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.

Pallidone tablets contain lactose, maize starch, microcrystalline cellulose, polyvinylpyrolidone, sodium starch glycolate, magnesium stearate, Hypromellose, macrogol 400, titanium dioxide and indigo carmine (FD & C Blue 2) in addition to the methadone hydrochloride

Uses

Actions

Methadone is a potent synthetic opioid agonist analgesic with actions and uses similar to those of morphine. Methadone is a racemic mixture and levo-methadone is the active isomer. 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 and has high oral bioavailability. Peak plasma concentrations have been reported 1 to 5 hours after oral administration of a single dose in tablet form while peak effect is obtained within 1.5 to 2 hours.

Elimination half-lives vary considerably with a range of 15-to 60 hours being reported as a result of increase in methadone-tolerant subjects and decrease in the presence of acidic urine. Careful adjustment of dosage is necessary with repeated administration.

Methadone undergoes considerable tissue distribution, and protein binding is reported to be 60 to 90% with oc-acid glycoprotein being the main binding protein in plasma.
Metabolism mainly by N-demethylation and cyclisation occurs in the liver. The major metabolite 2-ethylidine-1,5-dimethyl-3,3-diphenyl-5-methylypyrrolidine is inactive. All metabolites are excreted in the faeces and urine together with unchanged methadone.

Other metabolites, including methanol and nor-methadon (reported to be pharmacologically active), have also been described, but account for a small proportion of the dose. The liver may also serve as a major storage site of unchanged methadone which is taken up, bound non-specifically by the liver and released again mainly unchanged.

Marked inter individual variation in kinetics have been observed with methadone.

Plasma concentrations have been found to vary widely during methadone maintenance therapy with large differences between patients and wide fluctuations in individual patients.

**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**

**Treatment of moderate to severe pain**

Adults: Starting oral doses of methadone may range from 5 to 10mg (1 to 2 tablets) given every 6 to 8 hours or longer and thereafter adjusted as necessary. 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.

**Treatment of dependence on opioid drugs**

A dose of 10 to 20mg (2 to 4 tablets) by mouth may be given initially and increased as necessary by 5 to 10mg daily. The dose must not be increased by more than 5 to 10mg daily and by no more than 30mg in any 7-day period. After stabilisation, which can often be achieved with a dose of 30 to 50mg daily (up to a maximum of 80mg daily), the dose of methadone is gradually decreased until total withdrawal is achieved. Some treatment schedules for opioid dependence involve prolonged maintenance therapy with methadone where the daily dose is adjusted carefully for the individual.

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

**Children:** Methadone is not suitable for use in children.
Contraindications

Methadone is contraindicated in individuals who are hypersensitive to methadone or other components in Pallidone Tablets (see Presentation). 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).

As with other opioids, methadone is contraindicated in patients with ulcerative colitis, since it may precipitate toxic dilation or spasm of the colon.

As with all narcotics, Methadone should not be administered to patients with severe hepatic impairment as it may precipitate hepatic encephalopathy (see Warnings and Precautions)

Methadone is contraindicated in biliary and renal tract spasm.

Warnings and Precautions

In common with all opioids, prolonged use of methadone has the potential to produce dependence of the morphine type and patients should be reminded of the necessity of adhering to the prescribed dosage.

Pallidone tablets should be used with caution in the presence of hypothyroidism, adrenocortical insufficiency, hypopituitarism, prostatic hypertrophy, shock, diabetes mellitus and impaired kidney or liver function.

Pallidone should be used with caution in patients with obstructive bowel disorders and those with myasthenia gravis. Pallidone is not recommended for use in obstetrical analgesia or in ambulant patients.

Extreme caution should be exercised when administering Pallidone tablets to patients with phaeochromocytoma, since aggravated hypertension has been reported in association with diamorphine.

In common with other opioids, methadone may produce orthostatic hypotension and drowsiness in ambulatory patients. They should be cautioned, therefore, against driving a vehicle operating machinery or other activities requiring vigilance after taking Pallidone tablets.

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 (torsade’s 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 (> 100mg/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 of opioid addiction.

Pallidone tablets should be administered with particular caution to patients already at risk for development of prolonged QT interval. These risks include cardiac hypertrophy, history of cardiac conduction abnormalities, advanced heart disease or ischaemic heart disease, liver disease, family history of sudden death, hypokalaemia, hypomagnesaemia, concomitant treatments with medicines that have a potential for QT prolongation, concomitant treatment with medicines which may cause electrolyte abnormalities (e.g. diuretics) and concomitant treatment with CYP3A4 inhibitors.

