ANAREX TABLET

DESCRIPTION

Anarex Tablet is a 12 mm diameter, round, flat, marked "DUO" with scored line on one side, plain on the other side, blue tablet.. It is an analgesic with muscle relaxant preparation containing Paracetamol 450mg and Orphenadrine Citrate 35mg.

PHARMACODYNAMICS

Paracetamol may act predominantly by inhibiting prostaglandin synthesis in the central nervous system (CNS) and, to a lesser extent, through a peripheral action by blocking pain-impulse generation. The peripheral action may also be due to inhibition of prostaglandin synthesis or to inhibition of the synthesis or actions of other substances that sensitize pain receptors to mechanical or chemical stimulation. Paracetamol probably produces antipyretic by acting centrally on the hypothalamic heat-regulating center to produce peripheral vasodilation resulting in increased blood flow through the skin, sweating and heat loss. The central action probably involves inhibition of prostaglandin synthesis in the hypothalamus.
The skeletal muscle relaxant effect of orphenadrine is mediated through the CNS rather than directly on skeletal muscle. The relaxant effect may be related to its CNS depressant (sedative) effects by preferentially depressing polysynaptic reflexes. Orphenadrine also has analgesic activity, which may contribute to its skeletal muscle relaxant properties. It also has anticholinergic properties.

PHARMACOKINETICS

Paracetamol

Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract. Absorption may be decreased if paracetamol is taken following a high carbohydrate meal. Peak plasma concentrations of 5-20 mcg/mL has occurred about 0.5-2 hours following oral administration of doses up to 650 mg. Paracetamol is distributed into most body tissues. It crosses the placenta and is present in breast milk. Plasma protein binding is negligible at usual doses producing plasma concentrations below 60 mcg/mL. The half-life of paracetamol varies from 1-4 hours. Peak effect occurs after 1-3 hours while its duration of action is reported to be 3-4 hours. Paracetamol is primarily (90%-95%) metabolised in the liver, mainly by conjugation with glucuronic acid, sulphuric acid, and cysteine. An intermediate metabolite (N-acteyl-p-benzo-qui-noneimine), which is usually produced in very small amounts by mixed-function oxidases in the liver and kidney and which is usually detoxified by conjugation with glutathione may accumulate following paracetamol overdosage after the primary metabolic pathways have become saturated, is hepatotoxic and potentially nephrotoxic. Paracetamol is renally excreted, mainly as conjugates, with about 3% of a dose excreted unchanged. Haemodialysis (120mL per minute), haemoperfusion (200 mL per minute) and peritoneal dialysis << 10 mL per minute) can remove unmetabolised drug. Metabolites are also cleared rapidly by haemodialysis.

Orphenadrine Citrate

Orphenadrine is readily absorbed from the gastrointestinal tract and is almost completely metabolised in the liver to at least 8 metabolites. Plasma protein binding is low. It is mainly excreted in the urine as metabolites and small amounts of unchanged drug. There is also some faecal elimination. A half-life of 14 hours has been reported for the parent compound while half-life of its metabolites may range from 2-25 hours.

INDICATIONS

Anarex tablet is indicated for symptomatic relief of mild to moderate pain of acute musculoskeletal disorders. It is used as an adjunct to rest, physical therapy and other measures for the relief of discomfort associated with acute painful musculoskeletal conditions.

DOSAGE

Adult
1-2 tablets 3-4 times daily.
Children up to 12 years of age
Dosage has not been established.

CONTRAINDICATIONS

Because of the mild anticholinergic effect of orphenadrine, Anarex should not be used in patients with glaucoma, duodenal or pyloric obstruction, stenosing peptic ulcer, achalasia, prostatic hypertrophy, or obstructions at the bladder neck. Anarex is also contraindicated in patients with myasthenia gravis and in patients known to be sensitive to paracetamol or orphenadrine.

