APO - NAPRO-Na *Apotex*

Naproxen Sodium **Analgesic-Anti-inflammatory**

Pharmacology: Naproxen sodium has demonstrated analgesic, anti-inflammatory and antipyretic properties in human clinical studies and in classical animal test systems. It exhibits an anti-inflammatory effect even in adrenalectomized animals and therefore its action is not mediated through the pituitary adrenal axis. It is not a corticosteroid. It inhibits prostaglandin synthetase, as do certain other nonsteroidal analgesic/anti-inflammatory agents. As with other agents, however, the exact mechanism of its anti-inflammatory and analgesic actions is not known.

Blood loss and gastroscopy studies with normal volunteers showed that daily administration of 1100 mg of naproxen sodium casued significantly less gastric bleeding and erosion than 3250 mg of ASA.

At the recommended dosage, the analgestic effect of naproxen sodium was shown to be comparable to that observed using 650 mg of ASA. The analgesic effect is obtained within 1 hour and can last at least 7 hours.

Naproxen sodium is freely soluble in water and is completely absorbed from the gastrointestinal tract. Plasma levels are obtained in patients within 20 minutes and peak level in 1 hour. It is extensively bound to plasma protein and has a plasma half-life of approximately 13 hours. The preferred route of excretion is via the urine with only 1% of the dose excreted in the feces.

Indications: For the relief of mild to moderately severe pain accompanied by inflammation in conditions such as musculoskeletal trauma and postdental extraction. Also indicated for the relief of pain associated with post partum cramping and dysmenorrhea.

Contraindications: Peptic ulcer or active inflammatory diseases of the gastrointestinal system.

Known or suspected hypersensitivity to the drug. Naproxen sodium should not be used in patients in whom acute asthmatic attacks, urticaria, rhinitis or other allergic manifestations are precopitated by ASA or other nonsteroidal anti-inflammatory agents. Fatal anaphylactoid reations have occurred in such individuals.

Warnings: Peptic ulceration, perforation and gastrointestinal bleeding, sometimes severe and occasionally fatal have been reported during therapy with nonsteroidal anti-flammatory drugs (NSAIDs) including naproxen sodium.

Naproxen sodium should be given under close medical supervision to patients prone to gastrointestinal tract irritation particularly those with a history of pepic ulcer, divericulosis or other inflammatory disease of the gastrointestinal tract. In these cases the physician must weigh the benefits of treatment against the possible hazards.

Patients taking any NSAID including this drug should be instructed to contact a physician immediately if they experience symptoms or signs suggestive of peptic ulceration or gastrointestinal bleeding. These reactions can occur without warning symptons or signs and at any time during the treatment.

Elderly, frail and debilitated patients appear to be at higher risk from a variety of adverse reactions from NSAIDs. For such patients, consideration should be given to a starting dose lower than usual, with individual adjustment when necessary and under close supervision (See Precautions).

Pregnancy and Lactation: The safety of this drug in pregnancy and lactation has not been established and its use during these events is therefore not recommended. Use of NSAIDs at about 20 weeks gestation or later in pregnancy may cause foetal renal dysfunction leading to oligohydramnios and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Reproduction studies have been performed in rats, rabbits and mice. In rats, pregnancy was prolonged when naproxen sodium was given before the onset of labor; when it was given after the delivery process had begun, labor was protracted. Similar results have been found with other NSAIDs and the evidence suggests that this may be due to decreased uterine contractility resulting from the inhibition of protaglandin synthesis. Moreover, because of the known effect of drugs of this class on the human fetal cardiovascular system (Closure of ductus arteriosus) use during late pregnancy should be avoided.

The naproxen anion readily crosses the placental barrier. It has been found in the milk of lactating women at a concentration approximately 1% of that found in the plasma.

Precautions: Naproxen sodium should not be used concomitantly with the related drug naproxen since they both circulate in plasma as the naproxen anion.

Geriatrics: One study indicated that after the administration of naproxen, although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly. The implication of this finding for naproxen sodium dosing is unknown, but caution is advised when high doses are required. As with other drugs used in the elderly, it is prudent to use the lowest effective dose.

Gastrointestinal: If peptic ulceration is suspected or confirmed, or if gastrointestinal bleeding or perforation occurs naproxen sodium should be discontinued, an appropriate treatment instituted and patient closely monitored.

There is no definitive evidence that the concomitant administration of histamine H2-receptor antagonists and/or antacids will ither prevent the occurrence of gastrointestinal side effects or allow continuation of naproxen sodium therapy when and if these adverse reactions appear.

Naproxen sodium should be given under close supervision to patients prone to gastrointestinal tract irriation: in patients with a history of peptic ulcer, or in patients with diverticulosis. Gastrointestinal bleeding, sometimes severe and occasionally fatal, and peptic ulcer have occurred in patients receiving naproxen.

