CHAPTER I

INTRODUCTION

Background and rational

Musculoskeletal problems e.g., osteoarthritis (OA), rheumatoid arthritis (RA), crystal induced arthritis, tendinitis and muscle pain are the most common causes of disability.[1] Treatment of these problems focuses on reducing pain, minimizing functional limitation and avoiding the adverse effects associated with pharmacotherapy.[2]

The common pharmacotherapy widely used for the treatment of musculoskeletal problems is nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs have anti-inflammatory, analgesic and antipyretic effects therefore they have been shown to benefit in patients with OA and RA.[3] Moreover, NSAIDs are widely used for antipyretic, sport injuries and acute pain conditions. However, these drugs have some distinctive side effects. Gastrointestinal tract injuries such as dyspepsia, upper gastrointestinal bleeding (UGIB) and perforation are the most common side effects of NSAIDs therapy whereas renal complications occur in small proportion of patients treated with NSAIDs.[4]

Principle mechanism of NSAIDs is shown to be an inhibition of cyclooxygenase (COX). The COX enzyme catalyzes the initial steps in the conversion of arachidonic acid to various prostaglandins (PGs) and thromboxane (TxA).[5] Prostaglandins have major roles on renal functions in patients with decrease effective volume e.g., elderly patients, hypertension (HT), cirrhosis, coronary artery disease (CAD), diabetes mellitus (DM), chronic renal failure (CRF) and renal insufficiency.[6-7] Therefore, these conditions appear to be a potential renal risk factors of NSAIDs. Renal complications from NSAIDs include acute hemodynamically mediated renal

insufficiency, fluid and electrolyte disturbance, hyperkalemia, interstitial nephritis and papillary necrosis[8-10]

Until recently, it was demonstrated that the COX enzyme exists as two isoforms. COX-1, is constitutively expressed as house keeping in various tissues such as gastrointestinal, kidney and platelet. COX-2 is inducible isoenzyme which regulates response to stress and inflammatory stimuli in many tissues. The house keeping theory has shown that the inhibition of COX-1 and COX-2 by NSAIDs causes efficacy by inhibiting COX-2 and causes side effects by inhibiting COX-1.[11-12] This knowledge is the major cause for the development of highly selective COX-2 inhibitors which inhibit COX-2 while sparing COX-1 at therapeutic doses to receive fewer side effects medication than non-selective NSAIDs.[13]

Two highly selective COX-2 inhibitors, celecoxib and rofecoxib have become available and approved for use in various clinical conditions in Thailand. Initial clinical data indicated that these agents have comparable efficacy to non-selective NSAIDs.[14-17] The Celecoxib Long Term Arthritis Safety Study (CLASS) and Vioxx Gastrointestinal Outcomes Research (VIGOR) trial showed that celecoxib and rofecoxib reduced ulcerogenic potential moreover have no effect on platelet aggregation.[18-19]

Regarding renal effects of highly selective COX-2 inhibitors, this question has remained unclear. It was hoped that highly selective COX-2 inhibitors might have fewer renal side effects than non-selective NSAIDs. Available data on renal effects of highly selective COX-2 inhibitors are conflicting due to differences in patient's numbers, baseline patient characteristics, dose and duration of drug treatments. The results from recent studies support the belief that highly selective COX-2 inhibitors may affect blood pressure, electrolyte excretion while less decreasing the glomerular filtration rate (GFR) rather than non-selective NSAIDs.[20]

Recent evidences support a role of COX-1 and COX-2 on renal functions that electrolyte excretion in healthy human can be regulated by COX-2 while GFR can be

regulated by COX –1. Therefore inferred that use of highly selective COX-2 inhibitors may spare the kidneys.[21]

A retrospective study at Rajavithi Hospital in Thailand found that elderly patients were the most common populations received celecoxib for treatment OA, muscle pain and RA respectively. These populations also had many risk factors such as HT, renal insufficiency and DM, which affected renal functions during the treatment of highly selective COX-2 inhibitors.[22] However, there were few studies which determine the renal effects of highly selective COX-2 inhibitors in these populations.

Therefore, the purpose of this study was to investigate renal effects between celecoxib which is the first highly selective COX-2 inhibitor and naproxen which is non-selective NSAIDs. The study was conducted in elderly patients with underlying diseases such as HT, renal insufficiency and DM 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.

Objectives

1. To compare renal effects between celecoxib and naproxen in elderly patients.
2. To examine other adverse effects between celecoxib and naproxen in elderly patients.

The significance of the study

This study will provide the answer of renal effects and other adverse effects of celecoxib and naproxen in elderly Thai patients.