PRECAUTIONS

Anarex Tablet should be given with care to active alcoholics, and patients with hepatic diseases or viral hepatitis as there is an increased risk of hepatotoxicity. Risk of adverse renal effects may be increased with prolonged use of high doses of Anarex Tablet in patients with renal function impairment. It should be used cautiously in patients with cardiac disease, arrhythmias and tachycardia as ophenadrine may cause tachycardia. CNS depression may also be exarcebated. Blood count, hepatic and renal function determinations may be required at periodic intervals during prolonged or high-dose therapy since the safety of continuous long-term use has not been established.
Paracetamol may cause falsely decreased values in blood glucose determinations when the glucose oxidase/peroxidase method is used, but probably not when the hexokinase/glucose-6-phosphate dehydrohenase (G6PD) method is used.
Values may also be falsely increased when certain instruments are used in glucose analysis if high paracetamol concentrations are present. Paracetamol may cause false-positive results in qualitative screening tests of serum 5-Hydroxyindoleacetic acid (5-HIAA) using nitrosonaphthol reagent; the quantitative test is unaffected.
Administration of paracetamol prior to the pancreatic function test using bentiromide will invalidate test results because paracetamol is also metabolized to an arylamine and will thus increase the apparent quantity of para-aminobenzoic acid (PABA) recovered; it is recommended that paracetamol be discontinued at least 3 days prior to administration of bentiromide. Falsely increased values are also obtained when the phosphotungstate uric acid test method is employed in serum uric acid determinations. Serum bilirubin concentrations, serum lactate dehydrogenase activity, prothrombin time and serum transaminase activity may be increased, indicating hepatotoxicity, especially in alcoholics, patients taking other hepatic enzyme inducer, or patients with pre-existing hepatic disease, when single toxic doses (>8-10g) of paracetamol are taken or with prolonged use of lower doses (>3-5g daily).

This preparation contains PARACETAMOL. Do not take any other PARACETAMOL containing medicines at the same time.

Allergy alert: Paracetamol may cause severe skin reactions. Symptoms may include skin reddening, blisters or rash.These could be signs of a serious condition. If these reactions occur, stop use and seek medical assistance right away.

DRUG INTERACTIONS

Risk of hepatotoxicity with single toxic doses or prolonged use of high doses of paracetamol may be increased in chronic alcoholics or in patients regularly taking other hepatotoxic medications or hepatic enzyme inducers. Chronic use of barbiturates or primidone has been reported to decrease the therapeutic effects of paracetamol, probably because of increased metabolism resulting from induction of hepatic microsomal enzyme activity. Concurrent chronic, high dose administration of paracetamol with anticoagulant may increase the anticoagulant effect, probably by decreasing hepatic synthesis of procoagulant factors. Prolonged concurrent use of paracetamol and a salicylate is not recommended because recent evidence suggests that chronic, high-dose administration of the combined analgesics significantly increases the risk of analgesic nephropathy, renal papillary necrosis, end-stage renal disease, and cancer of the kidney or urinary bladder, also, it is recommended that for short-term use, the combined dose of paracetamol plus salicylate not exceed that recommended for paracetamol or a salicylate given alone. Prolonged concurrent use of paracetamol and non-steroidal anti-inflammatory drug (NSAIDs) other than aspirin may also increase the risk of adverse renal effects. Diflunisal may increase the plasma concentration of paracetamol by 50% to increased risk of paracetamol induced hepatotoxicity.

ANAREX

170mm(w) x 197mm (h)

Black 100%

The absorption of paracetamol may be accelerated by metoclopramide. Excretion may be affected and plasma concentrations altered when administered with probenecid. Concurrent use of Anarex Tablet with CNS-depressants may result in additive CNS depressant effects. Anticholinergic effects of orphenadrine may be intensified when used concomitantly with medicines with anticholinergic effects.

SIDE EFFECTS

Side effects of Anarex Tablet are those seen with paracetamol and those usually associated with anticholinergic agents. Anticholonergic side effects include dry mouth, decreased and difficulty in urination, constipation, confusion (especially in the elderly), increased intraocular pressure, unusually large pupils, blurred or double vision and weakness. Fast and pounding heartbeat, dizziness or lightheadedness, syncope, drowsiness, headache, paradoxical stimulation, trembling and gastrointestinal irritation have also been reported. Haematological reactions such as agranulocytosis, anaemia, thrombocytopaenia, leukopenia, pancytopaenia and neutropaenia have rarely been reported. Allergic dermatitis characterized by skin rash, hives, or itching, hepatitis, renal colic, renal failure, sterile pyuria, hallucinations and muscle weakness occur rarely. Paracetamol induced renal function impairment may be sufficiently severe to result in uraemia, especially with prolonged use of high doses in patients with pre-existing renal impairment.

A retrospective study has suggested that long-term daily use of paracetamol may be associated with an increase risk of chronic renal failure (analgesic nephropathy) in individuals without pre-existing renal function impairment.

Cutaneous hypersensitivity reactions including skin rashes, angioedema, Stevens Johnson Syndrome/Toxic Epidermal Necrolysis have been reported.

