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DOLESTINE דולסטין

SOLUTION FOR I.M., I.V. or S.C. INJECTION **תמיסה להזרקה לתוך השריר, לתוך הוריד או מתחת לעור**

Composition

Active Ingredient
Each ampoule of 1 ml contains:
Pethidine (meperidine) hydrochloride 50 mg
Each ampoule of 2 ml contains:
Pethidine (meperidine) hydrochloride 100 mg

Other Ingredients
Water for injections, sodium hydroxide (q.s.for pH adjustment).

Mechanism of Action

Dolestine is a powerful narcotic analgesic.

WARNING: RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see Precautions and Drug Interactions).

Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Limit dosages and durations to the minimum required.

Follow patients for signs and symptoms of respiratory depression and sedation.

Indications

- Relief of severe pain.
- Pre-operative medication.
- Support of anesthesia.
- Obstetrical analgesia.

Contraindications

Known hypersensitivity to the preparation.

Pethidine is contraindicated in patients who are receiving monoamine oxidase inhibitors, or those who have recently received such agents. Therapeutic doses of pethidine have occasionally precipitated unpredictable, severe, and occasionally fatal reactions in patients who have received monoamine oxidase inhibitors within the last 14 days. The mechanism of these reactions is unclear, but may be related to a pre-existing hyperphenylalaninemia. Some have been characterized by coma, severe respiratory depression, cyanosis and hypotension, and have resembled the syndrome of acute narcotic overdose. In other reactions, the predominant manifestations have been hyperexcitability, convulsions, tachycardia, hyperpyrexia, and hypertension.

Although it is not known that other narcotics are free of the risk of such reactions, virtually all of the reported reactions have occurred with pethidine. If a narcotic is needed in such patients, a sensitivity test should be performed in which repeated, small, incremental doses of morphine are administered over the course of several hours while the patient's condition and vital signs are under careful observation. (Intravenous hydrocortisone or prednisolone have been used to treat severe reactions, with the addition of intravenous chlorpromazine in those cases exhibiting hypertension and hyperpyrexia. The usefulness and safety of narcotic antagonists in the treatment of these reactions is unknown).

Pethidine is also contraindicated in the following cases:

- Respiratory depression, or where respiratory reserve is depleted (acute bronchial asthma, chronic airway disease, severe emphysema, severe chronic bronchitis, kyphoscoliosis).
- Head injury, raised intracranial pressure (apart from introducing monitoring and diagnostic problems, hypercapnia associated with respiratory depression can itself result in elevated intracranial pressure), brain tumour.
- Cardiac arrhythmias, especially supraventricular tachycardias, cor pulmonale. Pethidine has a vagolytic action and may produce a significant increase in the ventricular response rate.
- Pre-eclampsia, eclampsia.
- Convulsive states such as status epilepticus, tetanus and strychnine poisoning, due to the stimulatory effects of pethidine on the spinal cord.
- Diabetic acidosis where there is a danger of coma.
- Acute alcoholism or delirium tremens.
- Severe liver disease, incipient hepatic encephalopathy.
- Patients with a low platelet count, coagulation disorders or receiving anticoagulant treatment.

Pethidine is not recommended for use in infants under 1 year of age.

Warnings

Intravenous Use

Pethidine should not be administered intravenously unless a narcotic antagonist and facilities for assisted or controlled respiration are immediately available. When pethidine is administered parenterally, especially intravenously, the patient should be lying down.

If pethidine is to be given intravenously, the injection should be administered very slowly, preferably in the form of a diluted solution. Rapid I.V. injection of narcotic analgesics, including pethidine, increases the incidence of adverse reactions; severe respiratory depression, apnea, hypotension, peripheral circulatory collapse, and cardiac arrest have occurred.

Head Injury and Increased Intracranial Pressure

The respiratory depressant effects of pethidine and its capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries. In such patients, pethidine must be used with extreme caution and only if its use is deemed essential.

Opioids may obscure the diagnosis and/or mask the clinical course of patients with head injuries or acute abdominal conditions and should not be used unless absolutely necessary in these conditions. The respiratory depressant effects of pethidine may be markedly exaggerated in the presence of head injury.

