., elderly patients, congestive heart failure, hepatic cirrhosis, nephrotic syndrome, hypertension, diabetic mellitus and volume depletion due to diuretics or extrarenal fluid losses) leading to synthesis of angiotensin II (AII), increase sympathetic outflow and release norepinephrine (NE) which results in renal vasoconstriction and impaired renal function. In these conditions, renal PGs synthesis are stimulated to normalize renal function by antagonizing the above vasoconstrictors.[40-41]

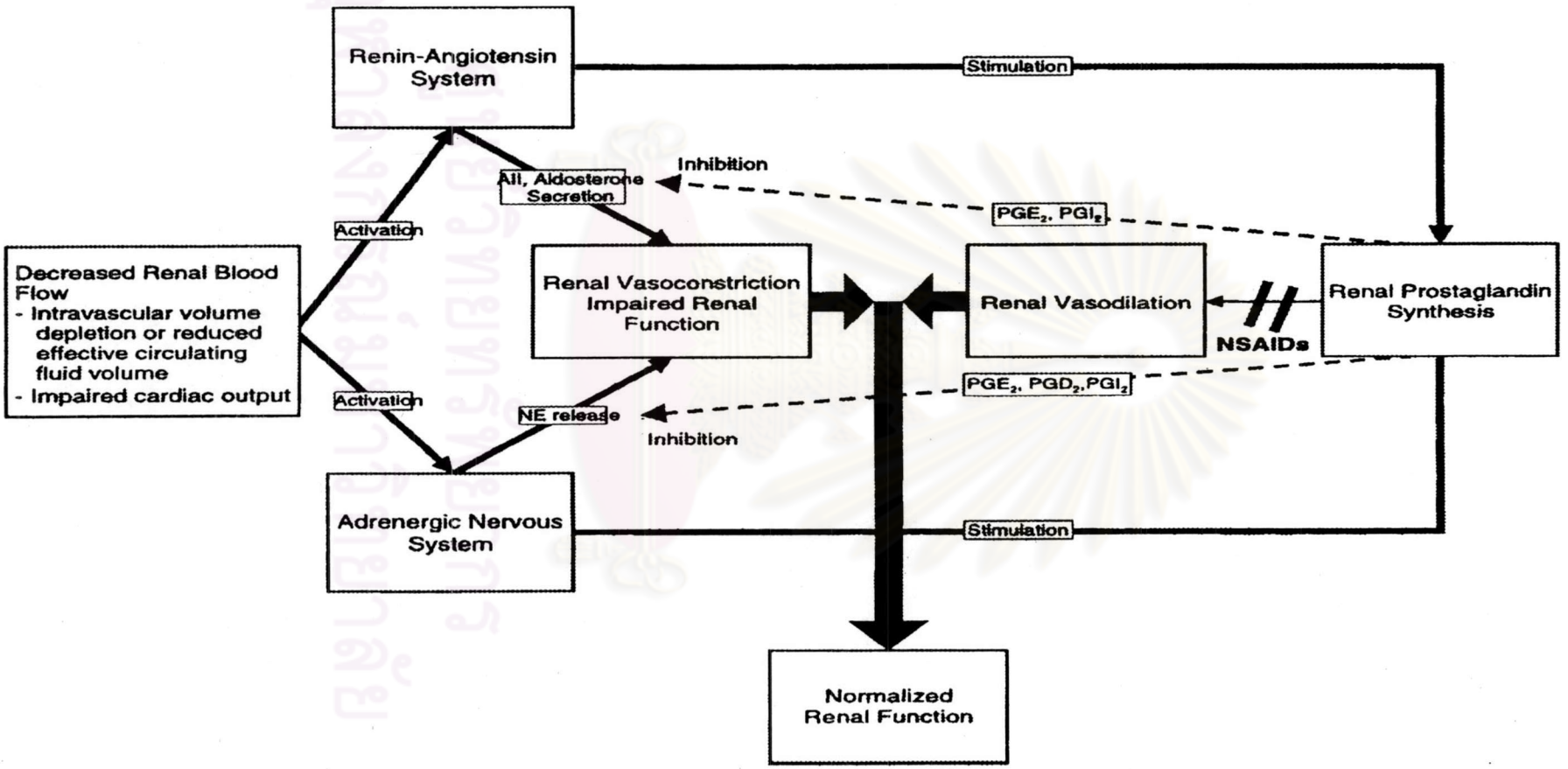

Figure 3: Renal actions of prostaglandins[42]

NSAIDs blocking PGs formation in these renal risk factor conditions can decline renal functions by inhibiting PGE_2, PGI_2.[43]

As shown in Figure 4, the majority of PGs in renal area are PGI_2 and PGE_2. PGE_2 decreases sodium reabsorption at the thick ascending limb of the loop of Henle.[1] Therefore inhibition of PGE_2 leads to sodium retention that can manifest in several ways such as peripheral edema, increase blood pressure (mainly in treated hypertensive patients) and weight gain. PGE_2 also decreases the action of antidiuretic hormone (ADH) which acts on stimulate water reabsorption. Thus the inhibition of PGE_2 by NSAIDs can also occur in edema by increasing water reabsorption.[39, 44]

PGI_2 stimulates renin release which consequently increases secretion of aldosterone, that acts on the kidney by stimulating sodium reabsorption in exchange for potassium and hydrogen ions in the distal nephron. The inhibition of PGI_2 can result in hyperkalemia. PGI_2 is also a potent vasodilator that maintains renal perfusion in condition of decrease effective circulating volume. Therefore, inhibition of PGI_2 can also results in acute renal failure.[39, 44-45]

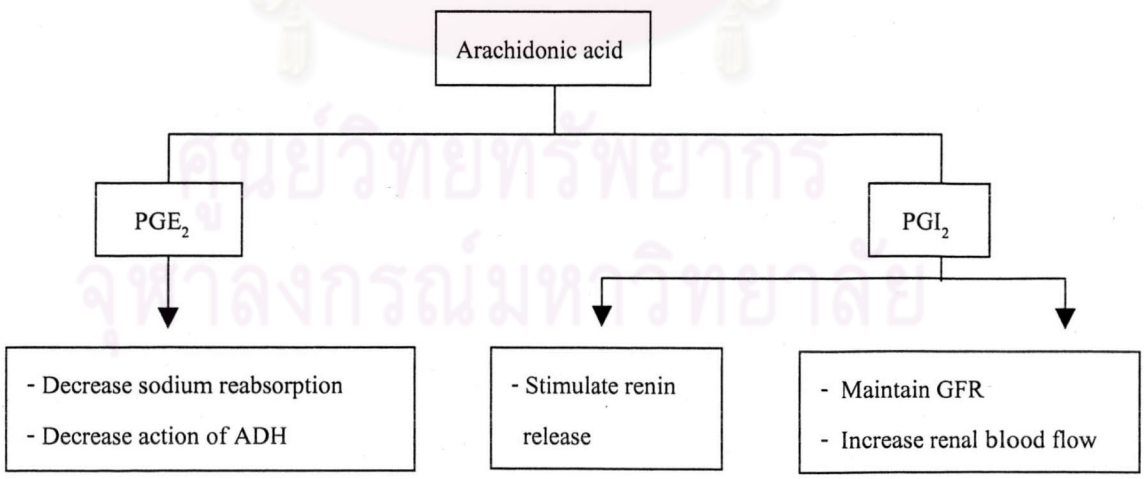

Figure 4: Renal actions of PGE_2 and PGI_2[89]

Complications of nonsteroidal anti-inflammatory drugs

1. GI complications

Gastrointestinal complications such as perforation, ulcer, obstructions and upper gastrointestinal bleeding (UGIB) from NSAIDs are a result of inhibition of COX-1 leading to decrease gastroprotection.[7]

Epidemiological data have shown that the risk of UGIB among NSAIDs users is three to four times greater than nonusers. Medium to less daily dose users have shown twofold to threefold increase in risk, whereas high daily dose users have shown fivefold increase in risk. Piroxicam (RR 18.0) had the highest risk of UGIB and ibuprofen had the lowest risk of UGIB whereas naproxen, diclofenac, ketoprofen and indometacin at equipotent dose had similar relative risk of UGIB.[46-47]

2. Platelet aggregation [36, 48]

Aspirin is more potent inhibitor of COX-1 than COX-2 and its antithrombotic efficacy has been clearly demonstrated. Low dose aspirin induces irreversible inhibition of TxA_2 without inhibition of PGs, due to inhibit platelet aggregation.

