# CHAPTER II

## REVIEW OF LITERATURE

### Review of Naproxen

### Physico-chemical Properties (1, 3, 8)

Naproxen is a naphthalene derivative with a propionic acid side chain. It's chemical name is (+)-2-(6-methoxy-2-naphthyl) propionic acid or d-2-(6'-methoxy-2'-naphthyl) propionic acid.

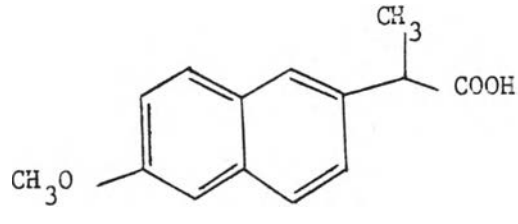


Figure 1 Structural formula of naproxen

Empirical formula : $C_{14}H_{14}O_3$

Molecular weight : 230.27

Description : It is an odorless, white to off-white crystalline powder.

Solubility : Practically insoluble in water, soluble 1 in 25 of alcohol, 1 in 15 of chloroform, 1 in 40 of ether, and 1 in 20 of methyl alcohol.

Melting point : about 156 °C

Mechanism of Action (1, 4)

Naproxen is an nonsteroidal-antiinflammatory drug (NSAID) which had an anti-inflammatory, analgesic, and antipyretic effects. Like the other NSAIDs, naproxen has been shown to inhibit specifically cyclooxygenase, the enzyme responsible for a step in the arachidonic cascade, thus limiting production of prostaglandins in all tissues. Many studies in animals indicated that naproxen inhibited prostaglandins synthesis, for example, PGE, PGF in full-term pregnant rat uterus (9), $PGF_{2\alpha}$ in rabbit tissues (10). Furthermore, Crook et al. (11) has been reported that naproxen inhibited $PGE_2$ synthesis in human rheumatoid synovial microsomes and Tomlinson et al. (1) found a positive correlation between the inhibition of prostaglandin synthesis in vitro and in vivo anti-inflammatory effect which may be related to its ability to inhibit the biosynthesis of prostaglandins.

Additionally, naproxen has been shown to inhibit lysosomal enzyme and chemotaxis of PMNs which concerning inflammatory process.

Adverse Drug Reaction

Effect on gastrointestinal tract (1)

Like other NSAIDs, the gastrointestinal complaints of naproxen have been recorded in many investigations. They have been frequently associated with abdominal discomfort and pain, indigestion, nausea, diarrhea, stomatitis, constipation and heartburn. Naproxen appeared to have less adverse effect on the human gastric mucosa than aspirin when given at the same dose used in the treatment of rheumatic disorders.

In gastroscopy study, naproxen 250 mg. twice daily caused less acute pathology of gastric mucosa than 4.8 g. daily of aspirin in 12 subjects whom without recent history of gastrointestinal complaints (12). Eventhough it had the effect on gastric mucosa, rare events on gastrointestinal bleeding, hematemesis, and peptic ulceration have been occured. In comparison with other NSAIDs, naproxen at 250 mg. twice daily has been shown to be similar to ibuprofen, fenoprofen and ketoprofen (13) but less gastrointestinal upset than indomethacin 100 mg. to 150 mg. daily in patients with rheumatoid arthritis or osteoarthritis (14).

### Effect on central nervous system

The central nervous system adverse effect of naproxen were headache, vertigo, drawsiness, inability to concentrate, and insomnia but fewer effect than aspirin or indomethacin (1).

### Other effects

Some aspirin-sensitive patients may be sensitive to naproxen such as skinrash because of the same action on prostaglandins (1, 4). The prolongation of bleeding time was found in subjects who received naproxen but less effect than aspirin. Also for the evaluations of liver function tests such as SGOT and SGPT may be occured but in a few cases.

## Pharmacokinetics

### Animal Studies

From the result of Runkel et al. (15), maximum levels of radioactivity were achieved in 10-20 minutes in the rat and in 1-2

hours in the dog and the minipig after oral administration. Studies performed in beable dog by Runkel et al. (16) indicated that naproxen was rapidly absorbed after oral administration. In different animal species, the half-life of naproxen varied from 1.9 hours in the rhesus monkey to 35 hours in the dog (15, 16). Runkel et al. (15) reported that there was very little $^{3}H$-labeled naproxen remained in the tissue analyzed 24-hour after oral administration of the radioactive dose in the rat, that was approximately 0.01% was found in the spleen and heart, and 0.05% was found in the GI tract. Naproxen has a relatively small volume of distribution which indicates that a large fraction of the drug is held in the central circulatory system. The range of volume of distribution in different animal species was 0.09 l/kg. in man to 0.18 l/kg. in the rodent (16). Like other NSAIDs, naproxen has high degree of protein binding to plasma, about 99% which probably result in low volume of distribution (16). Naproxen was largely biotransformed in animals and the metabolites varied in different species. Thompson and Collins (1) reported that the pattern of biotransformation in the rat and the pig resembled to that in the human. The majority of $^{3}H$-labeled naproxen was excreted in the urine and about 1 to 5% in the feces.

Human studies

The pharmacokinetics of naproxen after oral administration in human were reported by several investigations (15, 17-21). Runkel et al. (15) showed that naproxen was rapidly absorbed and it produced peak plasma level in 2 hours. Naproxen also readily absorbed rectally from suppositories (17). The study of 250 mg. naproxen in fasted and non-fasted subjects indicated that the absorption rate occured more rapidly in fasted

than in non-fasted subjects but the amount of naproxen absorbed was not significantly different (1, 18). Additionally, antacid compounds concomitantly administered with naproxen affected the absorption of naproxen, for example, the absorption rate of naproxen was enhanced by concomitant administration of sodiumbicarbonate, but was reduced by concomitant administration of magnesium oxide or aluminium hydroxide (1, 22).

The volume of distribution in human was about 0.09 l/kg. and plasma protein binding was about 99% (15, 16). Naproxen crossed the placental barrier within 20 to 30 minutes after administering orally to pregnant women and appeared in the milk of lactating women at approximately 1% of the concentration in the maternal plasma (1). About 94% of the injected radio-labelled naproxen was excreted in the urine and only 0.5 to 2.5% was found in feces (1, 16). 70% of the dose was eliminated either as unchanged drug (10%) or as conjugated naproxen (60%) and about 28% of the dose was excreted as demethyled naproxen (15, 16). The plasma half-life of naproxen after oral administration of single or multiple doses or single intravenous dose ranged between 12 to 15 hours (18, 23).

## Therapeutic efficacy

### Rheumatoid arthritis

Controlled studies of naproxen have demonstrated that naproxen 500 mg. or 750 mg. daily, indomethacin 150 mg. daily, ibuprofen 2.4 g. daily, fenoprofen 2.4 g. daily, and aspirin 3.6-4.8 g. daily were equally effective in rheumatoid arthritis patients (1, 2). However, the less frequency of side effects treated with naproxen was observed.

Acute gout

The acute gout patients showed a good response to naproxen at a dose of 600 mg followed by 300 mg every 8 hours or 750 mg followed by 250 mg every 8 hours by reduction in pain and swelling (1).

Analgesic effect

Naproxen in a single oral dose of 400 to 600 mg has been shown to be an effective analgesics in patients with severe or moderate postoperative pain resulting from orthopaedic, dental and other surgical procedure (1).