Asthma and Other Respiratory Conditions

Pethidine should be used with extreme caution in patients undergoing an acute asthmatic attack, patients with chronic obstructive pulmonary disease or cor pulmonale, patients having a substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia, or hypercapnia. In such patients, even unusual therapeutic doses of narcotics may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea.

Large doses and/or rapid intravenous administration of pethidine may produce rapid onset respiratory depression, apnoea, hypotension, peripheral circulatory collapse, bradycardia (as a result of stimulation of medullary vagal nuclei) or even cardiac arrest. Pethidine should not be administered by intravenous injection unless an opioid antagonist and facilities for controlled or assisted respiration are available.

Hypotensive Effect

The administration of pethidine may result in severe hypotension in the postoperative patient or any individual whose ability to maintain blood pressure has been compromised by a depleted blood volume or the concurrent administration of drugs such as phenothiazines or certain anesthetics.

Drug Dependence

Pethidine can produce drug dependence of the morphine type and therefore has the potential for being abused. Psychic and physical dependence, and tolerance may develop upon repeated administration of the drug.

Pethidine should be restricted to short-term administration for the relief of severe pain not responding to non-opioid analgesics. Abrupt withdrawal of pethidine in those physically dependent may precipitate withdrawal syndrome, including convulsions.

Use in Pregnancy

Safe use of pethidine prior to the labor period has not been established. Therefore, it should not be used at this time, unless the potential benefits to the mother outweigh the possible hazards to the fetus.

Use in Labor and Delivery

Pethidine crosses the placental barrier and can produce depression of respiration and psychophysiologic functions in the newborn. Resuscitation may be required. Therefore, pethidine is not recommended during labor.

Other

Cross-tolerance between narcotic analgesics can occur.

Seizures may result from prolonged exposure or high doses of pethidine due to pethidine-associated neurotoxicity (PAN). PAN is a recognised clinical entity which is mainly due to the metabolite norpethidine. Norpethidine concentrations are enhanced by reduction in renal excretion as in the elderly and the very young and by increased conversion of pethidine to norpethidine due to the effects of drugs such as phenobarbitone and phenytoin. Furthermore, pethidine-associated neurotoxicity is dose-related, so pethidine should not be used for periods greater than 24 to 36 hours.

Because of the spasmogenic properties of pethidine on the biliary tract and sphincter of Oddi, it should be used only when necessary and then with caution in biliary colic, operations on the biliary tract and acute pancreatitis. Pethidine may render surgical exploration of the common bile duct difficult.

Decreased gastric emptying associated with pethidine may be expected to increase the risks of aspiration either associated with pethidine induced CNS depression/coma or during or after general anaesthesia, e.g., a labouring patient going on the cesarean section.

Inadvertent intra-arterial administration can produce severe necrosis and gangrene.

Use in Breastfeeding

Pethidine is secreted in breast milk. Therefore, having taken into account the importance of the drug to the mother, either discontinue nursing or discontinue the drug.

Use in Patients with Hepatic Impairment

Accumulation of pethidine and/or its active metabolite, norpethidine, can occur in patients with hepatic impairment. Pethidine should therefore be used with caution in patients with hepatic impairment.

Use in Patients with Renal Impairment

Accumulation of pethidine and/or its active metabolite, norpethidine, can also occur in patients with renal impairment. Pethidine should therefore be used with caution in patients with renal impairment.

Use in Geriatrics

Clinical studies of pethidine during product development did not include sufficient numbers of subjects aged 65 and over to evaluate age-related differences in safety or efficacy. Literature reports indicate that geriatric patients have a slower elimination rate compared to young patients and they may be more susceptible to the effects of pethidine. A reduction in the total daily dose of pethidine may be required in elderly patients, and the potential benefits of the drug weighed against the relative risk to a geriatric patient.

Adverse Reactions

As with other opioid analgesics, respiratory depression is the major hazard associated with parenteral pethidine therapy.

Other adverse reactions include:

More Common Reactions

Central Nervous System

Lightheadedness, dizziness, sedation, sweating, bizarre feelings, disorientation, hallucinations, psychosis. Some of these effects seem to be more prominent in ambulatory patients and those not experiencing severe pain, and may be relieved by reducing the dose slightly and lying down.

