

NEW ZEALAND DATA SHEET

DIASTOP

***Diphenoxylate hydrochloride 2.5 mg and
Atropine sulphate 0.025 mg Tablet***



Presentation

White biconvex tablet, 7/32" in diameter and blank on both sides. Each DIASTOP tablet contains 2.5 mg of diphenoxylate hydrochloride and 0.025 mg of atropine sulphate.

Uses

Actions

Diphenoxylate is an opiate derivative. The antidiarrhoeal effects of opioids may be due to their effects on the opiate receptors controlling smooth muscle contraction in the small intestine and colon. The resulting increase in tone and segmenting activity increases the resistance to flow of luminal contents. It is essentially devoid of "morphine type subjective effects" at therapeutic doses.

Atropine is a non-selective muscarinic antagonist. It is included in the formulation as an anti-abusing agent contributing to the safe use of the product. The dose of atropine sulphate contained in each tablet is sub-therapeutic therefore a pharmaceutical effect due to atropine should not be detected taken at normal therapeutic doses.

Pharmacokinetics

Diphenoxylate hydrochloride

Diphenoxylate is rapidly absorbed reaching peak blood levels in about two hours. Its relatively short plasma half-life (about 2.5 hours) and large plasma clearance suggests its rapid biotransformation. Metabolism is principally in the liver. The major metabolic pathway of diphenoxylate in man is the hydrolysis of the ester group to give diphenoxylic acid - a pharmacologically active metabolite. Diphenoxylate metabolites probably undergo enterohepatic circulation. Diphenoxylic acid has a greater average peak plasma concentration, and a shorter time to maximum plasma concentration, than diphenoxylate. The AUC is about five times greater for diphenoxylic acid than for diphenoxylate, and may reflect enhanced bioavailability of diphenoxylic acid. Onset of pharmacological effect is 45 to 60 minutes, and duration of effect is about 3 to 4 hours. Diphenoxylate has a volume of distribution of 3.8 L/kg, with penetration into the cerebrospinal fluid. Plasma levels decline in a biphasic manner, with plasma half-lives of about 6 hours (for 2-24 hours) and 23 hours (for 24-72 hours). Approximately 10% of a dose of diphenoxylate is excreted in the urine and 40% in the faeces. Urinary excretion is mainly in the form of metabolites, while faecal excretion is mainly as unchanged drug. Diphenoxylic acid is also eliminated from plasma in a biphasic manner, and is excreted principally in urine.

Atropine

Atropine is rapidly absorbed from the gastrointestinal tract, with a time to peak plasma concentration of 30 minutes. Time to peak pharmacological effect is 4 to 6 hours. About 50% of a dose is bound to plasma proteins. Atropine is partially metabolised by hepatic oxidation, and distribution is throughout the body, including the CNS. Atropine has a half-life of about 4 hours. The principal route of elimination is in urine; with about 30% to 50% of a dose excreted as unchanged drug. Only trace amounts are in the faeces.

Indications

DIASTOP is indicated as an adjunctive therapy to proper rehydration in acute and chronic diarrhoea; after colostomy or ileostomy for control of stool formation; and for relief of symptoms in ulcerative colitis (see Warnings and Precautions).

Dosage and Administration

Each DIASTOP tablet contains 2.5 mg diphenoxylate hydrochloride plus 0.025 mg atropine sulphate.

Adults:

The usual initial dose is 5 mg (two tablets) three or four times daily. In cases of acute diarrhoea an initial dose of up to 10 mg (four tablets) may be given, followed by 5 mg (two tablets) every six or eight hours, not to exceed a maximum daily dose of 20 mg. After initial control is achieved, the dosage should be reduced to meet the requirements of the individual patients. Do not exceed recommended dosage.

Children:

NOTE: DIASTOP is not recommended for use in children under two years of age.

The recommended initial dosage is 0.3 to 0.4 mg/kg diphenoxylate hydrochloride daily administered in divided doses.

Age	Approximate body weight	Dosage
2 to 5 years	15 – 20 kg	1 tablet b.i.d.
5 to 8 years	20 – 27 kg	1 tablet t.i.d.
8 to 12 years	27 – 36 kg	1 tablet q.i.d.
12 years and over		2 tablets t.i.d. - q.i.d. (adult dosage)

These paediatric schedules are the best approximation of an average dose recommendation which should be adjusted according to the overall nutritional status and degree of dehydration encountered in the sick child. The recommended doses must not be exceeded. (See Overdosage).

This dosage should be reduced commensurate with the patient's needs once initial control of symptoms is achieved. Doses as low as 0.25 mg/kg per day have proven effective in severely malnourished children in underdeveloped countries.

If no improvement in acute diarrhoea has been observed after 48 hours, DIASTOP should be discontinued. If clinical improvement in chronic diarrhoea is not observed after 10 days' treatment with the maximum daily dose of 20 mg (in adults), further administration is unlikely to result in any benefit.

Contraindications

DIASTOP is contraindicated in patients with known hypersensitivity to diphenoxylate hydrochloride or atropine, in patients with jaundice, intestinal obstruction, any inflammatory bowel disease, including all forms of ulcerative colitis, and in the treatment of diarrhoea associated with pseudomembranous enterocolitis. DIASTOP is also contraindicated in patients with Down's syndrome, in patients with a raised intracranial pressure, and patients with head injury.

Also contraindicated in myasthenia gravis, pyloric stenosis, paralytic ileus and prostatic enlargement.