Other NSAIDs inhibit both TxA_2 and PGI_2 and their cardiovascular protection has not been established. A retrospective epidemiological study has concluded that chronic use of other NSAIDs is absence of protective effect on risk of the cardiovascular disease.[49]

3. Renal complications

The epidemiological studies have shown that NSAIDs users showed a twofold to fourfold increase in the risk of chronic renal complications. As mentioned above, the risk increased with elderly patients, cardiovascular comorbidity, renal insufficiency and volume depletion moreover related to dose and duration of NSAIDs intake.[7, 9-10]

Among patients with risk factors, NSAIDs exposure causes a sevenfold increase in the risk of acute renal failure.[10] Indomethacin presented a higher relative risk (RR) of acute renal failure than other NSAIDs.[7,9] Major renal syndromes from NSAIDs include fluid and electrolyte disturbance, hypertension, acute deterioration of renal function, nephrotic syndrome with interstitial nephritis and renal papillary necrosis.[4,7]

3.1 Fluid and electrolyte disturbance

- Sodium retention and edema [37, 50-51]

Sodium retention and edema are the most common and happen within the first week of therapy. Edema occurs in 3-5% or up to 25% and may be higher in patients who receive prolong treatment with long acting NSAIDs. Mechanism by inhibiting PGE_2 synthesis, which decreases sodium reabsorption at the thick ascending loop of Henle and in the collecting ducts. Furthermore, PGE_2 antagonizes antidiuretic effect of ADH in the collecting tubules, where inhibiting PGE_2 synthesis by NSAIDs increases both sodium and water reabsorption. This alteration usually results in a net fluid retention of 0.5 to 1.0 liter due to weight gain of 1 to 2 pounds and decreases response to diuretics and antihypertensive agents.

The other mechanism that causes sodium retention and edema is the shunting of arachidonic acid metabolites into lipoxygenase pathway, which leads to the formation of leukotrienes and possibly increases capillary permeability with edema formation.

- Hyperkalemia [45,50,52-53]

Hyperkalemia is a rare but serious abnormality. First mechanism by decrease PGI_2. PGI_2 stimulate renal renin release, which increases the secretion of aldosterone formation that consequently increases potassium excretion by distal nephron. The inhibition of renal renin-aldosterone release by NSAIDs may compromise renal potassium excretion. The decrease in potassium secretion begins to occur with the first

dose of NSAIDs. Patients who are prone to hyperkalemia would also have increase risk, including those with diabetes mellitus plus renal insufficiency and also receiving other drugs that decrease potassium secretion such as angiotensin converting enzyme inhibitors (ACEIs), potassium sparing diuretic. Hyperkalemia is readily reversible after discontinuation of NSAIDs.

3.2 Hypertension

Epidemiological data showed that increase in either SBP or DBP significantly linear correlated with cardiovascular and cerebrovascular disease.[54-58] Several studies have also suggested an association between NSAIDs and hypertension. Risk factors that are associated with increased blood pressure in NSAIDs treated patients are elderly people, hypertension, renal problems, liver problems and patients with rheumatoid arthritis whereas normal patients may be at lower risk for NSAIDs mediated increased in blood pressure.[59]

An association between NSAIDs therapy and elevated blood pressure has been found by several epidemiological studies.[43, 59-61] An analysis of pool data from 54 trials with the total 1,324 patients found that NSAIDs increased blood pressure slightly in normotensive subjects (1.1 mmHg) and to a greater degree in hypertensive subjects. (3.3 mmHg). Different NSAIDs had different degrees of effect on blood pressure. The greatest increased in blood pressure was seen in naproxen and indometacin. The effects of sulindac and aspirin were similar to that of placebo.[60]

The other meta-analysis used data from 50 randomized studies with 771 patients, found that mean blood pressure increased by an average of 5 mmHg in subjects treated with NSAIDs and increase in mean blood pressure depended on the hypertensive status of patients. Aspirin and sulindac had little or no effect whereas piroxicam, indometacin, naproxen and ibuprofen had the greatest effect. Moreover, interaction effect between NSAIDs treatment and hypertensive patients was also

associated with classes of antihypertensives medications such as beta-blockers, calcium channel blockers and ACE inhibitors. [59]

3.3 Acute deterioration of renal functions

Acute deterioration of renal functions rarely cause in patients with normal renal function because in normal conditions, PGs do not play a physiological role in the maintenance of renal blood flow, which may result in any clinical condition that leads to decrease renal perfusion or organ perfusion. Administration of NSAIDs in these conditions can interfere nephroprotective PGs that can induce renal ischemia and acute renal failure.[4,7,37-38,62]

Acute renal failure can develop with the first month of use NSAIDs and reverses within 3 to 5 days after discontinuation of NSAIDs, but in chronic NSAIDs ingestion may take a prolonged period of time.[6,63] Although dose and duration of NSAIDs is associated with renal functions, short courses with small doses may induce acute renal failure in patients who are at risk.[6] Epidemiological data indicating a high risk of renal failure with patients who are at renal risk factors and/or taking NSIADs which have a half life of more than 12 hours.[45]

3.4 Nephrotic syndrome with interstitial nephritis [45,50]

Proteinuria with interstitial nephritis is rare (less than 0.1%). Eventhough, the mechanism is unclear, the effect is not an allergic, hypersensitivity phenomenon. However, a possible mechanism can inhibit the COX pathway and can shunt arachidonate metabolites into lipoxygenase pathway resulting in the production of leukotrienes leading to nephritic range and proteinuria.

In contrast to other renal effects, this effect occurs after months or years of therapy. Cross among NSAIDs is unknown because the syndrome is not hypersensitivity. Clinicians should avoid any other NSAIDs when developing this

syndrome. A different structural class should be selected and the patients should be mornitored closely.

3.5 Paillary necrosis [50,64]

Both acute and subacute form of papillary necrosis have been observed with NSAIDs overdose in dehydration patients. This clinical result in elevate intrapapillary concentration of NSAIDs and/or NSAIDs metabolites which may be cytotoxic or inhibition of vasodilate PGs leading to renal papillary necrosis.

Classes of NSAIDs [11,15,29,31,65]

The discovery of COX-1, COX-2 and difference in pharmacology between COX-1 and COX-2 leads to the classification of NSAIDs based on 50% inhibitory concentration of NSAIDs on COX-1 divided by 50% inhibitory concentration of NSAIDs on COX-2 (COX-1/COX-2 IC_{50} ratio). If NSAIDs is equally potent on both COX-1 and COX-2 , the COX-1/COX-2 IC50 ratio would equal 1. NSAIDs is more specific for COX-2 than COX-1, the COX-1/COX-2 IC50 ratio > 1. NSAIDs is more specific for COX-1 than COX-2, the COX-1/COX-2 IC50 ratio < 1. The three classes of NSAIDs are described by COX-1/COX-2 IC_{50} ratio (Table 3).