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 Pallidone treatment should be evaluated for the presence of modifiable risk factors, such as concomitant medications with cardiac effects, medicines which might cause electrolyte abnormalities, and medicines which might act as inhibitors of methadone metabolism.

In patients with recognised risk factors of QT prolongation, or in case of concomitant treatment with medicines that have a potential for QT prolongation, ECG monitoring is recommended prior to methadone treatment, at dose stabilisation, after dose increases, or after starting any potentially interacting medicine. In patients without recognised risk factors for QT prolongation, ECG monitoring is recommended before dose titration above 100mg/day, and at seven days after titration.

For use of pallidone 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.

**Mutagenicity:**
Methadone did not demonstrable mutagenic activity in a wide range of standard in vitro and in vivo mutagenicity assays. However, in a Dominant Lethal assay in mice, treatment with methadone at doses of 1 to 6 mg/kg was associated with increased pre-implantation deaths and chromosomal aberrations of sperm cells, when compared with controls.

**Carcinogenicity:**
Long term carcinogenicity tests in rodents did not reveal any evidence of methadone-related neoplasia.

**Teratogenicity:**
No teratogenic effects have been observed in standard teratogenicity studies in rats and rabbits given methadone at doses from 10 to 50 times the average daily human maintenance dose. Developmental abnormalities of the central nervous system have been reported in hamsters and mice given high doses in early pregnancy.
Fertility:
Methadone does not appear to impair human female fertility. Studies in men on methadone maintenance programmes have shown that methadone reduces serum testosterone and markedly depresses the ejaculate volume and sperm motility. The sperm counts of methadone subjects were twice that of controls, reflecting the lack of dilution through reduced seminal secretions.

Use in Pregnancy:
There is inadequate evidence of the safety of methadone in human pregnancy although use of methadone by pregnant women participating in methadone maintenance programmes has been associated with foetal distress in utero and low birth weight. Autopsies on five infants who died in utero did not reveal any physical abnormality attributable to methadone use by their dependent mothers. Regular use during pregnancy, however, 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. Therefore, the use of methadone in pregnancy should be avoided unless there is no safer alternative.

Although teratogenic effects in humans have not been documented, controlled studies have not been done.

Narcotics may cause respiratory depression in the newborn infant. During the last 2 to 3 hours before expected delivery, narcotics should therefore only be used after weighing the needs of the mother against the risk to the foetus.

Use in Lactation:
Breast feeding is permissible in mothers receiving methadone for maintenance therapy but the baby should be monitored to avoid sedation. Withdrawal symptoms can occur in the infant. Assays of breast milk from Methadone-maintained mothers showed methadone concentrations of 0.17 to 5.6 µg/ml.

Use in Children:
Pallidone is not recommended for use in children less than 18 years of age since documented clinical experience has been insufficient to establish a suitable dosage regimen. Furthermore, children are particularly sensitive to the respiratory and central nervous system effects of methadone.

Use in the Elderly:
Methadone has a long plasma half life which may lead to accumulation, particularly if renal function is impaired (see Renal Impairment). In common with other opioids, methadone may cause confusion in this age group, therefore careful monitoring is advised.

Hepatic Impairment:
Particular care should be taken when Pallidone is to be used in patients with hepatic impairment as these patients metabolise methadone more slowly than normal patients. Where not contraindicated, methadone should be given at less than the normal recommended dose and the patient's response used as a guide to further dosage requirements (see Contraindications).
**Renal Impairment**
Methadone should be used with caution in patients with renal dysfunction.

**Adverse Effects**
The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea, vomiting, and sweating. These effects seem to be more prominent in ambulatory patients and in those who are not suffering severe pain. In such individuals, lower doses are advisable.

The major hazards of methadone are respiratory depression and, to a lesser degree, systemic hypotension. Respiratory arrest, shock, cardiac arrest, and death have occurred.