Renal Function: As with other NSAIDs, long-term administration of naproxen to animals has resulted in renal papiltary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to the reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of a NSAID may cause a dose-dependent reduction in prostagtandin formation and may precipiate overtrenal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, extracellular volume depletion, sodium restrictions, heart lailure, liver dyfunction, those taking diuretics and the elderly. Discontinuation of non steroidal anti- inflammatory therapy is typically followed by recovery to the pretreatment state.

Naproxen sodium and its metabolites are eliminated primarily by the kidneys, therefore, the drug should be used with great caution in patients with significantly impaired renal function. In these cases lower doses of naproxen sodium should be anticipated and patients carefully monitored.

During long-term therapy kidney function should be monitored periodically. In clinical trials a few patients developed mild elevations in BUN. The significance of this is unknown.

Naproxen sodium should not be used chronically in patients having baseline creatinine less than 20 mL/min.

Hepatic Function: As with other NSAIDs, borderline elevations of one or more liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. A patient with symptoms and/or signs suggesting liver dysfunction or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hapatic reaction while on therapy with this drug. Severe hepatic reactions including jaundice and cases of fatal hepatitis have been reported with this drug as with other NSAIDs . Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, if systemic manifestations occur (e.g. eosinophilia, rash, etc.), this drug should be discontinued.

During long-term therapy, liver function tests should be monitored periodically. If this drug is to be used in the presence of impaired liver function, it must be done under strict observation.

Chronic alcoholic liver disease and probable also other forms of cirrhosis reduce the total plasma concentration of naproxen, but the plasma concentrating of unbound naporxen is increased. The implication of this finding of naproxen sodium dosing is unknown, but caution is advised when high doses are required. It is prudent to use the lowest effective dose.

Fluid and Electrolyte Balance: retention and edema have been observed in patient treated with naproxen sodium. Therefore, as with many other NSAIDs, the possibility of precipitating congestive heart failure in elderly patients or those with compromised cardiac function should be born in mind. Naproxen sodium should be used with caution in patient with heart failure, hypertension or other conditions predisposing to fluid retention.

Serum electrolytes should be monitored periodically during long-term therapy, especially in those patients at risk.

Each naproxen sodium tablet contains approximately 25 mg of sodium. This should be considered in patients whose overall intake of sodium must be markedly restricted. Although sodium retention has not been reported in metabolic studeies, the drug should be used with caution in patients with fluid retention, hypertension or heart failure.

Hematology: Drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to some degree; therefore, patients who may be adversely affected by such an action should be carefully observed when naproxen sodium is administered.

Blood dyscrasias associated with the use of NSAIDs are rare, but could be with severe consequences.

Patients with initial hemoglobin values of 10 g or less who are to receive long-term therapy should have hemoglobin values determined frequently.

Infection: The anti-inflammatory, antipyretic and analgesic effects of naproxen sodium may mask the usual signs of infection and the physician should be alert for development of infection in patients receiving naproxen sodium.

Ophthalmology: Because of adverse eye findings in animal studies with drugs of this class it is recommended that ophthalmic studies be carried out within a reasonable period of time after starting therapy and at periodic intervals thereafter if the drug is to be used for an extended period of time.

CNS: Caution should be exercised by patients whose activities require alertness if they experience drowsiness, dizziness, vertigo or depression during therapy with the drug.

Hypersensitivity: Anaphylactoid reactions to naproxen or naproxen sodium, whether of the true allergic type or the pharmacologic idiosyncratic (e.g. ASA syndrome) type, usually but not always occur in patients with a known history of such reactions. Therefore, careful questioning of patients for such things as asthma, nasal polyps, urticaria and hypotension associated to NSAIDs before starting therapy is important. In additional, if such symptoms occur during therapy, treatment should be discontinued.

Cardiovascular Function: It is possible that patients with questionable or compromised cardiac function may be at greater risk when taking naproxen sodium.

Children: Naproxen sodium is not recommended in children under 16 years of age because the safety and dose schedule have not been established in this ago group.

Drug Interactions: The naproxen anion may displace from their binding sites other drugs which are also albumin-bound and may lead to drug interactions. For example, in patients receiving bishydroxycoumarin or warfarin, the addition of naproxen sodium could prolong the prothrombin time. These patients should, therefore, be under careful observation. Similarly, patients receiving naproxen sodium and a hydantoin, sulfonamide or sulfonamide or sultonylurea should be observed for signs of toxicity of these drugs.

The natriuretic effect of furosemide has been reported to be inhibited by some drugs of this class. Inhibition of renal lithium clearance leading to increases in plasma lithium concentrations have also been reported.

Naproxen sodium and other NSAIDs can reduce the antihypertensive effect of propranolol and other beta-blockers.

The rate of absorption of naproxen sodium is altered by concomitant administration of antacids but its not adversely influenced by the presence of food. Probenecid given concurrently increases naproxen anion plasma levels and extends its plasma half-life significantly.

