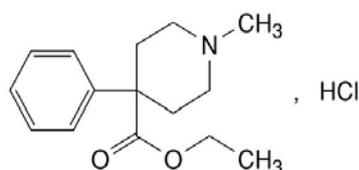


Pethidine Injection BP 50 mg/mL PRODUCT INFORMATION

NAME OF THE MEDICINE

The active ingredient in Pethidine Injection BP is pethidine hydrochloride. The chemical name for pethidine hydrochloride is ethyl 1-methyl-4-phenylpiperidine-4-carboxylate hydrochloride. The CAS number for pethidine hydrochloride is 50-13-5. The Australian Approved Name is pethidine hydrochloride. Empirical formula $C_{15}H_{21}NO_2 \cdot HCl$, MW: 283.8.

The chemical structure of pethidine hydrochloride is:



DESCRIPTION

Pethidine Injection BP contains the hydrochloride of ethyl 1-methyl-4-phenylpiperidine-4-carboxylate (pethidine hydrochloride) 50 mg/mL in Water for Injections BP in polyethylene sterile ampoules. Pethidine Injection BP contains no antimicrobial agent. It should be used only once and any residue discarded. The pH ranges from 3.5 to 6.

PHARMACOLOGY

Pethidine is a synthetic opioid with analgesic and sedative properties, its actions qualitatively similar to those of morphine. In addition to providing analgesia, pethidine, in common with other opioids, produces respiratory depression, drowsiness, sedation, mood changes, euphoria, dysphoria, mental clouding, nausea, vomiting and electroencephalographic changes. Large doses of pethidine may cause excitation and convulsions.

After parenteral administration, 75 to 100 mg of pethidine has comparable analgesic, euphoric and respiratory depressant effects to 10 mg of morphine. Pethidine has a more rapid onset of action but shorter duration of analgesic effect than does morphine.

The depressant effect of pethidine on the cough reflex may be less than morphine at equianalgesic doses. Pethidine has spasmolytic as well as spasmogenic effects and may produce less constipation than morphine. Atropine like effects such as dry mouth and blurred vision have been reported with pethidine.

Pharmacokinetics

Pethidine undergoes rapid first-pass metabolism after oral administration and although well absorbed from the gastrointestinal tract it is considerably less effective orally than parenterally. Absorption after intramuscular use may be erratic; 80% or more after a 100 mg intramuscular dose of pethidine has been shown to be absorbed over 6 hours with a T_{max} of 24 minutes. Analgesia may persist for 2 to 4 hours following intramuscular and subcutaneous administration.

Pethidine is mainly metabolised in the liver, primarily undergoing hydrolysis to pethidinic acid followed by partial conjugation with glucuronic acid. Other metabolic pathways include demethylation to norpethidine, which may be hydrolysed to norpethidinic acid and then conjugated with the glucuronic acid.

Though there is limited information on the distribution of pethidine, data indicate that it is extensively distributed extravascularly, primarily in rapidly perfused tissues.

Pethidine has an average plasma elimination half-life of approximately 3.2 ± 0.8 hours, a volume of distribution of 4 L/Kg and is approximately 70% plasma protein bound. The elimination of pethidine may be prolonged in patients with cirrhosis, acute viral hepatitis or other hepatic dysfunction.

Norpethidine, which is a major metabolite, is twice as potent as pethidine as a convulsive agent and half as active as an analgesic. The elimination half-life of norpethidine is prolonged in patients with impaired renal function, persons over 60 years and neonates, which may lead to accumulation and toxic effects, such as seizures, agitation, irritability, tremors, twitching and myoclonus.

Elimination of both pethidine and norpethidine is prolonged in pregnant women, with the possibility of accumulation of both compounds following multiple doses of pethidine in labour. The foetus will be exposed to high levels of pethidine and norpethidine because of a continued diffusion gradient from mother to foetus, with the potential for clinically significant levels of norpethidine being achieved in the newborn.

Approximately 5% of an IV dose of pethidine is excreted in the urine unchanged. Acidification of the urine enhances the excretion of unchanged pethidine and the metabolite norpethidine, but is not recommended as treatment in cases of overdose.

INDICATIONS

1. Relief of moderate to severe pain not responsive to non-opioid analgesics.
2. Pre-operative medication.
3. Analgesic adjunct in general anaesthesia.
4. Obstetrical analgesia.