Other adverse reactions include the following:

Body as a whole: weakness, oedema, headache

Cardiovascular: arrhythmias, bigeminal rhythms, bradycardia, cardiomyopathy, ECG abnormalities, extrasystoles, flushing, heart failure, hypotension, palpitations, phlebitis, QT interval prolongation, syncope, T-wave inversion, tachycardia, torsade de pointes, ventricular fibrillation, ventricular tachycardia

Endocrine: hypogonadism

Gastrointestinal: abdominal pain, anorexia, biliary tract spasm, constipation, dry mouth, glossitis

Hematologic: reversible thrombocytopenia has described in opioid addicts with chronic hepatitis

Metabolic: hypokalaemia, hypomagnesaemia, weight gain

Musculoskeletal: decreased muscle mass and strength, osteoporosis and fractures

Nervous system disorders: raised intracranial pressure, sedation

Psychiatric: agitation, changes of mood, dependence, disorientation, dysphoria, euphoria, hallucinations, insomnia

Renal: antidiuretic effect, urinary retention or hesitancy

Reproductive: amenorrhoea, reduced libido and/or potency, reduced ejaculate volume, reduced seminal vesicle and prostate secretions, decreased sperm motility, abnormalities in sperm morphology

Respiratory: pulmonary oedema, respiratory depression

Skin and subcutaneous tissue: pruritus, urticaria, other skin rashes, and rarely, haemorrhagic urticaria
Maintenance on a stabilised dose: during prolonged administration of methadone, as in a methadone maintenance programme, constipation and sweating often persist and hypogonadism, decreased serum testosterone and reproductive effects are thought to be related to chronic opioid use.

Interactions

NOTE: Patients with hepatitis C may have impaired liver function. This needs to be taken into account when the use of medicines metabolised by the liver is considered. The dose of paracetamol, for example, needs to be well within the standard 4 g per day.