Table 3: Classes of NSAIDs based on COX-1/COX-2 IC_{50} ratio[65]

Classes of NSAIDs	Criteria	Drugs
COX non specific (non-selective NSAIDs)	COX-1/COX-2 < 2	aspirin, indometacin, Ibuprofen, naproxen, ketoprofen, diclofenac, tiaprofenic acid, piroxicam, tenoxicam
Selective COX-2 inhibitors (COX-2 preferential)	COX-1/COX- 2 = 2-100	meloxicam, nimesulide,
Highly selective COX-2 inhibitors	COX-1/ COX-2 > 100	celecoxib, rofecoxib, valdecoxib, parecoxib etoricoxib

Highly selective COX-2 inhibitors

NSAIDs which inhibit COX-2 enzyme but do not inhibit COX-1 enzyme at therapeutic doses are defined as "selective COX-2 inhibitors", which would have anti-inflammatory effects and fewer side effects than non-selective NSAIDs. The several highly selective COX-2 inhibitors are now available for treatment of musculoskeletal problems as the follows.[31,35,66]

Table 4: Available highly selective COX-2 inhibitors [31,65,67-68]

Generic name	Trade name	Dosage form	Manufacturer
Celecoxib	Celebrex	Oral	Pharmacia
Rofecoxib	Vioxx	Oral	Merck
Valdecoxib	Bextra	Oral	Pharmacia
Parecoxib	-	IV	Pharmacia
Etoricoxib	Arcoxia	Oral	Merck

Recommend use of highly selective COX-2 inhibitors [69-70]

Highly selective COX-2 inhibitors have comparable efficacy to non-selective NSAIDs. In patients not taking low-dose aspirin, the risk of symptomatic ulcers and confirmed complicated upper gastrointestinal events is significantly reduced in patients taking highly selective COX-2 inhibitors compared with taking nonselective NSAIDs.[18] A recent recommendations for the use of highly selective COX-2 inhibitors in clinical practice that use of these agents preferred in high risk of serious upper GI complications patients (Table 5).

Table 5: Patients especially recommended the use of highly selective COX-2 inhibitors[69]

• **Patients increase risk of serious GI complications**
- Age more than 65 years old
- History of peptic ulcer disease
- Taking glucocorticoid, anticoagulants or aspirin
- Requiring high doses of nonsteroidal anti-inflammatory drugs
• Patients with multiple medical problems or taking multiple medications
• Patients with excessive alcohol intake
• Patients with active bleeding or bleeding tendency

Efficacy of highly selective COX-2 inhibitors

Both celecoxib and rofecoxib are superior to placebo in the relief of both subjective and objective measurements of pain and inflammatory in patients with osteoarthritis of the hip and knee[14-16,71-73] and patients with rheumatoid arthritis [16-17,19]

The Food and Drug Administration (FDA) approved celecoxib for the treatment of patients with osteoarthritis, rheumatoid arthritis, acute pain, familial adenomatous polyps (FAP) and rofecoxib for the treatment of patients with osteoarthritis, rheumatoid arthritis and acute pain.[5]

Two large trials, the Celecoxib Long-Term Arthritis Safety Study (CLASS) have investigated gastrointestinal complications of celecoxib. The CLASS study consisted of two separate studies. In one, celecoxib (400 mg twice daily) was compared with diclofenac (75 mg twice daily) in the other, celecoxib was compared with ibuprofen (800 mg three times daily) in 8059 patients. Seventy-two percent of the patients had osteoarthritis and twenty-eight percent of the patients had rheumatoid arthritis. The study lasted 13 months but only the data from 6 months have been published. The CLASS study was not designed to compare the efficacy of the drugs.

More patients were withdrawn from the NSAIDs group than from celecoxib group (14.8% and 12.6%, p = 0.005) because of lack of efficacy. [18]

The Vioxx Gastrointestinal Outcomes Research (VIGOR) trial, a daily dose of 50 mg of rofecoxib was compared with a twice-daily dose of 500 mg naproxen in 8076 RA patients. Both drugs were similarly effective according to either the patient's or the investigator's global assessment of disease activity scores or the modified health assessment scores. [19]

Complications of highly selective COX-2 inhibitors

1. GI complications of highly selective COX-2 inhibitors

The data from 6 months in CLASS trial include 8059 patients with OA and RA. Patients were randomized to receive celecoxib 400 mg twice daily per day, ibuprofen 800 mg 3 times per day or diclofenac 75 mg twice per day. Aspirin use (< 325 mg/d) was permitted. In the CLASS trial, low dose aspirin was found to be a significant risk factor for upper gastrointestinal ulcer complications. Thus in patients with arthritis not taking low-dose aspirin, celecoxib was associated with a significantly lower risk of both serious upper gastrointestinal ulcer complications and symptomatic ulcers than the use of nonselective NSAIDs. [18]

The overall conclusion is highly selective COX-2 inhibitors are associated with significantly fewer ulceration and symptomatic gastrointestinal adverse effects (acid reflux, dyspepsia, epigastric discomfort, heartburn, nausea and vomiting) than nonselective NSAIDs. As compared to placebo, highly selective COX-2 inhibitors exhibit a slightly higher ulceration rate and symptomatic gastrointestinal adverse effects but not statistical significance. [74-76]

Concerning patients with gastric ulcer, COX-2 inhibitors may delay ulcer healing. [77] Up-regulation of COX-2 during healing of gastric ulcer and Helicobacter pyroli infected stomachs has been demonstrated. [78] Inhibition of COX-2 by highly selective COX-2 inhibitors has been shown to slow the healing of ulcer but not differ

from non-selective NSIADs.[79-80] Patients with gastric ulcer should be switched to other medications while undergoing treatment for ulcer healing.[77]

2. Cardiovascular effects of highly selective COX-2 inhibitors

The COX-2 isoform produces PGI_2, which is a vasodilator and inhibitor of platelet aggregation while COX-1 isoform produce TxA_2 which promote platelet aggregation.[36] Non-selective NSIADs inhibit the production of both TxA_2 and PGI_2 but highly selective COX-2 inhibitors have no effect on TxA_2 production. The decrease only PGI_2 by highly selective COX-2 inhibitors may tip the natural balance between prothrombotic TxA_2 and antithrombotic PGI_2 leading to increase in thrombotic cardiovascular events[5] (Table 6).

The cardiovascular effects of highly selective COX-2 inhibitors was unclear due to in the CLASS study showed that there was no significant difference in cardiovascular events (myocardial infarction, stroke and death) rates between celecoxib and non-selective NSAIDs,[18] but in the VIGOR trial showed that the relative risk (RR) of developing cardiovascular event (myocardial infarction, unstable angina, cardiac thrombus, resuscitated cardiac arrest, sudden or unexplained death, ischemic stroke and transient ischemic stroke) with rofecoxib treatment compared with naproxen was 2.38% (p= 0.002).[19]

A meta-analysis of the US Physicians Health Study included 48,450 patients (25,133 patients were treated with aspirin and 23,407 patients were given placebo). The myocardial infarction rates for highly selective COX-2 inhibitors in both CLASS and VIGOR were significantly more higher than placebo group, 0.74 % with rofecoxib (p=0.04 compared with placebo group of the meta-analysis) and 0.80% with celecoxib (p=0.02 compared with placebo group of the meta-analysis).[81]

Table 6: Different patterns of inhibition TxA_2 and PGI_2 by low dose aspirin, non-selective NSAIDs and highly selective COX-2 inhibitors.[36]

NSAIDs	PGI_2	TxA_2	Thrombotic Risk
Low dose aspirin	=	↓↓	↓
Non-selective NSAIDs	↓	↓	=
Highly selective COX-2 inhibitors	↓	=	Unclear