CONTRAINDICATIONS

1. Hypersensitivity to pethidine.
2. Patients who are taking or have taken a mono-amine oxidase inhibitor (including selegiline) within the previous fourteen days. The combination of mono-amine oxidase inhibitors and pethidine has caused hypotension, hypertension, excitation, rigidity, hyperpyrexia and/or convulsions, and in some cases fatalities have been reported. This combination should be avoided.
3. Respiratory depression, or patients in whom respiratory reserve is significantly depleted (e.g. severe emphysema, severe chronic bronchitis, kyphoscoliosis, acute bronchial asthma, chronic airway disease).
4. Convulsive states such as status epilepticus, tetanus and strychnine poisoning, due to the stimulatory effects of pethidine on the spinal cord. Similarly, pethidine should not be used in pre-eclampsia or eclampsia.
5. Cardiac arrhythmias, especially supraventricular tachycardias; cor pulmonale. Pethidine has a possible vagolytic action which may produce a significant increase in the ventricular response rate.
6. Diabetic acidosis where there is a danger of coma.
7. Acute alcoholism or delirium tremens.
8. Severe liver disease, incipient hepatic encephalopathy.
9. Head injury, raised intracranial pressure (may cause diagnostic and monitoring problems; also hypercapnia associated with depressed respiration may increase intracranial pressure by itself); brain tumour.
10. Patients with a low platelet count, coagulation disorders or receiving anticoagulant treatment.

PRECAUTIONS

Serious and/or life-threatening reactions have been associated with the use of pethidine. The recommendations in the Precautions sections should be carefully observed. These reactions include respiratory depression, coma, convulsions (possibly due to elevated levels of norpethidine) and hypotension.

1. Pethidine should not be administered by intravenous injection unless resuscitative equipment and opioid antagonists are readily available.

2. Large doses and/or rapid intravenous administration of pethidine may produce rapid onset respiratory depression, apnoea, hypotension, peripheral circulatory collapse, bradycardia (due to stimulation of medullary vagal nuclei) or even cardiac arrest. Pethidine injections should be given slowly and preferably as a diluted solution.
3. Use is not recommended in patients with head injury and increased intracranial pressure. Respiratory depressant effects and ability to increase cerebrospinal fluid pressure may be exaggerated, and the clinical course obscured.
4. Pethidine may obscure the diagnosis and clinical course in patients with acute abdominal conditions. The risk of toxic megacolon may be increased in patients with severe inflammatory bowel disease.
5. Only use when necessary, and then with caution, in biliary colic, operations on the biliary tract and acute pancreatitis in view of the spasmogenic properties of pethidine on the biliary tract and the sphincter of Oddi. Pethidine may make surgical exploration of the common bile duct difficult.
6. Inadvertent intra-arterial administration of pethidine can produce severe necrosis and gangrene.
7. Pethidine produces reduced gastric emptying and the risk of aspiration may be expected to increase, whether associated with pethidine induced CNS depression/coma or during or after general anaesthesia, as for example a patient in labour who proceeds to caesarean section.
8. Opioid analgesics have abuse potential. Psychological and physical dependence may occur with repeated dosing. Except in patients with terminal conditions, pethidine should be restricted to short-term administration for the relief of severe pain not responding to non-opioid analgesics.
9. Abrupt withdrawal of pethidine in those physically dependent may precipitate withdrawal syndrome, including convulsions.
10. Pethidine associated neurotoxicity (PAN) is a range of excitatory central nervous system effects including tremor, hallucinations, seizures and mood changes attributed to the metabolite norpethidine (see ADVERSE REACTIONS). As norpethidine is primarily cleared by renal excretion, pethidine should be used with caution in patients with impaired renal function, the elderly, the very young and in patients receiving concomitant therapy with drugs such as phenobarbitone or phenylhydantoin. The problems of PAN are essentially dose-related, so pethidine should not be used for periods greater than 24 to 36 hours.
11. The administration of pethidine may result in profound hypotension in patients whose ability to maintain blood pressure is compromised by depleted blood volume or concurrent administration of certain anaesthetics or phenothiazines. Pethidine may also produce orthostatic hypotension in ambulatory patients.

12. Special risk patients: caution and an initial reduction in dose is recommended in patients who are elderly or debilitated and those with severely impaired pulmonary, hepatic or renal function and those with hypothyroidism, adrenocortical insufficiency, prostatic hypertrophy or urethral stricture.
13. The elderly demonstrate an increased sensitivity to opioids relative to younger patients. Reduced hepatic function, renal function and plasma protein binding may contribute to the elevated plasma levels found in elderly subjects. Lower doses or an increased dosing interval may be sufficient to provide effective analgesia in elderly patients.
14. Seizures may result from high doses. Patients with known seizure disorders should be carefully observed, as pethidine use may aggravate pre-existing convulsions. (See CONTRAINDICATIONS).
15. 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).
16. Since pethidine may cause drowsiness and general impairment of co-ordination, ambulatory patients should be cautioned against driving or operating machinery. Driving and operating dangerous machinery should not be contemplated until the day following the last dose of pethidine.
17. Pethidine should be used with considerable caution in patients taking other CNS depressant drugs such as hypnotics and sedatives (including barbiturates and benzodiazepines), phenothiazines, tranquillisers, anaesthetics, alcohol and antidepressants (including tricyclic antidepressants).
18. Patients with severe pain may tolerate very high doses of pethidine but may exhibit respiratory depression should their pain suddenly subside.
19. Reduced renal function may lead to accumulation of the toxic metabolite, norpethidine.
20. Reduced cardiac output may lead to reduced hepatic perfusion and diminished metabolism of pethidine leading to accumulation of pethidine with possible toxic results.
21. A transient rise in blood pressure and systemic vascular resistance as well as an increased heart rate may be caused by pethidine, therefore it is not recommended for pain relief in cardiac infarction.
22. The administration of pethidine to patients with phaeochromocytoma may result in a hypertensive crisis.
23. Hyperglycaemia has been reported with opioid agonists. This should be considered when diabetics require treatment with these agents.