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Status of effect</th>
<th>Interaction</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Clinically important</td>
<td>Increased sedation</td>
<td>Additive central nervous system depression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased respiratory depression; combination may also have increased hepatoxic potential</td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Clinically important</td>
<td>Enhanced sedative effect</td>
<td>Additive CNS depression</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>Clinically important</td>
<td>Antagonistic effect or enhanced sedative and respiratory depression</td>
<td>Partial agonist of opiate receptors</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Clinically important</td>
<td>Reduced methadone levels</td>
<td>Stimulates hepatic enzymes involved in methadone metabolism</td>
</tr>
<tr>
<td>Chlormethiazole</td>
<td>Clinically important</td>
<td>Enhanced sedative effect</td>
<td>Additive CNS depression</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Two cases have been shown in patients taking methadone as analgesia</td>
<td>Possible increase in methadone levels</td>
<td>Inhibits hepatic enzymes involved in methadone metabolism</td>
</tr>
<tr>
<td>Cisapride, domperidone, metoclopramide</td>
<td>Theoretical</td>
<td>Theoretically might increase the speed of onset of methadone absorption, but not the extent</td>
<td>Possibly by reversing the delayed gastric emptying associated with opioids</td>
</tr>
<tr>
<td>Cyclizine and other sedating antihistamines</td>
<td>Clinically important</td>
<td>Anecdotal reports of injection of cyclizine with opioids causing hallucinations</td>
<td>Additive psychoactive effects; anti-muscarinic effects at high doses</td>
</tr>
<tr>
<td>Desipramine</td>
<td>Clinically important</td>
<td>Raised desipramine levels by up to a factor of two</td>
<td>Unknown interaction not seen with other tricyclic antidepressants</td>
</tr>
<tr>
<td>Other tricyclic antidepressants</td>
<td>Theoretical</td>
<td>Enhanced sedative effect, which is dependent.</td>
<td>Additive CNS dose depression</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>In theory should</td>
<td>Increase in</td>
<td>Decreased</td>
</tr>
<tr>
<td>Drug</td>
<td>Interaction</td>
<td>Effect on Methadone Levels</td>
<td>Effect on Methadone Metabolism</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>--------------------------------------------------</td>
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</tr>
<tr>
<td>Fluconazole</td>
<td>In theory the same as ketoconazole</td>
<td>Raised methadone levels</td>
<td>Decreased methadone metabolism</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Clinically important</td>
<td>Raised methadone levels</td>
<td>Decreased methadone metabolism</td>
</tr>
<tr>
<td>Fluvoxamine, other SSRI</td>
<td>Clinically important, theoretical</td>
<td>Raised plasma methadone levels</td>
<td>Decreased methadone metabolism</td>
</tr>
<tr>
<td>Grapefruit juice</td>
<td>Should interact in theory and there have been several anecdotal reports</td>
<td>Raised methadone levels</td>
<td>Decreased methadone metabolism</td>
</tr>
<tr>
<td>Indinavir</td>
<td>Clinically important</td>
<td>Raised methadone levels</td>
<td>Decreased methadone metabolism</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Clinically important</td>
<td>Raised methadone levels</td>
<td>Decreased methadone metabolism</td>
</tr>
<tr>
<td>MAOI (including selegiline and moclobamide)</td>
<td>Severe with pethidine though unlikely with methadone and has never been described</td>
<td>CNS excitation, delirium, hyperpyrexia, convulsions, hypotension or respiratory depression</td>
<td>Unclear; avoid the combination if possible</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>Clinically important</td>
<td>Blocks effect of methadone (long acting)</td>
<td>Opioid agonist-competes for opiate receptors</td>
</tr>
<tr>
<td>Naloxone</td>
<td>Clinically important</td>
<td>Blocks effect of methadone (long acting) but may be needed if overdose suspected</td>
<td>Opioid agonist-competes for opiate receptors</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Clinically important</td>
<td>Decreased methadone levels</td>
<td>Increased methadone metabolism</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Has been demonstrated in vitro only</td>
<td>Increased nifedipine levels; no effect on methadone levels</td>
<td>Methadone decreases the metabolism of nifedipine</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>To date, demonstrated only in animals</td>
<td>Increased methadone levels</td>
<td>Possibly affects methadone absorption from the gut</td>
</tr>
<tr>
<td>Phenobarbitone</td>
<td>Clinically important</td>
<td>Reduced methadone levels; increased sedation, additive CNS depression</td>
<td>Barbiturates stimulate hepatic enzymes involved in methadone metabolism</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Clinically important</td>
<td>Reduced methadone levels</td>
<td>Phenytoin stimulates hepatic enzymes</td>
</tr>
<tr>
<td>Drug Type</td>
<td>Importance</td>
<td>Effect on Methadone Levels</td>
<td>Effect on Metabolism</td>
</tr>
<tr>
<td>-----------</td>
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</tr>
<tr>
<td>Rifampicin</td>
<td>Very important: most patients are likely to be affected.</td>
<td>Reduced methadone levels</td>
<td>Rifampicin stimulates hepatic enzymes involved in methadone metabolism</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Occasionally clinically important</td>
<td>Decreased methadone levels</td>
<td>Increased methadone metabolism</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Clinically important</td>
<td>Ritonavir may increase methadone levels</td>
<td>Inhibits methadone metabolism</td>
</tr>
<tr>
<td>Other protease inhibitors</td>
<td>Theoretical</td>
<td>May raise or lower plasma methadone levels</td>
<td>Inhibits methadone metabolism</td>
</tr>
<tr>
<td>Urine acidifiers (e.g. ascorbic acid/vitamin C)</td>
<td>Clinically important</td>
<td>Reduced plasma methadone levels</td>
<td>Raised urinary excretion of methadone</td>
</tr>
<tr>
<td>Urine alkalinisers (e.g. sodium bicarbonate)</td>
<td>Clinically important</td>
<td>Increased plasma methadone levels</td>
<td>Reduced urinary excretion of methadone</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Clinically important</td>
<td>Raised plasma levels of zidovudine; no effect on methadone levels</td>
<td>Unknown</td>
</tr>
<tr>
<td>Zopiclone</td>
<td>Clinically important</td>
<td>Enhanced sedative effects</td>
<td>Additive CNS depression</td>
</tr>
<tr>
<td>Other opioids</td>
<td>May be clinically important</td>
<td>Enhanced sedative effect</td>
<td>Additive CNS depression; enhanced respiratory depression</td>
</tr>
<tr>
<td>Other CNS depressant medicines (e.g. neuroleptics, hyoscine)</td>
<td>Clinically important</td>
<td>Enhanced sedative effects which are dose dependent</td>
<td>Additive CNS depression</td>
</tr>
</tbody>
</table>

**Overdosage**

**Symptoms:** Toxic doses of methadone may cause unconsciousness, profound respiratory depression, pin-point pupils, hypotension, circulatory failure, 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.

Mydriasis may replace miosis as asphyxia intervenes. Drowsiness, floppiness, pin-point pupils and apnoea have been reported in children.

**Treatment:** Lavage, dialysis and CNS stimulation are contraindicated.

General supportive measures should be employed as required. The specific opioid antagonist naloxone is the treatment of choice for the reversal of coma and the
restoration of spontaneous respiration. A dose of 0.4 to 2 mg is given by intravenous
injection repeated at intervals of 2 to 3 minutes if necessary, up to 10 mg. Naloxone
may also be given by subcutaneous or intramuscular injection or intravenous
infusion.

Patients should be monitored closely for at least 48 hours after apparent recovery in
case of relapse, since the duration of action of the antagonist may be substantially
shorter than that of methadone.

The use of other respiratory or central stimulants is not recommended.

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.

The shelf-life of Pallidone tablets is 4 years from date of manufacture.

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Date of Preparation

16 June 2014