3. Renal effects of highly selective COX-2 inhibitors

Highly selective COX-2 inhibitors have become widely available. These medications are used to treat pain and other inflammatory conditions and to reduce adverse gastrointestinal effects. The different localization of the COX-1 and COX-2 enzymes in the kidney bring to the hope that these drugs may also spare renal functions.[37,82]

3.1 Localization and roles of cyclooxygenase on renal functions

As shown in Table 7, cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) has located in different sites in the kidney. COX-1 is found in glomerulus and derives PGE_2, PGI_2 for maintaining glomerular filtration rate. In medulla, COX-1 has primary expression in afferent arterioles, medullary collecting ducts and interstitium,[37,83-85] which functions on antagonism of angiotensin II and enhances excretion of sodium. Therefore, inhibition of COX-1 by non-selective NSIADs can decline GFR, hyperkalemia and sodium retention (manifest in variety ways e.g., peripheral edema, increase blood pressure, weight gain).[86]

COX-2 is present in low but detectable levels in normal human kidney.[5] Initial studies of COX-2 localization in the human kidney failed to detect COX-2 in either the

Table 7: Localization of COX and possible functions in renal human[21, 85-90]

Location	COX-1	COX-2	Prostaglandins	Possible functions
Glomerulus	(+)	(+)	PGE_2, PGI_2	Podocyte contractility and maintenance of GFR
Thick ascending limb of the loop of Henle	(-)	(+)	PGE_2	Enhance excretion of sodium and chloride
Macula densa	(-)	(+)[a]	PGE_2	Regulation of renin release
Interstitium	(+)	(+)	PGE_2, TxA_2	Enhance vasodilatation and natriuresis
Renal vasculature[b]	(+)	(+)	PGE_2, PGI_2, TxA_2	Regulation of blood flow, antagonism of angiotensin II induced vasoconstriction
Collecting ducts	(+)	(-)	PGE_2	Enhance excretion of sodium, chloride and water

(-) no staining (+) staining

[a] up regulation in elderly, congestive heart failure, hypertension

[b] includes arteries, arterioles and veins

macula densa or medullary interstitial cells but it is reported to be found in podocytes and arteriolar smooth muscle cells. However, more recent studies detected COX-2 in macula densa[84,91] , along the cortical thick ascending limb of the loop of Henle[88], medullary interstitial cells[90] and also in endothelial cells of the vasa recta, that supply the inner medulla.[37,92]

COX-2 in medullary interstitial cells produce PGE_2[93] which has shown directly to dilate vasa recta, counteracting the effect of angiotensin, therefore helping to maintain renal medullary blood flow. In the medulla thick limb of the loop of Henle, PGE_2 decreases sodium reabsorption.[94] PGE_2 in macula densa is involved in the regulation of renin release.[95] Inhibition of COX-2 can also increases sodium reabsorption in the medulla thick limb of the loop of Henle and decreases renin release from macula densa.[96-98] Suggestion that inhibition of COX-2 activity in the renal might contribute to salt retention, hypertention and also compromises medullary blood flow.

3.2 Identification of renal risk factors for COX inhibitors

In normal condition prostaglandins play negligible role in renal function, but in decrease renal perfusion conditions (e.g., elderly, diabetic mellitus, hypertension, congestive heart failure, coronary artery disease, volume depletion), PGs play a major role on renal functions. Thus these conditions are renal risk factors from either non-selective NSAIDs or highly selective COX-2 inhibitors.[42,50,99-101] Furthermore, elderly, CHF, HT or diabetic nephropathy patients are associated with increase of renal COX-2 expression particularly in macula densa.[84,91,102]

Moreover, the level of COX-2 expression was altered by changing in physiologic state.[86,103] Yang et al. showed that COX-2 increased in the medullary interstitium with high salt diet condition but not observed with low salt diet condition. In contrast to medullary interstitium, COX-2 decreased with high salt diet condition and increased with low salt diet condition in cortical thick ascending limb while COX-

1 was not affected in any region of the kidney with either diet.[103] Therefore, electrolyte intake is also one of renal risk factors from highly selective COX-2 inhibitors.

In addition to these risk factors, pharmacokinetics aspect is one of risk factors that can affect renal functions of NSAIDs. Most NSAIDs are metabolized by hepatic deactivation via cytochrome P450 (CYP 3A4) prior to excretion by the kidney.[5] Furthermore, most NSAIDs are highly albumin bound (greater than 90%). Elderly patients particularly have chronic diseases or decline liver functions with low albumin levels that result in high free level of NSAIDs and prolonged half life more than healthy persons[38,104] (Figure 5).

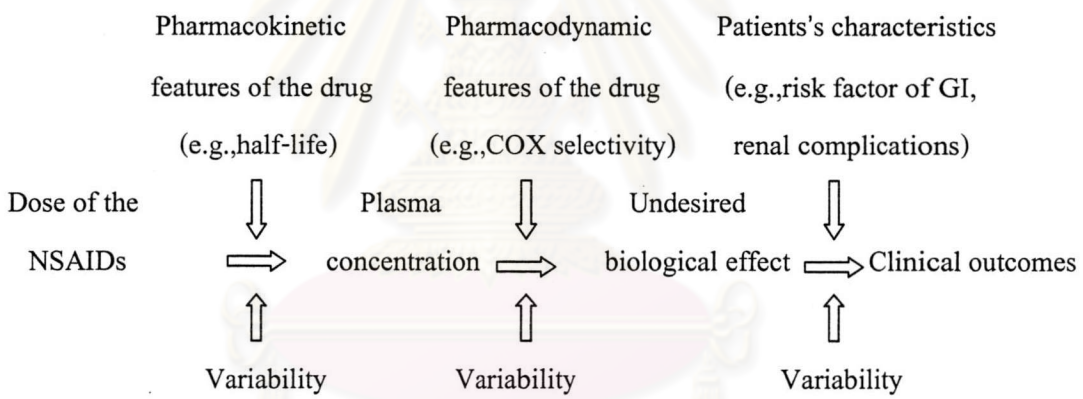

Figure 5: Factors that may influence safety of NSAIDs in an individual patients.[5]

3.3 Studies of highly selective COX-2 inhibitors on renal functions

Silverstein et al. reported data from the CLASS study. Celecoxib 400 mg twice daily was compared with diclofenac 75 mg twice daily and was compared with ibuprofen 800 mg three times daily. The percentage of patients having the adverse event of peripheral edema from celecoxib was similar to that of patients from non-selective NSAIDs (2.8% and 3.5%). The percentage of patients having the adverse event of hypertension from celecoxib was significantly lower than that of NSAIDs treated patients (1.7% and 2.3%). Creatinine level significantly increased in only NSAIDs group[18](Table 8).

Table 8: Adverse renal effects during the 6-month treatment period of celecoxib when compared with non-selective NSAIDs

Adverse effects	celecoxib group (n = 3,987)	NSAIDs group (n = 3,981)
Peripheral edema	113(2.8)	138(3.5)
Hypertension	66(1.7)	90(2.3)[a]
Increase creatinine level	28(0.7)	48(1.2)[a]
Total	200(5.0)	263(6.6)[a]

* Data are given as number (%) of patients

[a] $P < 0.05$ versus celecoxib group

Bombardier et al. reported data from the VIGOR trial. Rofecoxib 50 mg once daily was compared with naproxen 500 mg twice daily. Rofecoxib significantly occurred edema and hypertension more than naproxen[19] (Table 9).