24. Although pethidine is commonly used for pain relief in obstetrics, it is known to cross the placenta, and may cause respiratory depression in the neonate. An opioid antagonist may be required to reverse this depression. Metabolism and excretion of pethidine in the neonate is significantly reduced in comparison to adults, therefore accumulation and toxic levels may be reached following low doses.
25. If serious respiratory depression requiring treatment occurs in a patient who is physically dependent on opioids, an opioid antagonist should be administered **with extreme care** at a dose of 10 - 20% of the recommended initial dose. The administration of the usual dose will precipitate an acute withdrawal syndrome in these individuals, the severity of which 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.
26. 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 receive pethidine.

Use in pregnancy Category C

Opioid analgesics may cause respiratory depression in the newborn infant. These products should only be used during labour after weighing the needs of the mother against the risk to the foetus. Refer to PHARMACOKINETICS regarding pethidine and norpethidine levels in the foetus.

Animal reproduction studies have not been conducted with pethidine hydrochloride and safe use in pregnancy prior to labour has not been established in respect to possible adverse effects on foetal development.

Infants born of mothers who have been taking pethidine chronically may exhibit withdrawal symptoms.

Use in lactation

Pethidine appears in breast milk. As the concentrations in breast milk following usual therapeutic doses in the mother have not been determined and the clinical significance is not known, pethidine administration to nursing mothers is not recommended.

Interactions with other medicines

1. CNS Depressants

The depressant effects of pethidine are potentiated by other CNS depressants such as alcohol, barbiturates, chloral hydrate, benzodiazepines, sedatives, antihistamines, neuroleptics (e.g. phenothiazines, butyrophenones) tricyclic antidepressants and general anaesthetics.

2. **Phenothiazines**
CNS toxicity, hypotension and respiratory depression may occur when pethidine and phenothiazines are given together.
3. **Monoamine oxidase inhibitors (MAOIs)**
Excitation, sweating, rigidity, hypertension or hypotension, and coma have occurred when pethidine is given to patients who are taking MAOIs. On occasion this interaction has proved fatal. Selegiline, a MAO-B inhibitor, has also been reported to interact with pethidine, causing delirium, restlessness, sweating and rigidity.
4. **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 MAOIs.
5. **Delayed absorption**
The actions of pethidine on the gastrointestinal tract may influence absorption of other drugs. For example, paracetamol absorption may be reduced.
6. **Phenytoin / phenobarbitone**
Concomitant phenytoin or phenobarbitone therapy may increase the metabolism of pethidine, which may produce increased CNS effects due to norpethidine and reduce analgesia. (See ADVERSE REACTIONS)
7. **Coumarin, indanedione**
The effects of these derivative anticoagulants may be increased.
8. **Cimetidine**
Cimetidine inhibits metabolism of pethidine and therefore increases plasma concentration.

ADVERSE EFFECTS

As with other opioid analgesics respiratory depression is the major hazard of parenteral pethidine therapy. Other adverse experiences include:

More common

Central Nervous System: Light-headedness, dizziness, sedation, sweating, disorientation, bizarre feelings, hallucinations, psychosis. 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 the patient down.

Gastrointestinal: nausea, vomiting, constipation.

Less common

Central Nervous System: Euphoria, dysphoria, weakness, headache, delirium, insomnia, anxiety, hyperactivity or agitation, convulsions or tremor, drowsiness, coma, vertigo, uncoordinated muscle movements, respiratory depression, cold clammy skin, pallor, visual disturbances, miosis, depression, mental clouding,

occasional reports of mydriasis. Inadvertent injection around a nerve trunk may cause sensorineural effects, which is usually, but not always, transitory.

Pethidine associated neurotoxicity (PAN) is a range of excitatory central nervous system effects including tremor, hallucinations, seizures and mood changes attributed to the metabolite norpethidine. As norpethidine is primarily cleared by renal excretion, pethidine should be used with caution in patients with impaired renal function, the elderly, the very young and in patients receiving concomitant therapy with drugs such as phenobarbitone or phenylhydantoin. The problems of PAN are essentially dose-related.

