

DATA SHEET

PALLIDONE

Methadone Hydrochloride 5 mg tablets

Presentation

PALLIDONE tablets are white, scored, circular, film-coated tablets engraved with DP on one side and '5' on the other.

Uses

Actions

Methadone is a potent synthetic opioid agonist analgesic with actions and uses similar to those of morphine. Activity is exerted primarily at the mu opioid receptor. Methadone is said to have a less marked sedative action than morphine. Analgesia begins 30 to 60 minutes after oral administration, lasting about 4 to 6 hours. As accumulation occurs following repeated doses, the effects become more prolonged.

Methadone depresses the cough centre. It also depresses the respiratory centre and is therefore undesirable as an obstetric analgesic. Its action on the gastro-intestinal tract is weaker than that of morphine and constipation seldom occurs. 20mg of methadone via oral administration is therapeutically equivalent to 10mg of intramuscular morphine.

Pharmacokinetics

Methadone is readily absorbed from the gastro-intestinal tract. Peak effect is obtained within 1.5 to 2 hours.

The plasma half-life of methadone is between 15 to 25 hours which may be increased in methadone-tolerant subjects and decreased in subjects whose urine is acidic.

Methadone is widely distributed in the tissues and diffuses across the placenta. 60-85% is bound to plasma proteins.

Metabolism occurs in the liver, mainly by N-demethylation and cyclisation, and the metabolites are excreted in the bile and urine.

Indications

Methadone is indicated in the treatment of moderate to severe pain (particularly of visceral origin) and in the treatment of dependence on opioid drugs. It effectively controls the symptoms

of morphine withdrawal and dependence on methadone is easier to treat than dependence on morphine. It may also be used as an antitussive agent.

Dosage and Administration

Adults: Pallidone tablets are given orally at a dose of 5-10mg twice daily, adjusted as necessary to achieve relief of pain. When used in the treatment of dependence, methadone is given initially in doses sufficient to suppress withdrawal symptoms. Doses of 15-40mg daily by mouth have been used. After stabilisation the dose is gradually decreased according to individual requirements until total withdrawal is achieved.

Owing to its long plasma half-life caution with repeated dosage should be observed in the very ill or elderly.

Where the drug is given orally for the control of pain associated with a chronic condition, it is wise to restrict the dose to the smallest amount, which will adequately control the symptoms.

Children: Not suitable.

Contraindications

Methadone is generally contraindicated in respiratory depression, especially in the presence of cyanosis and excessive bronchial secretion. It is also contraindicated in the presence of acute alcoholism, head injuries, and conditions in which intracranial pressure is raised. It should not be given during an attack of bronchial asthma or in heart failure secondary to chronic lung disease.

Concurrent administration with monoamine oxidase inhibitors, or within two weeks of discontinuation with them is contraindicated (*see Warnings and Precautions*).

Warnings and Precautions

Methadone should be given with caution or in reduced doses to patients with hypothyroidism, adrenocortical insufficiency, impaired kidney or liver function, prostatic hypertrophy or shock. It should be used with caution in patients with obstructive bowel disorders and those with myasthenia gravis. Methadone is not recommended for use in obstetrical analgesia or in ambulant patients.

When used in therapeutic doses for prolonged periods, methadone may lead to the development of dependence of the morphine type and patients should be reminded of the necessity of adhering to the prescribed dosage.

Use in Pregnancy: Risk-benefit must be considered because opioid analgesics cross the placenta. Regular use during pregnancy may cause physical dependence in the foetus, leading to withdrawal symptoms (convulsions, irritability, excessive crying, tremors, hyperactive reflexes, fever, vomiting, diarrhoea, sneezing and yawning) in the neonate.

Use of methadone by pregnant women participating in methadone maintenance programmes has also been associated with foetal distress in utero and low birth weight. Although teratogenic effects in humans have not been documented, controlled studies have not been done.

Use in Lactation: Problems in humans with most opioid analgesics have not been documented. Methadone is readily excreted into breast milk. Risk-benefit must be considered when methadone is administered to a nursing mother in a methadone maintenance programme because use of maintenance doses may cause physical dependence in the infant.

Use in Children: Children up to 2 years of age may be more susceptible to the effects, especially the respiratory depressant effects of these agents. Paradoxical excitation is especially likely to occur in paediatric patients receiving opioid analgesics.