Table 9: Adverse renal effects of rofecoxib when compared with non-selective NSAIDs

Adverse effects	Rofecoxib (n = 4047)	Naproxen (n = 4029)
Peripheral edema	3.4%	3.0%[a]
Hypertension	8.0 %	5.0 %[a]

[a] $P < 0.05$ versus rofecoxib group

Whelton et al. reported data from SUCCESS VI study (a 6 week, randomized, parallel group, double-blind trial in patients with osteoarthritis who were > 65 years old and were taking antihypertensive agents). Patients received celecoxib 200 mg once daily or rofecoxib 25 mg once daily. Significant edema developed almost twice in rofecoxib treated patients (9.5% and 4.9%) and rofecoxib group significantly increased in systolic blood pressure and diastolic blood pressure[104] (Table 10).

Rossat et al. examined renal effects of celecoxib and naproxen in fourty normotensive salt-depleted subjects. Randomize four parallel group compared celecoxib 200 mg twice a day, 400 mg celecoxib twice a day, 500 mg naproxen twice a day and placebo for 7 days. Celecoxib had no effect on systemic blood pressure but short term transient decrease in renal blood flow and glomerular filtration rate were found with the highest dose of 400 mg on day 1. On the first day, both celecoxib and naproxen decreased urine output and sodium, potassium excretion. On day 7, similar effects on water and sodium excretion were observed [105](Table 11).

Whelton et al. studied renal effects of celecoxib and naproxen in 29 healthy elderly subjects in a single blind randomized cross over study. Subjects received either celecoxib 200 mg twice daily for 5 days follow by celecoxib 400 mg twice daily for the next 5 days or they received naproxen 500 mg twice daily for 10 days. After 7 day wash out, subjects were crossed over to receive the other regimen. After the first dose,

naproxen greater decreased in glomerular filtration rate compared with celecoxib and statistically significant on day 6. Small transient decrease in urinary sodium excretion were observed after the initiation of both celecoxib and naproxen treatment[106] (Table 11).

Swan et al. investigated renal effects of rofecoxib and indometacin in 75 elderly subjects receiving low salt diet. Randomized three periods, single dose crossover study and a randomized, parallel group, multiple dose study. In the first study, single dose of rofecoxib 250 mg, indometacin 75 mg and placebo were administered to 15 patients. In the second study, multiple doses of rofecoxib 12.5 or 25 mg/day, indometacin 50 mg three times daily or placebo was administered to 60 patients. Single dose of rofecoxib and indometacin decreased glomerular filtration rate when compare with placebo[107] (Table 11).

Catella-Lawson et al. studied renal effects of rofecoxib and indometacin in 36 healthy elderly subjects. Randomized double blind three parallel groups compare rofecoxib 50 mg once daily, indometacin 50 mg three times a day or placebo for 2 weeks. The first 72 hours of treatment, blood pressure and body weight did not change significantly in any group. Indometacin decreased glomerular filtration rate and caused sodium retention. Rofecoxib caused a clinically insignificant and transient retention of sodium but not decline glomerular filtration rate[108] (Table 11).

3.4 Case reports of highly selective COX-2 inhibitors on renal functions

Apart from these clinical studies, there are some case reports of acute renal failure that associated with the use of highly selective COX-2 inhibitors. All cases occurred in patients with known renal risk factors for NSAIDs. Renal function of all patients returned to baseline within 3 days to 3 weeks after discontinuation of highly selective COX-2 inhibitors (Table 12).

Table10 : Comparison of renal effects between celecoxib and rofecoxib[104]

Reference	study design	Treatment	Number of patients	Results			
				systolic HT [a]	diastolic HT [b]	mean BP change(mmHg)	edema(%)
Whelton et al.	double blind randomized parallel study	celecoxib 200 mg/day	411	45 (11%)	6 (1.5%)	-1.1	4.9
		rofecoxib 25 mg/day	399	66 (17%)*	9 (2.3%)	5.9***	9.5**

a increase > 20 mmHg with an absolute value >140 mmHg

b increase > 15 mmHg with an absolute value >90 mmHg

* p = 0.032 vs celecoxib group

** p = 0.014 vs celecoxib group

*** p = 0.003 vs celecoxib group

Table 11: Comparison of renal effects between highly selective COX-2 inhibitors and non-selective NSAIDs

References	Study design	Treatment	Patients no.	Results	
				Decrease GFR	Electrolyte excretion
Rossat et al.[105]	randomized parallel design	C 200 mg BID C 400 mg BID N 500 mg BID Placebo	40 normotensive salt depleted subjects	No change in GFR with N decreased in GFR with C 400 mg on the first day	Decrease sodium excretion caused by C 200 mg and N
Whelton et al.[106]	cross over design	C 200 mg BID C 400 mg BID N 500 mg BID	29 healthy elderly	No change in GFR with C 200 mg decrease in GFR with N	Decrease sodium excretion caused by C 400 mg and N
Swan et al.[107]	cross over and parallel design	single dose R 250 mg single dose I 75 mg R 12.5 mg OD/BID I 50 mg TID	75 elderly, sodium restricted subject:	Mild decrease in GFR with single dose R and I	Decrease sodium and potassium excretion after a single high dose of R and I
Catella-Lawson et al.[108]	randomized parallel design	R 50 mg OD I 50 mg TID Placebo	36 elderly sodium loaded subjects	No change in GFR with R slight decrease with I	Decrease sodium excretion with R and I

C = celecoxib
N = naproxen
R = rofecoxib
I = indometacin

Table 12: Case reports of renal adverse events associated with highly selective COX-2 inhibitors therapy

Reference	Drug Dose (Duration)	Patients characteristic	Manifestration of nephrotoxicity	Outcomes after discontinuing COX-2 therapy
100	Celecoxib 200 mg/day 13 days	80 years old female with CAD, CRF,DM,HT,atrial fibrillation, neuropathy, anemia type IV renal tubular acidosis Cr 1.7-2.0 mg/dl	Cr 2.4 mg/dl, BUN 111 mg/dl, K 6.9 mEq/L, Na 140 mEq/L, HCO_3 13mEq/L, urine: few tubular cells and casts	One hemodialysis session. 4 days after celecoxib discontinued; volume status and K returned to baseline, Cr 1.9 mg/dl
100	Rofecoxib 25 mg/day 21 days	69 years old male with CAD, CRF, HT,DM, gout, anemia,neuropathy, peripheral vascular disease Cr 2.8-3.0 mg/dl	Cr 4.1 mg/dl, BUN 88 mg/dl K 5.6 mEq/L, Na 130 mEq/L, HCO_3 18 mEq/L, urine: few tubular cells and casts	3 days after rofecoxib and enalapril discontinued, intravenous furosemide given: volume status and K returned to baseline, 6 days later Cr 3 mg/dl
100	Celecoxib 200 mg/day 18 days	75 years old female with CRF, HT, DM, dementia, peripheral vascular disease Cr 1.4-1.8 mg/dl	Cr 5.6 mg/dl, BUN 83 mg/dl K 8.5 mEq/L, Na 132 mEq/L, HCO_3 12 mEq/L, urine: few tubular cells and white cells	One hemodialysis session 6 days after celecoxib discontinued; volume status and K returned to baseline, Cr 1.7 mg/dl