Gastrointestinal

Nausea and vomiting, constipation.

Less Common Reactions

Cardiovascular

Hypotension, vasodilation, hypertension, tachycardia, bradycardia, gangrene, following inadvertent intra-arterial administration.

Dermatological

Rash, pruritus, urticaria, erythema, injection site complications e.g., local irritation and induration, fibrosis of muscle tissue with frequent repetition of intramuscular injection.

Gastrointestinal

Decreased gastric emptying.

Genito-urinary

Urinary retention and anuria.

Hepatic

Increased biliary tract pressure, choledochoduodenal sphincter spasm.

Nervous System

Pethidine associated neurotoxicity (see Warnings and Precautions), or neuropsychiatric toxicity, i.e., auditory and visual hallucinations, irritability, agitation, hypomania, paranoia, delirium and complex partial seizures, vertigo, dizziness, coma, headache, convulsions or tremor, respiratory depression, cold clammy skin, sweating and pallor. Inadvertent injection around a nerve trunk may cause sensory-neural effects, which is usually, but not always transitory.

Psychiatric

Neuropsychiatric toxicity, hyperactivity or agitation, depression, mental clouding, dysphoria.

General

Dry mouth, weakness, hypersensitivity.

Pain at injection site; local tissue irritation and induration following subcutaneous injection (particularly when repeated) and antidiuretic effect.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formtype=AdverseEffectMedic@moh.gov.il

Precautions

Some adverse reactions have been reported more frequently after intravenous administration. Pethidine should only be administered I.V. if a narcotic antagonist and facilities for assisted or controlled respiration are available.

Pethidine should always be administered with caution, and in reduced dosage, to elderly and debilitated patients and patients with head injuries, severe hepatic or renal impairment, biliary tract disorders, hypothyroidism, adrenocortical insufficiency, shock, prostatic hypertrophy, urethral stricture and Addison's disease.

Supraventricular Tachycardia

Pethidine should be used with caution in patients with atrial flutter and other supraventricular tachycardias because of a possible vagolytic action which may produce a significant increase in the ventricular response rate.

Acute Abdominal Conditions

As with other narcotics, pethidine may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Convulsions

Pethidine may aggravate pre-existing convulsions in patients with convulsive disorders.

Convulsions may occur in individuals without a history of convulsive disorders, following use of a higher than recommended dosage of the drug.

Other Precautions

Caution is also required in patients exhibiting acute alcoholism, raised intracranial pressure or convulsive disorders.

Serious or life-threatening reactions such as respiratory depression, coma, convulsions, possibly due to elevated levels of norpethidine and hypotension have been associated with the use of pethidine.

Pethidine should be used with caution in patients taking other CNS depressant drugs such as hypnotics and sedatives including barbiturates and benzodiazepines, phenothiazines, and other tranquillisers, anaesthetics, alcohol and antidepressants.

Patients with severe pain may tolerate very high doses of pethidine but may exhibit respiratory depression should their pain suddenly subside.

The elderly demonstrate an increased sensitivity to opioids relative to younger patients. Reduced liver function, renal function and plasma protein binding may contribute to the elevated plasma levels found in elderly subjects.

Since pethidine is metabolized in the liver and excreted via the kidneys, the possibility of accumulation of the toxic metabolic norpethidine should be considered in patients with hepatic and/or renal impairment.

Reduced cardiac output may lead to reduced hepatic perfusion and diminished metabolism of pethidine, leading to accumulation of pethidine with possible toxic results.

Pethidine may cause a transient rise in blood pressure and systemic vascular resistance and increased heart rate. Therefore, it is not recommended for pain relief in cardiac infarction.

Pethidine in patients with pheochromocytoma may result in a hypertensive crisis.

In an individual physically dependent on opioids, the administration of the usual dose of an opioid antagonist will precipitate an acute withdrawal syndrome. The severity of this syndrome will depend on the degree of physical dependence and the dose of antagonist administered. The use of opioid antagonists in such individuals should be avoided if possible. If an opioid antagonist must be used to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with extreme care and only 10 to 20% of the usual initial dose administered.

