CHAPTER II

REVIEW OF RELATED LITERATURE

Conventional nonsteroidal anti-inflammatory drugs (NSAIDs), widely used for postoperative pain management, are associated with adverse events that limit their clinical utility. Acute NSAID administration increases the risk of upper gastrointestinal (GI) bleeding, acute renal failure, and excessive intra- or postoperative bleeding. Hemorrhagic lesions and ulcers can occur within a few days of conventional NSAID treatment, and patients with coagulation abnormalities or those receiving antiplatelet agents or anticoagulants are high risk of NSAID-related hemorrhage. The risk of excessive intra- or postoperative bleeding may preclude the use of NSAIDS during surgical procedures in which optimal homeostasis is critical.[10]

PARECOXIB is a highly selective nonsteroidal cyclooxygenase-2 (COX-2) inhibitor undergoing clinical development with intended use perioperative as an analgesic agent[11]. Parecoxib sodium is prepared dosage of 40 mg. in dry powder and 2 cc. of NSS for solvent. The onset of action is 7-13 minutes after administration; a clinical analgesic effect is 23-29 minutes; the peak effect of action is 2 hours and duration of action is 6-12 hours. The analgesic and anti-inflammatory effects of cyclooxygenase (COX)-2-specific inhibitors and conventional NSAIDs are mediated by COX-2 inhibition. Conventional nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit COX-1, resulting in upper GI and hematological adverse effects, whereas COX-2-specific inhibitors spare COX-1 At therapeutic concentrations and, therefore, have a superior safety and tolerability profile.[10]Single intravenous doses of parecoxib sodium, 20 mg and 40 mg, have comparable analgesic effects and are well tolerated after laparotomy surgery. Parecoxib sodium appears to be as effective as intravenous ketorolac, 30 mg, and superior to intravenous morphine, 4 mg.[10] The 40-mg dose was comparable to ketorolac 60 mg on most measures of analgesia but had a longer duration of action.[12, 13] In the post surgical orthopedic pain model, intravenous parecoxib sodium 40 mg is as effective as ketorolac 30 mg and is more effective than morphine 4 mg and therefore has potential widespread utility in acute postoperative

pain management.[14] About patients undergoing major gynecologic surgical procedures, intravenous parecoxib (20 or 40 mg) was effective in decreasing the PCA opioid requirement after lower abdominal surgical procedures. However, it failed to improve pain management or reduce opioid-related side effects in the early postoperative period.[15]

Parecoxib sodium is well tolerated after dental, gynaecological or orthopaedic surgery. The most common adverse events irrespective of treatment (parecoxib, ketorolac or placebo) after dental surgery were nausea, alveolar osteitis, dizziness and headache. Nausea, abdominal pain, headache, abdominal fullness, dizziness, back pain, fever, hypoactive bowel sounds, vomiting, tachycardia, somnolence, abnormal breath sounds and pruritus occurred in greater than 10% of parecoxib recipients after gynaecological surgery. Similar results were seen in placebo recipients.[16] Multiple dose administration of parecoxib sodium is safe and well tolerated in healthy elderly subjects, with a decreased risk of gastroduodenal mucosal injury compared with ketorolac.[17]

About renal toxicity, caution should be used when initiating treatment with parecoxib in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with parecoxib. Caution is also recommended in patients with pre-existing renal disease. Even though, pharmacokinetically, there was no difference in excretion, in patients with severe renal disease treatment with parecoxib should be initiated with caution. Close monitoring of the patient's renal function is advisable. Acute renal failure has been reported through post-marketing surveillance in patients receiving parecoxib. On the basis of pharmacokinetics, no dosage adjustment is necessary in patients with mild to moderate (creatinine clearance of 30-80 mL/min) or severe (creatinine clearance < 30 mL/min) renal impairment. However, caution should be observed in patients with severe renal impairment or patients who may be predisposed to fluid retention.[18]

Postsurgical pain has commonly been managed with opioid analgesics alone. Although effective, opioids (e.g. morphine) are associated with adverse effects such as respiratory depression, sedation, nausea, vomiting, constipation, and intestinal ileus. The

availability of an effective, but safer analgesic, that would be co-administered and reduce the amount of opioids used, would therefore be an advantage. Multimodal analgesia was applied to acute postoperative pain because of reduction doses of each analgesic, improving antinociception (due to synergistic, additive effects), and may reduce severity of side effects of each drug. So this study will show the advantage of parecoxib sodium in postoperative analgesia.