Reference	Drug Dose (Duration)	Patients characteristic	Manifestration of nephrotoxicity	Outcomes after discontinuing COX-2 therapy
100	Rofecoxib 50 mg/day 6 days	83 years old female with CAD, CRF,OA,hyperlipidemia, anemia Cr 1.4 mg/dl	Cr 3.5 mg/dl, BUN 94 mg/dl K 6.0 mEq/L, Na 129 mEq/L, HCO_3 17 mEq/L, urine: few hyaline casts	2 days after spironolactone, furosemide lisinopril and rofecoxib discontinued; volume status and K returned to baseline
100	Celecoxib 200 mg/day 12 days	69 years old female with CRF,DM, anemia, hyperlipidemia chronic atrial fibrillation, Cr 1.6-2.1 mg/dl	Leg edema and severe heart failure Cr 5.5 mg/dl, BUN 112 mg/dl K 7.3 mEq/L, Na 126 mEq/L, HCO_3 14 mEq/L, urine: few tubular cell casts	One hemodialysis session 8 days after celecoxib and enalapril discontinued; volume status and K returned to baseline, Cr 1.8 mg/dl
109	Celecoxib 400 mg/day 16 days	63 years old male with HT, CRF, CAD,left ventricular hypertrophy Cr 2.8 mg/dl	Ankle edema, hypertension Cr 4.9 mg/dl, BUN 73 mg/dl K 5.1 mEq/L	Recovered to baseline within 5 days after discontinued celecoxib, Cr 2.9 mg/dl
109	Celecoxib 400 mg/day 13 days	69 years old male with HT, CRF, CAD, DM,cardiomyopathy, Cr 3.5 mg/dl	Ankle edema, hypertension Cr 5.6 mg/dl, BUN 95 mg/dl K 5.4 mEq/L	Recovered to baseline within 7 days after discontinued celecoxib, Cr 3.3 mg/dl

Reference	Drug Dose (Duration)	Patients characteristic	Manifestration of nephrotoxicity	Outcomes after discontinuing COX-2 therapy
109	Rofecoxib 25 mg/day 14 days	73 years old female with CRF, DM,CAD, type 4 renal tubular acidosis	Dehydration, Cr 9.0 mg/dl, BUN 169 mg/dl, K 8.5 mEq/L	Recovered to baseline within 8 days after discontinued rofecoxib, Cr 2.0 mg/dl
110	Celecoxib(n = 2) Rofecoxib (n = 3) (0.5-3 weeks)	Mean age 63 years, hypertension(n =2), CHF(n = 2), mean GFR = 60 ml/min	Mean laboratory results ; Cr 2.8 mg/dl BUN 84 mg/dl, HCO_3 19 mEq/L K 5.1-6.4 mEq/L	All 5 patients recovered to baseline within 2-3 weeks after discontinued COX-2 inhibitions
111	Celecoxib 200 mg/day 5 days	52 years old male with cirrhosis, gout, COPD creatinine 1.1 mg/dl	Cr 9.7 mg/dl	Recovered to baseline after discontinued celecoxib
112	Rofecoxib 25 mg/day 2 days	49 years old male with CAD, renal insufficiency, Cr 1.6 mg/dl K 4.4 mEq/L,CrCl 76 ml/min	Cr 2.07 mg/dl	Recovered to baseline after discontinued rofecoxib
112	Rofecoxib 25 mg/day 5 days	43 years old male with renal transplant, Cr 2.1 mg/dl	Pitting edema, hemodialysis, Cr 6.2 mg/dl	Recovered to baseline after discontinued rofecoxib

Summarized on overall the effects of highly selective COX-2 inhibitors

As literatures review, the overall differences and similarities between highly selective COX-2 inhibitors and non-selective NSAIDs have described following in Figure 6. [20]

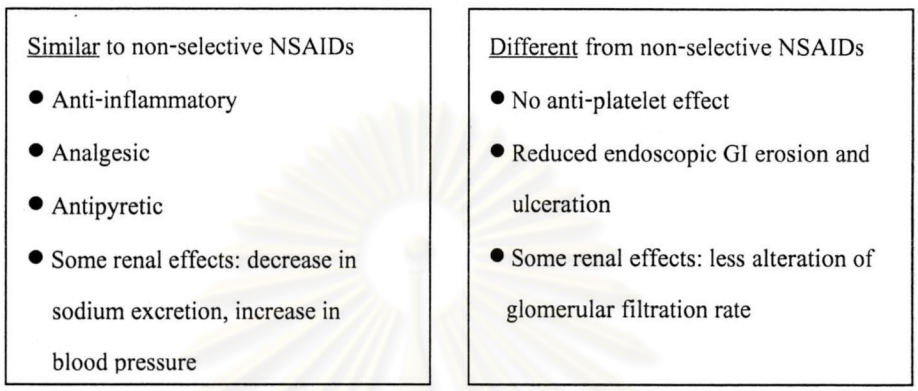

Figure 6: Differences and similarities between COX-2 inhibitors and non-selective NSAIDs [20]

1. Alteration in glomerular filtration rate (GFR)

Alteration in GFR causes primarily by COX-1. Data from clinical trials have confirmed these assumptions. In two clinical trials indicated that highly selective COX-2 inhibitors have similar effects on sodium excretion to non-selective NSIADs. In these studies highly selective COX-2 inhibitors did not affect GFR, whereas GFR was reduced in patients receiving therapy with non-selective NSAIDs.[106-107]

Although highly selective COX-2 inhibitors have less declined GFR than non-selective NSAIDs, but in patients with risk factors have reported acute renal failure. All renal functions recovered renal function after discontinuation of COX-2 inhibitors.[100, 109-112]

As mentioned above, it was hypothesized that highly selective COX-2 inhibitors can decline GFR but less than non-selective NSAIDs. Renal effects occurred in very small percentage of normal subjects but more significant percentage in high-risk patients. However, patients with multiple risk factors are rarely included in

clinical studies. A clinical study of patients with two risk factors, elderly patients on a salt-restricted diet demonstrated that rofecoxib decreased GFR by approximately 15%.[107] Some studies have suggested that highly selective COX-2 inhibitors may not cause a severe decline in renal functions as non-selective NSAIDs because subjects of these studies were not a multiple risk factors patients.[106,108]

2. Sodium retention and edema

The pattern of COX-2 expression in the kidney have suggested that this enzyme plays an important role in the regulation of water and electrolyte homeostasis under a variety of physiologic conditions whereas COX-1 seems to have a dominant role in hemodynamic regulation.[83-84, 86-88]

Highly selective COX-2 inhibitors have similar frequencies of edema to non-selective NSAIDs. In CLASS study, the incidence of edema was 2.8% for celecoxib and 3.5% for the other two NSAIDs (diclofenac and ibuprofen).[18] In the VIGOR trial, the incidence of edema was 3.4% for rofecoxib and 3.0% for naproxen.[19]

Moreover, peripheral edema is frequently seen in hypertensive patients due to increase blood pressure leads to greater loss of fluid into extravascular space. Renal factors that lead to hypertension, such as sodium retention may also lead to peripheral edema.[86]

A recent study compared between celecoxib 200 mg daily and rofecoxib 25 mg in more than 800 hypertensive patients. Higher incidence of edema occurred in rofecoxib when compared with celecoxib (9.5% and 4.9%).[104]

3. Hypertension

Arthritis and hypertension are overlapping diseases in the elderly. Use of nonsteroidal anti-inflammatory drugs in patients treated with antihypertensive medications can lead to induce blood pressure elevation.[37]

Highly selective COX-2 inhibitors also have been shown to increase blood pressure level[113] and more patients in the VIGOR trial developed hypertension in rofecoxib compared with naproxen. For rofecoxib, the mean increase in systolic blood pressure was 4.6 mmHg and the mean increase in diastolic blood pressure was 1.7 mmHg. In naproxen, the mean increase in systolic blood pressure was 1.0 mmHg and the mean increase in diastolic blood pressure was 0.1 mmHg. Incidence of hypertension was 8.0% for rofecoxib and 5.0% for naproxen.[19]

In CLASS study, incidence of hypertension was 1.7% for celecoxib group and 2.3% for the other two NSAIDs but mean change in blood pressure were not reported.[18] Comparison between celecoxib and rofecoxib in 810 older (≥ 65 years old) found that rofecoxib and celecoxib increased in systolic blood pressure (SBP) 17% and 11% respectively and diastolic blood pressure (DBP) was also increased in larger percentage of rofecoxib (2.3% and 1.5%).[104] Catella-Lawson et al. and Rossat et al. showed that COX-2 inhibitors caused transient sodium retention but did not lead to hypertension.[105,108]

In summary, the effect of COX-2 inhibitors on blood pressure is small. The incidence of hypertension appears to be similar to other NSAIDs but greater occurred in hypertensive patients. This suggested that patients with risk for hypertension should be monitored during treatment with these agents.[44]

4. Hyperkalemia

Hyperkalemia is uncommon side effects of NSAIDs therapy and in highly selective COX-2 inhibitors it has been rare event with no report cases.