In eclampsia the combination of pethidine with phenothiazines has been reported to induce recurrence of seizures rather than stopping them. Therefore, the use of pethidine in eclampsia and pre-eclampsia is not recommended (see Contraindications).

Pethidine, while commonly used for pain relief in obstetrics, is known to pass the placenta and may cause neonatal depression, including respiratory depression. An opioid antagonist such as naloxone may be required to reverse such depression. In the neonate, pethidine is excreted and metabolized at a significantly reduced rate compared to adults.

Orthostatic hypotension has been reported in ambulatory patients administered pethidine.

Pethidine should be given with caution and the initial dose should be reduced in patients with hypothyroidism or Addison's disease.

Pethidine should be used with caution in patients with prostatic hypertrophy or urethral stricture.

As opiate agonists may produce hyperglycemia, this effect should be considered when diabetics require pethidine.

There are conflicting reports about the effect of pethidine on the eye. Some reports state that pethidine and its congeners produce miosis, whereas others indicate that these drugs tend to produce mydriasis or no pupillary change. Until the effects are better defined, intraocular tension should be monitored in patients with glaucoma who received pethidine.

Patients may experience drowsiness while receiving pethidine and should therefore be cautioned not to engage in potentially-hazardous activities requiring mental alertness, such as driving a car or operating machinery.

Drug Interactions

Pethidine has been found to interact with the following drugs:

Barbiturates, Chloral Hydrate, Benzodiazepines: Pethidine enhances the CNS depressant effects of these drugs. In addition, the combination of pethidine and phenobarbitone may reduce the analgesic effect of pethidine in part due to the increased conversion of pethidine to the toxic metabolite, norpethidine.

Phenothiazines: CNS toxicity and hypotension including respiratory depression may occur when given together. In eclampsia the combination has been reported to induce recurrence of seizures (see Precautions).

Butyrophenones: The CNS depressant effect of tranquillisers may be increased by pethidine.

Monoamine Oxidase Inhibitors (see Contraindications): Excitation, sweating, rigidity, hypertension or hypotension, coma have occurred with combination. Interaction with furazolidone is not likely until it has been taken for five days. Interaction with selegiline, a MAOI Type B, has been reported as causing delirium, restlessness, sweating and rigidity.

Paracetamol: Absorption may be reduced due to delayed gastric emptying caused by pethidine.

CNS Depressants (Including Alcohol): Depressant effects may be enhanced by pethidine.

Phenytoin: Increased metabolism of pethidine and generation of norpethidine resulting in the possibility of increased CNS effects of norpethidine and reduced analgesia.

Coumarin/Indandione-Derivative: The effects of coumarin or indandione-derivative anticoagulants may be increased.

Amphetamines: Concurrent use with amphetamines, which have some MAO inhibiting activity, is not recommended because of the risk of serious reactions similar to those reported with other MAO inhibitors.

Cimetidine: Cimetidine inhibits metabolism of pethidine and therefore increases plasma concentration.

Anticholinergics: Use of pethidine in prolonged increasing dosage or concomitantly with anticholinergics may result in neurotoxicity in patients with renal failure, cancer or sickle cell anemia.

Acyclovir: Plasma concentrations of pethidine and its metabolite, norpethidine, may be increased by acyclovir, thus caution should be used with concomitant administration.

Ritonavir: Plasma concentrations of the active metabolite norpethidine may be increased by ritonavir, thus concomitant administration should be avoided.

Skeletal Muscle Relaxants: Opioid analgesics, including pethidine, may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Diagnostic Interference

Narcotic analgesics may produce increases in plasma amylase and plasma lipase levels; the diagnostic utility of determinations of these enzymes may be compromised for up to 24 hours after the medication has been administered.

Information for Patients

CNS depression is increased when pethidine is co-administered with alcohol, butyrophenones, hypnotics, sedatives, phenothiazines, tricyclics, antihistamines and other CNS depressant agents.

Driving and operating dangerous machinery should not be contemplated until the day following the last dose of pethidine.

Dosage and Administration

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Relief of Pain

Dosage should be adjusted according to the severity of the pain and the response of the patient.

Adults

The usual dosage is 50-100 mg, administered intramuscularly or subcutaneously every 3 or 4 hours as necessary.