Gastrointestinal: Dry mouth, anorexia, biliary tract spasm.

Genitourinary: Urinary retention, antidiuretic effect, anuria, reduced libido and/or potency.

Cardiovascular: Facial flushing, vasodilation, tachycardia, bradycardia, palpitations, faintness, syncope, hypertension, hypotension, orthostatic hypotension, gangrene following inadvertent intra-arterial administration.

Dermatological: Hypersensitivity causing pruritus, urticaria and other skin rashes, erythema, oedema, pain at injection site, local tissue irritation and induration following subcutaneous administration (especially after repeated injection), fibrosis of muscle tissue with frequent repetition of intramuscular injection.

Hepatic: Increased biliary tract pressure, choledochoduodenal sphincter spasm.

DOSAGE AND ADMINISTRATION

Pethidine hydrochloride may be administered by subcutaneous, intramuscular or slow intravenous injection. Pethidine Injection BP contains no antimicrobial agent. It should be used only once and any residue discarded.

For intravenous administration the dosage should be decreased and the injection administered very slowly as a dilute solution. When pethidine is given parenterally, especially by the intravenous route, the patient should be lying down. While the subcutaneous route is suitable for occasional use, intramuscular administration is preferred for repeated doses.

When administered intravenously, an opioid antagonist and facilities for assisted or controlled respiration should be immediately available during and following the injection.

Adult:

Analgesia: 25 to 100 mg by SC or IM injection or 25 to 50 mg by slow IV injection every 3 to 4 hours (see PRECAUTIONS).

The dose should be adjusted according to the severity of pain and the response of the patient. Dosage reduction may be necessary in the elderly.

Premedication: 50 to 100 mg by SC or IM injection or 25 to 50 mg by slow IV injection (see PRECAUTIONS).

Obstetric analgesia: 50 to 100 mg by SC or IM injection at intervals of 1 to 3 hours if necessary. Up to 3 doses may be given in 24 hours.

Renal and Hepatic Dysfunction

Dosage reduction and/or increased dosage intervals may be necessary in patients with renal or hepatic impairment (see PRECAUTIONS).

Paediatric:

Analgesia: 0.5 to 2 mg per kg bodyweight IM (maximum 100mg) every 3 to 4 hours.

Premedication: 1 to 2 mg per kg bodyweight IM (maximum 100mg).

Neonates

Metabolism and excretion of pethidine is reduced in the neonate compared with adults. The safety of pethidine in neonates has not been established and no dosage regimen can be recommended.

INCOMPATIBILITIES

Pethidine has been reported to be physically or chemically incompatible with thiopentone solutions and solutions containing aminophylline, amylobarbitone sodium, heparin sodium, methicillin sodium, morphine sulfate, nitrofurantoin, phenobarbitone sodium, phenytoin sodium, aciclovir sodium, imipenem, frusemide, doxorubicin hydrochloride, idarubicin hydrochloride, sodium bicarbonate, sodium iodide or sulphafurazole diethanolamine.

Pethidine is also incompatible with alkalis, iodine and iodides.

OVERDOSAGE

Symptoms: Overdosage is characterised by respiratory depression which may progress to Cheyne-Stokes respiration and/or cyanosis. Concomitant CNS depression may be present, as may extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin and/or hypothermia, bradycardia and hypotension.

In severe overdosage, particularly following rapid intravenous administration, apnoea, circulatory collapse, cardiac arrest, respiratory arrest and death may occur.

Complications such as pneumonia, shock and/or pulmonary oedema may also prove fatal.

Overdosage of pethidine may produce mydriasis rather than miosis (pupillary constriction). 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: Since respiratory arrest may result either through direct depression of the respiratory centre or as the result of hypoxia, primary attention should be given to the establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation.

The opioid antagonist, naloxone, is a specific antidote. Naloxone (see package information for full information) should be administered intravenously, simultaneously with respiratory resuscitation. As the duration of effect of naloxone may be considerably shorter than that of pethidine repeated administration may be necessary.

Note: The administration of the usual dose of opioid antagonist to a patient who is physically dependent on opioids will precipitate an acute withdrawal syndrome, the severity of which will depend on the degree of physical dependence and the dose of antagonist administered. If serious respiratory depression requiring treatment occurs in a patient who is physically dependent on opioids, an opioid antagonist should be administered **with extreme care** at a dose of 10 - 20% of the usual initial dose.

PRESENTATION AND STORAGE CONDITIONS

Polyamp DuoFit[®] 100 mg/2 mL in packs of 10 and 50 stored for 18 months at or below 25°C

POISON SCHEDULE OF THE MEDICINE

Controlled Drug (S8)

NAME AND ADDRESS OF THE SPONSOR

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Date of TGA approval letter: 20 October 1994

Date of most recent amendment: 8 September 2011