Use in the Elderly: Geriatric patients may be more susceptible to the effects, especially the respiratory depressant effects of opioid analgesics. Also, geriatric patients are more likely to have prostatic hypertrophy or obstruction and age-related renal function impairment, and are therefore more likely to be adversely affected by opioid-induced urinary retention. In addition, geriatric patients may metabolise or eliminate opioid analgesics more slowly than younger adults. Lower doses or longer dosing intervals than those usually recommended for adults may be required, and are usually therapeutically effective for these patients.

Cardiac Conduction Effects: Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. These cases appear to be more commonly associated with, but not limited to, higher dose treatment (>200mg/day). Most cases involve patients being treated for pain with large, multiple daily doses of methadone although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.

Methadone should be administered with particular caution to patients already at risk for development of prolonged QT interval (eg cardiac hypertrophy, concomitant diuretic use, hypokalaemia, hypomagnesaemia). Careful monitoring is recommended when using methadone in patients with a history of cardiac conduction abnormalities, those taking medications affecting cardiac conduction, and in other cases where history or physical exam suggest an increased risk of dysrhythmia. QT prolongation has also been reported in patients with no prior cardiac history who have received high doses of methadone. Patients developing QT prolongation while on methadone treatment should be evaluated for the presence of modifiable risk factors, such as concomitant medications with cardiac effects, drugs which might cause electrolyte abnormalities, and drugs which might act as inhibitors of methadone metabolism. For use of methadone to treat pain, the risk of QT prolongation and development of dysrhythmias should be weighed against the benefit of adequate pain management and the availability of alternative therapies.

Adverse Effects

Euphoria, dizziness, drowsiness, constriction of the pupil, vomiting or nausea and respiratory depression may occur in some patients. Methadone has a relatively greater respiratory depressant effect than morphine.

In rare cases, a hypersensitive subject may react with a sudden transient fall in blood pressure; this is short-lived and self-terminating. Tolerance and dependence may occur as well as mild withdrawal symptoms.

Interactions

As serious and sometimes fatal reactions have occurred following administration of pethidine to patients receiving monoamine oxidase inhibitors, methadone and other opioid analgesics should be given with extreme caution. The depressant effects of methadone are enhanced by depressants of the central nervous system such as alcohol, anaesthetics, hypnotics and sedatives, tricyclic antidepressants, and phenothiazines. The actions of opioids may in turn affect the activities of other compounds. For instance, their gastro-intestinal effects may delay absorption as with mexilitine or may be counteractive as with metoclopramide.

Urinary acidifiers may increase methadone elimination, thereby reducing plasma concentration, withdrawal symptoms may occur in some physically dependant patients. Phenytoin or rifampicin may increase methadone metabolism and precipitate symptoms in physically dependent patients.

The antiviral agent, nevirapine, may increase plasma concentrations of methadone by increasing its hepatic metabolism. Some clinical reports suggest that patients who are taking methadone may experience narcotic withdrawal symptoms when they begin nevirapine therapy. Therefore the dose of methadone may need to be increased based on the emergence of withdrawal symptoms in some patients who begin nevirapine therapy. Methadone-maintained patients beginning nevirapine should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.

Propranolol has been reported to enhance the lethality of toxic doses of opioids in animals. Although the significance of this finding is not known for man, caution should be exercised when such drugs are co-administered.

Overdosage

Symptoms: Toxic doses of methadone may cause unconsciousness, pin-point pupils, slow shallow respiration, cyanosis and weak pulse. Often there is a 2 to 3 hour delay between ingestion and the appearance of symptoms. Pulmonary oedema after overdosage is a common cause of fatalities among addicts.

Treatment: Lavage, dialysis and CNS stimulation are contraindicated. Intravenous naloxone should be given and repeated at 5 to 10 minute intervals to attain full benefit. Acidification of the urine will increase the rate of elimination of the drug via the kidney.

Pharmaceutical Precautions

Protect from light and moisture. Store below 25 °C. Keep out of reach of children.

Medicine Classification

Controlled Drug B3.

Package Quantities

Pallidone tablets 10's

Further Information

Methadone hydrochloride occurs as odourless colourless crystals or as white crystalline powder. It has a molecular formula and weight of $C_{21}H_{27}NO.HCl$ and 345.9 respectively.

Name and Address

Douglas Pharmaceuticals Ltd
P.O. Box 45-027
AUCKLAND 0651

Ph: (09) 835-0660
Fax: (09) 835-0665

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