OVERDOSAGE

Symptoms

Acute overdosage with paracetamol is relatively common. The consequences can be extremely serious because of the narrow margin between therapeutic and toxic doses. Ingestion of as little as 10-15 g of paracetamol by adults may cause severe hepatocellular necrosis and, less often, renal tubular necrosis. Symptoms that may occur include nausea, vomiting, diarrhoea, loss of appetite, stomach cramps or pain, lethargy and sweating. The first indications of overdosage may be signs and symptoms of possible liver damage and abnormalities in liver function tests, which may not occur until 2-4 after ingestion of the overdose. Maximal changes in liver function tests usually occur 3-5 days after ingestion of the overdose.

Overt hepatic disease or failure may occur 4-6 days after ingestion of the overdose. Hepatic encephalopathy, convulsion, respiratory depression, coma, cerebral edema, coagulation defects, hypotension, gastrointestinal bleeding, disseminated intravascular coagulation, hypoglycaemia, metabolic acidosis, and infection may occur. Acute renal failure with acute tubular necrosis may develop, even in the absence of severe liver damage. Other non-hepatic symptoms include myocardial abnormalities such as cardiac arrhythmias and cardiovascular collapse, and pancreatitis.

Treatment

Recommended treatment for overdosage of Anarex Tablet includes:

a) Emptying the stomach via induction of emesis or gastric lavage.

b) Removing activated charcoal (if used) by gastric lavage may be advisable. Although activated charcoal is recommended in cases of mixed drug overdosage, it may interfere with absorption of orally administered acetylcysteine (antidote used to protect against paracetamol-induced hepatotoxicity) and decrease its efficacy.

c) Administering acetylcysteine. It is recommended that acetylcysteine administration be instituted as soon as possible after ingestion of an overdose has been reported, without waiting for the results of plasma paracetamol determinations or other laboratory tests. Acetylcysteine is most effective if treatment is started within 10-20 hours after ingestion of the overdose; however, it may be of some benefit if treatment is started within 24 hours. For oral administration, the recommended adult dosage of acetylcysteine is 140 mg/kg weight initially, then 70 mg/kg every 4 hours for 17 doses. Each dose should be diluted to a 5% solution with cola or other soft drinks prior to administration because of acetylcysteine's unpleasant odour and its irritating or sclerosing properties. Any dose vomited within 1 hour of administration must be repeated. If necessary, the antidote (diluted with water) may be given via duodenal intubation.

d) Determining plasma paracetamol concentration at least 4 hours following ingestion of the overdose. Determinations performed prior to this time are not reliable for assessing potential hepatotoxicity. Initial plasma concentrations above 150 mcg/mL at 4 hours, 100 mcg/mL at 6 hours, 70 mcg/mL at 8 hours, 50 mcg/mL at 10 hours, 20 mcg/mL at 15 hours, 8 mcg/mL at 20 hours, or 3.5 mcg/mL at 24 hours postingestion indicate possible hepatotixicity and the need for completing the full course of acetylcysteine treatment. If the initial determination indicates a plasma concentration below those listed at the times indicated, cessation of acetylcysteine therapy can be considered.

e) Instituting haemodialysisor haemoperfusion to remove paracetamol from the circulation may be beneficial. If acetylcysteine administration cannot be instituted within 24 hours following ingestion of a massive paracetamol overdosage. However, the efficacy of such treatment in preventing paracetamol-induced hepatotoxicity is not known.

f) Performing liver function tests (serum aspartate aminotransferase [AST], serum alanine aminotransferase [ALT], prothrombin time and bilirubin) at 24-hour intervals for at least 96 hours postingestion if the plasma paracetamol concentration indicates potential hepatotoxicity. If no abnormalities are detected within 96 hours, further determinations are not needed.

g) Monitoring renal and cardiac function and administering appropriate therapy as required.

h) Instituting supportive treatment, including maintaining fluid and electrolyte balance, correcting hypoglycaemia, maintaining circulatory support and high-volume urinary output, and administering vitamin K1 (if prothrombin time ratio exceeds 1.5) and fresh frozen plasma or clotting factor concentrate (if prothrombin time ration exceeds 3.0)

Up-to-date information on treatment of overdose can be obtained from the National Poison Center, University Sains Malaysia (Tel:800-8099)

PRESENTATION

3 x 10's, 10 x 10's, 50 x 10's and 100 x 10's
Not all pack sizes are available locally

STORAGE CONDITIONS AND USER INSTRUCTIONS

Store in a dry place below 30°C.
Protect from light.
Keep out of reach of children.
Jauhi daripada kanak-kanak.
Shelf life: please refer to outer package.

Route of administration: Oral.

Product Registration Holder:
Duopharma Manufacturing (Bangi) Sdn.Bhd.
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43650 Bandar Baru Bangi, Selangor,Malaysia.

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