Children

The usual dosage is 1-1.8 mg/kg body weight, administered intramuscularly or subcutaneously every 3 or 4 hours as necessary. Irrespective of body weight, the adult dose should not be exceeded.

Pre-operative Medication

Adults

The usual dosage is 50-100 mg, administered intramuscularly or subcutaneously, 30 to 90 minutes before anesthesia is started.

Children

The usual dosage is 1-2 mg/kg body weight, administered intramuscularly or subcutaneously 30-90 minutes before the start of anesthesia.

Irrespective of body weight, the adult dosage should not be exceeded.

Support of Anesthesia

The dose should be titrated to the needs of the patient, according to the premedication and type of anesthetic being employed, the characteristics of the particular patient, and the nature and duration of the operative procedure.

Dolestine may be administered intravenously, either by repeated slow injection of fractional doses of a solution diluted to 10 mg/ml, or by infusion as a solution diluted to 1 mg/ml.

Dosage may be individualized up to a maximum of 50 mg.

Obstetrical Analgesia

The usual dosage is 50-100 mg, administered intramuscularly or subcutaneously when pain becomes regular. It may be repeated at 1-3 hour intervals.

Incompatibilities

The mixing of thiopentone solutions with pethidine results in the formation of a pharmacologically inactive complex. A loss of clarity of solution was noted when solutions of pethidine hydrochloride were mixed with the following: aminophylline, heparin, amylobarbitone sodium, methicillin sodium, morphine sulphate, phenobarbitone sodium, phenytoin sodium, sodium bicarbonate or sodium iodide.

Pethidine is also incompatible with alkalis, iodine and iodides.

Overdosage

Manifestations

Opioid analgesic overdosage usually produces central nervous system depression ranging from stupor to a profound coma, respiratory depression which may progress to Cheyne-Stokes respiration and/or cyanosis, cold clammy skin and/or hypothermia, flaccid skeletal muscles, bradycardia and hypotension. In patients with severe overdosage, particularly following rapid intravenous administration of an opioid, apnoea, circulatory collapse, cardiac arrest, respiratory arrest and death may occur.

Complications such as pneumonia, shock and/or pulmonary oedema may also prove fatal. Although miosis (pupillary constriction) is characteristic of overdosage with morphine derivatives and methadone, mydriasis may occur in terminal narcosis or severe hypoxia. Overdosage of pethidine may produce mydriasis rather than miosis.

Toxic effects of pethidine may be excitatory, especially in patients who have developed tolerance to the depressant effects of the drug. These patients may exhibit dry mouth, increased muscular activity, muscle tremors and twitches, tachycardia, delirium with disorientation, hallucinations and, occasionally, grand mal seizures.

Treatment

In overdosage, if necessary, establish an airway and institute assisted or controlled ventilation.

Circulation should be maintained with infusions of plasma or suitable electrolyte solution. If consciousness is impaired and respiration depressed, an opioid antagonist should be administered. Naloxone, a pure antagonist, is now the treatment of choice. Consult naloxone (or nalorphine) product information. Administer I.V. naloxone (e.g., 0.4 mg) which may be repeated at 2 to 3 minute intervals.

For children, the initial dose recommended is 0.01 mg/kg naloxone. In neonates, a more rapid and improved antagonism was noted after 0.02 mg/kg was administered. A response should be seen after 2 or 3 doses. Note the duration of action of naloxone is usually shorter than that of pethidine and thus the patient should be carefully observed for signs of CNS depression returning. An opioid antagonist should not be administered in the absence of clinical signs of respiratory or cardiovascular depression.

Note: *In an individual physically dependent on opioids, the administration of the usual dose of an opioid antagonist will precipitate an acute withdrawal syndrome. The severity of this syndrome will depend on the degree of physical dependence and the dose of antagonist administered. The use of opioid antagonists in such individuals should be avoided if possible. If an opioid antagonist must be used to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with extreme care and only 10 to 20% of the usual initial dose administered.*

Storage

Store below 25°C.

Drug Registration No.:

021.04.21091

Manufacturer and Licence Holder

Teva Pharmaceutical Industries Ltd.,
P.O.Box 3190, Petah-Tikva, Israel.

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