Caution is advised in the concomitant administration of naproxen souium and methotrexate since naproxen and other NSAIDs have been reported to reduce the tubular secretion of methotrexate in an animal model, thereby possibly enhanciing its toxicity.

Laboratory Tests: Naproxen sodium decreases platelet aggregation and prolongs bleeding time. This effect should be kept in mind when bleeding times are determined.

The administration of naproxen sodium may result in increased urinary values of 17-ketogenic steroids because of an interaction between the drug and/or its metabolites with m-dinitrobenzene used in this assay. Although 17-hydroxycorticosteroid measurements (Porter-Silber test) do not appear to artificially altered, it is suggested that naproxen therapy be temporarily discontinued 49 hours before adrenal function tests are performed.

The drug may interfere with some urinary assays of s-hydroxy indoleacetic acid (SHIAA).

Adverse Effects: The most common adverse reactions encountered with NSAIDs are gastrointestinal, of which peptic ulcer, with or without bleeding, is the most severe. Fatalities have occurred on occasion, particulary in the elderly.

Adverse reactions reported in controlled clinical trials are listed below:

(1) Denotes incidence of reported reaction between 3% and 9%.

(2) Denotes incidence of reported reaction between 1% and 3%. Reactions occurring in less than 1% of the patients during controlled clinical trials and through voluntary reports since marketing are unmarked.

Gastrointestinal: Heartburn (1), constipation (1), abdominal pain (1), nausea (1), diarrhea (2), dyspepsia (2), stomatitis (2), diverticulitis (2), gastrointestinal bleeding, hematemesis, melena, peptic ulceration with or without bleeding and/or perforation, vomiting, ulcerative stomatitis.

CNS: head (1), dizziness (1), drowsiness (1), lightheadedness (2), vertigo (2), depression (2), and fatigue (2), occasionally patients had to discontinue treatment because of the severity of some of these complaints (headache and dizziness). Other adverse effects were inability to concentrate, malaise, myalgia, insomnia and congitive dysfunction (i.e. decreased attention span, loss of short-term memory, difficulty with calculations).

Dermatologic: pruritis (1), acchymoses (1), skin eruptions (1), sweating (2), purpura (2), alopecia, urticaria, skin rash, erythema multiforme, Stevens-Johnson syndrome, epidermal necrolysis, photosensitive dermatitis, exfoliative dermatitis and erythema nodosum.

Cardiovascular: Dyspnea (1), peripheral edema (1), palpitations (2), congestive heart failure and vasculitis.

Special Senses: Tinnitus (1), hearing disturbances (2), hearing impariment and visual disturbances.

Hematologic: eosinophilia, granulocytopenia, leukopenia, thrombocytoperia, aplastic anemia .

Renal: glomerular nephritis, hematuria, interstitial nephritis, nephrotic syndrome, nephropathy and tubular necrosis.

Hepatic Changes: abnormal liver function tests, jaundice, cholesstasis and hepatitis.

Others: thirst (2), muscle weakness, anaphylactoid reactions, menstrual disorders, pyrexia (chills and fever), angioneurotic edema, hyperglycemia, hypoglycamia, hematuria, hepatitis and eosincphilic pneumonitis.

Overdose: Symptoms and Treatment: Significant overdosage may be characterized by drowsiness, heartburn, indigestion, nausea or vomiting. No evidence of toxicity or late sequelae have been reported 5 to 15 months after ingestion for 3 to 7 days of doses of up to 3000 mg of naproxen. One patient ingested a single dose of 25 g naproxen and experienced mild nausea and indigestion. It is not known what dose of the drug would be life threatening. the oral LD 50 of the drug is 543 mg/kg in rats. 1234 mg/kg in mice. 4110 mg/kg in hamsters and greater than 1000 mg/kg in dogs.

Should a patient ingest a large number of naproxen sodium tablets, the stomach may be emptied and usual supportive measures employed. Animal studies suggest that the prompt administration of 5 grams of activated charcoal would tend to reduce markedly the absorption of the drug. In dogs. 0.5 g/kg of charcoal was effective in reducing the plasma levels of naproxen when given after the drug. Hemodialysis does not decrease the plasma concentration of naproxen because of the high degree of its protein binding. However, hemodialysis may still be appropriate in the management of renal failure.

Dosage: The recommended starting dose of naproxen sodium for adults is two 275 mg tablets followed by one 275 mg tablet every 6 to 8 hours, as required. The total daily dose should not exceed 5 tablets (1375 mg).

Information for the Patient: See Section-Information for the Patient *Apo-Napro-Na*.

Supplied: Each blue, round, film-coated table contains:
naproxen sodium 275 mg. Energy: 1KJ (0.2kcal).
Sodium: 1 mmol (25 mg). Bottles of 100 and 500.

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