Two recent studies in patients on salt restricted diet demonstrated that highly selective COX-2 inhibitors (either celecoxib or rofecoxib) decrease urinary potassium excretion but not occurred hyperkalemia.[105,107]

Drugs review

Celecoxib[16-17,31,71-72,114-116]

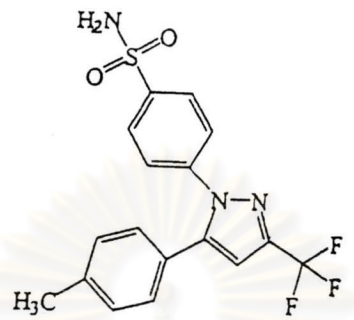

Figure 7: Chemical structure of celecoxib

Celecoxib (celebrex®; SC-58635; 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide) is the first highly selective COX-2 inhibitor that was approved by the United States Food and Drug Administration(US FDA) and Thailand Food and Drug Administration (Thai FDA) for (1) relief of sign and symptoms of OA and RA in adults(2) reduction of the number of adenomatous colorectal polyps and (3) management of acute pain and treatment of primary dysmenorrhea.

Pharmacology

Celecoxib is a selective inhibitor of the cyclooxygenase-2(COX-2) isoform of prostaglandin endoperoxide synthase (prostaglandin G/H synthase) and exhibit many of the pharmacologic actions of NSIADs including anti-inflammatory, analgesic and antipyretic activity. Celecoxib IC_{50} (concentrations that inhibit enzyme activity by 50%) for COX-1 and COX-2 are 15 and 0.04 μM respectively. This suggested that celecoxib has a 375 fold selectivity for COX-2.

Pharmacokinetic

1. Absorption

Celecoxib is well absorbed from the GI tract. The pharmacokinetic of celecoxib have been investigated in healthy volunteers. Peak plasma concentration (C_{max}) of 705 μg/L(1.85 μmol/L) was reached 2.8 hours(t_{max}) after a single 200 mg dose in volunteers under fasting conditions. C_{max} occurred between 2 and 4 hours after administration single oral 200 mg dose to healthy young volunteers. Steady state plasma concentrations are achieved within 5 days.

In elderly subjects (over 65 years old), 40% higher C_{max} and 50% higher AUC when compared in young individuals. Furthermore, peak plasma concentration and AUC values were higher in geriatric woman than geriatric men because of the lower body weight of these women.

The AUC of celecoxib has been reported approximately 47% lower in patients with GFR 35 to 60 ml/min than that seen in individuals with normal renal function.

2. Distribution

Distribution of celecoxib into body tissue and fluid has not been fully characterized. Celecoxib is 97% bound to plasma protein, principally albumin and to a lesser extent, α1-acid glycoprotein. The fraction of unbound drug remain essentially constant (mean 2.6% unbound).

The apparent volume of distribution at steady state of approximately 400 L, suggests extensive tissue distribution. The distribution of selective COX-2 inhibitors into the synovium may be important to determine the effectiveness. However, there are no data on distribution into synovial fluid of celecoxib.

3. Metabolism and elimination

Celecoxib is metabolized in the liver by cytochrome P450 system specifically CYP 2C9 into three inactive metabolites. Less than 2% is excreted unchanged in urine

and only 2.6% is excreted unchanged in feces. In vitro studies indicate that significant interactions may occur when celecoxib is administered with drugs that inhibit CYP 2C9. Celecoxib had significant hepatic metabolism, thus may be important in patients with hepatic disorder as albumin globulin and total protein decrease in patients with hepatic disease. These conditions leading to increase the plasma free fraction of celecoxib. It has been reported that in patients with mild and moderate (Child-Pugh class I and II) hepatic impairment, the AUC increased about 40 and 180% respectively compared with healthy control. In controlled clinical trials of celecoxib, the incidence of elevation of liver function tests was 6% for celecoxib and 5% for placebo, 0.2% of patients taking celecoxib and 0.3% of patients taking placebo had notable elevations of liver enzyme which resolved on cessation of treatment.

The plasma elimination half-life of celecoxib following oral administration of a single 200 mg under fasting condition is about 11 hours. The half life of celecoxib is prolonged in patients with renal or hepatic impairment and has been reported to be 13.1 hours in patients with chronic renal insufficiency and 11 or 13.1 hours in patients with mild or moderate hepatic impairment respectively.

Adverse drug reactions

Information on the safety of celecoxib has been obtained from clinical studies in about 8,000 patients (CLASS trial). Including patients with osteoarthritis and rheumatoid arthritis, 50 or 30% of these patients received the drug for at least 6 months or at least 1 year respectively but limited number of patients have received celecoxib for 2 years or longer.

- GI effects

Dyspepsia, diarrhea, abdominal pain, nausea or flatulence occurred in 8.8, 5.6, 4.1, 3.5 and 2.2% respectively. Anorexia, constipation, diverticulitis, dry mouth, dysphagia, esophagitis, gastritis, gastroenteritis, gastritis, gastroesophageal reflux, increase appetite, melena, stomatitis, taste perversion or vomiting has been reported in

0.1-1.9% of patients receiving celecoxib. Adverse GI effects reported in less than 0.1% of patients include intestinal obstruction, intestinal perforation, colitis with bleeding.

• Nervous system effects

Headache has been reported in about 16% of patients receiving celecoxib in clinical studies, whereas dizziness or insomnia occurred in 2 or 3% of patients respectively. Anxiety, asthenia, depression, migraine, nervousness or vertigo has been reported in 0.1-1.9% of celecoxib treated patients.

• Respiratory effects

Upper respiratory tract infection, sinusitis, pharyngitis or rhinitis has occurred in 8.1, 5, 2.3 and 2% respectively. Bronchitis, bronchospasm, cough, dyspnea, larngitis or pneumonia has been reported in 0.1-1.9% of patients.

• Cardiovascular effects

Peripheral edema has been reported in 2.1%. Angina pectoris, chest pain, coronary artery disorder, hot flushes, myocardial infarction, palpitation, tachycardia or aggravated hypertension has been reported in 0.1-1.9%.

• Dermatologic and sensitivity reactions

Rash occurred in 2.2% of patients receiving celecoxib. Adverse dermatologic effects occurring in 0.1-1.9% of patients receiving celecoxib include alopecia, dermatitis, dry skin, pruritis. Allergic reaction aggravated allergy, bronchospasm or generalized or facial edema has been reported in 0.1-1.9%. Erythema multiforme, exfoliative dermatitis, Steven-Johnson syndrome and toxic epidermal necrosis has been reported rarely in patients receiving celecoxib.

• Hematologic effects

Anemia has been reported 0.6% in celecoxib treated patients. Ecchymosis, epitaxis or thrombocytopenia has occurred in 0.1-1.9%. Agranulocytosis, aplastic anemia, pancytopenia and leukopenia has occurred in less than 0.1% of patients.

• Musculoskeletal effects

Back pain has been reported in 2.8% of patients receiving celecoxib. Arthralgia, leg cramps, myalgia, neck stiffness, tendinitis occurred 0.1-1.9% of patients receiving celecoxib.