Warnings and Precautions

DIASTOP is not an innocuous medicine and dose recommendations should be strictly adhered to, especially in children. Overdose may result in severe respiratory depression and coma, possibly leading to permanent brain damage, or death. Keep this medication out of reach of children. DIASTOP is not recommended for children under 2 years of age. DIASTOP should be used with special caution in young children because they may be predisposed to delayed toxicity and because of the greater variability of response in this age group.

Appropriate fluid and electrolyte therapy should be given to protect against dehydration. If severe dehydration or electrolyte imbalance is present, DIASTOP should be withheld until appropriate corrective therapy has been initiated. Drug-induced inhibition of peristalsis may result in fluid retention in the intestine, which may further aggravate dehydration and electrolyte imbalance.

DIASTOP should be used with extreme caution in patients with advanced hepatorenal disease and in all patients with abnormal liver function, since hepatic coma may be precipitated. Bacterially induced diarrhoea should be treated with appropriate antimicrobial therapy. DIASTOP should be avoided in patients with acute inflammatory bowel disease because it may mask a severe episode or the development of toxic megacolon.

The recommended dose should not be exceeded because addiction to DIASTOP is possible at high doses. Because a sub-therapeutic dose of atropine has been added to the medicine, atropine effects may occur in susceptible individuals or in overdosage. Therefore, consideration should be given to the precautions relating to the use of atropine in children.

Use in pregnancy and lactation

Because atropine crosses the placenta and the safety of DIASTOP in pregnancy has not been established, caution is recommended when DIASTOP is used during pregnancy. The use of any medicine during pregnancy or in women of childbearing potential requires that the potential benefits of the medicine be weighed against possible hazards to the mother and foetus.

Diphenoxylate hydrochloride and atropine sulphate may be excreted in human breast milk; therefore infants of nursing mothers taking DIASTOP may exhibit some effects of the medicine. If use of DIASTOP is necessary, an alternative method of infant feeding should be instituted.

Effects on ability to drive and use machines

Some of the undesirable effects such as sedation, drowsiness or dizziness may affect the ability to drive or operate machinery. If affected, patients should be advised not to drive or operate machinery.

Adverse Effects

Nervous system: malaise, lethargy, confusion, sedation/drowsiness, dizziness, restlessness, depression, hallucinations, somnolence, euphoria, headache, fever and paraesthesia.

Allergic: Anaphylaxis, angioedema, urticaria, pruritus.

Gastrointestinal system: toxic megacolon, paralytic ileus, vomiting, nausea, anorexia, abdominal discomfort, abdominal pain and constipation.

Atropine sulphate side effects include: hyperthermia, flushing, dryness of the skin and mucous membranes (including dry mouth), cardiac irregularities such as tachycardia, arrhythmias, bradycardia and palpitations, increased intra-ocular pressure, urinary retention and difficulty in micturition, and respiratory depression in children.

Dilation of pupils with loss of accommodation, photophobia, and very rarely, angle closure glaucoma can occur.

Interactions

Diphenoxylate may have an additive effect on certain central nervous system depressants, e.g. barbiturates, tranquillisers and alcohol. Concurrent use with MAO inhibitors may precipitate hypertensive crisis. Close observation is required when these medications are given concomitantly with diphenoxylate hydrochloride.

Diphenoxylate/atropine antagonises the effects of domperidone, metoclopramide, bethanecol/carbachol, cisapride, galantamine, neostigmine/pyridostigmine and pilcarpine.

The antimuscarinic side effects of diphenoxylate/atropine are increased by amantadine, antihistamines (sedative and non-sedative), clozapine, disopyramide, fluspiriline, loxapine, MAOI's, nefopam, olanzapine, phenothiazines, quetiapine, remoxipride, terfenadine, tricyclic antidepressants and zotepine.

Dry mouth prevents the dissolution of sublingual nitrate tablets, such as glyceryl trinitrate.

The effect of diphenoxylate/atropine is antagonised by donepezil.

The effect of diphenoxylate/atropine is increased by memantine.

Diphenoxylate/atropine may reduce the plasma levels of levodopa (in combination and sole products).

Diphenoxylate/atropine reduces the absorption of ketoconazole.

Overdosage

Accidental overdose may produce narcosis with respiratory depression or atropine poisoning or both, particularly in children. Symptoms of overdose include dryness of the skin and mucous membranes, flushing, hypothermia and tachycardia, nystagmus, pinpoint pupils, hypotonic reflexes, lethargy, coma and severe respiratory depression. The onset of symptoms of overdose may be considerably delayed and respiratory depression may not become evident until as late as 12 – 30 hours after ingestion, and may occur in spite of initial response to narcotic antagonists. Continuous observation should be maintained for at least 48 hours.

If respiratory depression develops, naloxone, a specific antidote, should be administered. The duration of action of naloxone hydrochloride is considerably shorter than that of diphenoxylate hydrochloride and repeated injections of the antidote may be required. Establishment of a patient airway and artificial ventilation may be needed. If the patient is not comatose, gastric lavage and administration of slurry of activated charcoal may be indicated.

Pharmaceutical Precautions

Store below 25°C.

Medicine Classification

Pharmacy medicine.

Package Quantities

Blister packs of 20 tablets and 100 tablets.

Further Information

DIASTOP tablets also contain microcrystalline cellulose, pregelatinised maize starch, magnesium stearate and colloidal silicon dioxide.

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