• Hepatic effects

The incidence of borderline elevations in liver function test results was similar in patients receiving celecoxib or placebo (6, 5% respectively). Increased in SGOT (AST) or SGPT (ALT) occurred in 0.2 or 0.3%of patients receiving the drug or placebo respectively.

Drug interactions

Metabolism of celecoxib is mediated by the cytochromeP-450 (CYP) isoenzyme 2C9. Drugs that inhibit this enzyme (e.g., fluconazole, fluvastatin) may affect the pharmacokinetic of celecoxib. In addition, celecoxib also inhibit CYP 2D6 which drugs that were metabolized by this isoenzyme e.g., many tricyclic and other antidepressants may alter pharmacokinetic of celecoxib.

• Fluconazole

Results of clinical studies indicated that clinically important drug interactions might occur if celecoxib is administered with fluconazole consequently increase plasma concentration of celecoxib. This suggested that celecoxib therapy should be initiate at the lowest recommended dosage in patients receiving fluconazole.

• Warfarin

In one short term (7-day) pre-marketing study in healthy individuals, celecoxib 200 mg twice daily did not appear to alter the anticoagulant effect of warfarin 2-5 mg daily as determined by the prothrombin time (PT). However, during post-marketing surveillance bleeding complications associated with increases in PT were reported in some (mainly geriatric) patients receiving celecoxib concomitantly with warfarin. Therefore, patients receiving such concomitant therapy should be monitored for

change in anticoagulant activity (e.g., PT) particularly during the first few days after initiating therapy.

- Antacids

Administration of an antacid containing magnesium or aluminium with celecoxib decreased peak plasma concentration of celecoxib by 37% and the area under the plasma concentration-time curve (AUC) by 10%in clinical studies but these effects are not considered clinically important.

- Aspirin

Although celecoxib may be used with low doses of aspirin, concomitant use of the two nonsteroidal anti-inflammatory agents (NSAIDs) may increase the incidence of GI ulceration.

- Angiotensin converting enzyme inhibitors (ACEIs)

Experience with other NSAIDs suggests that change in blood pressure response when celecoxib is administered concomitantly with an ACEIs. Celecoxib may reduce the blood pressure response to ACEIs.

Naproxen[115]

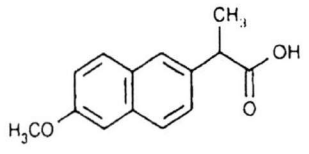

Figure 8: Chemical structures of naproxen

Naproxen, a propionic acid derivative, is a nonselective NSAIDs. The commercially available as the acid and as the sodium salt (naproxen and naproxen sodium). In this study used acid form (naproxen).

Naproxen are used to relieve mild to moderately severe musculoskeletal and soft tissue inflammation including rheumatoid arthritis, osteoarthritis, alkylosing spondilitis, tendinitis, bursitis and acute gouty arthritis.

Pharmacology

Naproxen has pharmacological actions similar to other nonselective NSAIDs. The drug exhibits anti-inflammatory, analgesic and antipyretc activity. Naproxen inhibits the synthesis of prostaglandins by inhibiting both cyclooxygenase-1 and cyclooxygenase-2.

Pharmacokinetic

Pharmacokinetics of naproxen have not been determined in patients with renal insufficiency and children younger than 5 years of age.

1. Absorption

In several studies, following administration single dose 500 mg of naproxen in healthy adults mean peak plasma concentration of the drug range from 62-96 μg/ml

and occurred at 1.5-2 hours. Steady state plasma concentrations of naproxen are achieved within 4-5 days. The duration of action is about 7-12 hours.

2. Distribution

The volume of distribution of naproxen is 0.16 L/kg. Naproxen is more than 99% bound to plasma proteins. In patients with severe liver disease, binding of naproxen to serum proteins was decreased compared to healthy adults, the decreased binding may have accounted for an increase in metabolism and apparent volume of distribution of the drug observed in these patients.

3. Metabolism and elimination

About 30% of naproxen is metabolized in the liver to 6-desmethynaproxen which is inactive. Approximately 95% of the drug is excreted in urine as unchanged naproxen and 6-desmethylnaproxen. In healthy adults, the plasma half-life of naproxen ranges from 10-20 hours and increase in patients with renal failure. The manufacturers state that the plasma half-life of naproxen is about 13 hours.

Adverse drug reaction

- GI effects

The mainly adverse reactions to naproxen involve the GI tract. Constipation, heartburn, abdominal pain and nausea occur in about 3-9% of patients. Less frequently, dyspepsia, diarrhea, stomatitis, vomitting, anorexia, colitis and flatulence.

- Nervous system effects

Adverse nervous system effects of naproxen include headache, drowsiness and dizziness occur in 3-9% of patients. Vertigo, lightheadedness, mental depression, nervousness, irritability, fatigue, malaise, insomnia may also occur.

• Hematologic effects

Adverse hematologic effects of naproxen include thrombocytopenia, leukopenia, granulocytopenia and eosinophilia. Naproxen can inhibit platelet aggregation and may prolong bleeding time. The frequency of prolong bleeding time may be greater in children than in adults.

• Hepatic effects

Jaundice (including cholestatic jaundice which clear promptly when naproxen was discontinued). Abnormal liver function test results including mild and generally transient increases in serum alkaline phosphatase have occurred in some patients. Borderline elevation of one or more liver function test results may occur in up to 15% of patients treated with NSAIDs.

• Other adverse effects

Pruritis, skin eruption or rash and ecchymosis occur frequently during naproxen administration. Sweating, photosensitive dermatitis have also occurred.

Peripheral edema has also occurred in patients receiving naproxen. Congestive heart failure, palpitation, tachycardia and dyspnea have occurred less frequently. Increases in blood pressure have been reported in hypertensive patients receiving naproxen. Thirst, alopecia, myalgia, muscle weakness and cramps have also been reported during naproxen therapy

Drug interactions

Because naproxen is highly protein bound, other protein-bound drugs such as oral anticoagulants, hydantoins, salicylates, sulfonamides and sulfonylureas. Although no clinically important drug interactions have been reported, patients receiving naproxen with of these drugs should be observed for adverse effects.

• Anticoagulants and thrombolytic agents

Administration of naproxen with warfarin results in a slight increase in free warfarin in serum but does not affect the hypoprothrombinemic effect of warfarin.

Because naproxen may cause GI bleeding and may inhibit platelet aggregation, the drug should be used with caution in patients receiving any anticoagulant or thrombolytic agents.

- Salicylates

Administration of aspirin with naproxen may decrease plasma naproxen concentrations, presumably by displacing naproxen from binding sites result in increases metabolism and excretion of naproxen. Although the clinical importance of this interaction has not been established. The manufacturers recommend that naproxen not be used in conjunction with salicylates.

- Methotrexate

Administration of NSAIDs concomitantly with methotrexate (principally high-dose therapy) in patients with various malignant neoplasms or rheumatoid arthritis. The toxicity was associated with elevated and prolonged blood concentration of methotrexate. The exact mechanism of the interaction remains to be established but it has been suggested that NSAIDs may inhibit renal elimination of methotrexate by decreasing renal perfusion via inhibition of renal prostaglandin synthesis or by competing for renal elimination.

- Other drugs

In patients with rheumatoid arthritis, concomitant administration of naproxen and prednisolone resulted in increased plasma concentration of free prednisolone. It was suggested that prednisolone may have a steroid sparing effect.

In a controlled study in healthy adults and geriatric patients, naproxen caused a decrease in furosemide-induced urine and sodium output in both groups of patients. It was suggested that NSAIDs not be used during diuretic therapy for cardiac failure.

Concomitant use of NSAIDs like naproxen and angiotensin converting enzyme inhibitors (ACEIs) may potentiate renal disease state.