NAME OF THE MEDICINE

Dothiepin hydrochloride

DESCRIPTION

Prothiaden is a tricyclic antidepressant that has anxiolytic properties. The chemical name is 3-(6H-dibenzo(b,e)-thiepin-11-ylidene) propyldimethylamine hydrochloride.

Dothiepin hydrochloride is a white to faintly yellow crystalline powder that is almost without odour. The compound is soluble in water, chloroform, and alcohol but is almost insoluble in ether. The molecular weight is 331.9.

Prothiaden is available for oral administration as red, round shaped, sugar-coated tablets printed with ‘P75’ in white, containing 75mg dothiepin hydrochloride and as a hard gelatin capsules with red and brown base, printed with ‘P’ on one end and ‘25’ on the other, containing 25mg dothiepin hydrochloride.


The capsule excipients are: magnesium stearate, starch – maize, brilliant scarlet 4R, iron oxide yellow, titanium dioxide, gelatin, iron oxide black and iron oxide red.

PHARMACOLOGY

Dothiepin is a thioanalogue of amitriptyline. In antireserpine activity it is generally equivalent to amitriptyline but less potent than imipramine.

Site and mode of Action: The site of action is thought to be in the CNS, but the mechanism by which this drug and all tricyclic antidepressants produce an antidepressant effect is unknown. Dothiepin possesses anticholinergic, antihistamine and central sedative properties. It is postulated that the aetiology of depression is associated with a functional abnormality of one or more of the biogenic amines, particularly the catecholamines, in the brain. The tricyclics inhibit uptake of noradrenaline and 5-hydroxytryptamine from the nerve endings thus increasing their availability at central noradrenergic synapses.

PHARMACOKINETICS

Absorption: Well absorbed. Animal studies show dothiepin is absorbed from the small intestine. After a single 50 mg oral dose in one patient, a peak level of 20 nanogram/mL was achieved after 3 hours, falling to 10 nanogram/mL at 6 hours. There are substantial inter-individual variations in steady state concentrations. In 10 patients taking 100 mg/day for two weeks, the serum
concentration ranged from 18 to 84 nanogram/mL (mean 41 ± 7 nanogram/mL). After increasing the dose to 175 mg/day for a further two weeks the concentration ranged from 43 to 196 nanogram/mL (mean 96 ± 15 nanogram/mL). Steady state concentrations appear to be reached after 10 to 14 days.

**Distribution:** Dothiepin is present in low concentrations in breast milk. It crosses the placental and blood-brain barriers in animals. Animal studies in the dog and cat show maximal concentration after 24 hours in liver, uveal tract of the eye, lung, kidney, pituitary and thyroid in descending order. In dogs, the tissue/plasma ratio for uveal tract tissue was 257:1.

**Protein Binding:** Unchanged drug is about 84% bound to serum protein.

**Metabolism:** Dothiepin is metabolised in the liver and in man 12 basic metabolites were found in the urine, the bulk of which are northiaden sulphoxide and dothiepin sulphone. The metabolic pathways are thought to consist of N-demethylation, S-oxidation and glucuronic acid conjugation. There is active enterohepatic circulation in animals but this has not been studied in humans.

**Excretion:** 71% of a 50 mg labelled dose is excreted in the urine and faeces within 4 days, 56% being by the renal route.

**Half-life:** The elimination half-life is biphasic; the first phase is 15 hours, the second 56 hours. Mean whole body elimination half-life is 51 hours.

**INDICATIONS**

Treatment of major depression.

**CONTRAINDICATIONS**

Epilepsy; seizure thresholds may be lowered by the drug.

Tricyclic antidepressants should not be used concomitantly or within 14 days of treatment with MAOIs since the combination may cause cerebral excitation followed by coma and dangerous hyperthermia.

Acute recovery phase following myocardial infarction; tricyclic antidepressants may produce conduction defects and arrhythmias.

Hepatic failure (see Dosage with impaired liver or renal function).

Hypersensitivity to dothiepin.

**PRECAUTIONS**

Due to its toxicity in overdose, Prothiaden should only be used in patients intolerant of or unresponsive to alternative treatment options (see OVERDOSAGE).
Toxicity in overdose
Dothiepin is associated with high mortality in overdose. There is a low margin of safety between the (maximum) therapeutic dose and potentially fatal doses. Onset of toxicity occurs within 4 – 6 hours.

- A limited number of tablets should be prescribed to reduce the risk from overdose for all patients and especially for patients at risk of suicide.
- A maximum prescription equivalent to two weeks supply of 75mg/day should be considered in patients with increased risk factors for suicide at initiation of treatment, during any dosage adjustment and until improvement occurs.
- Avoid concomitant medications which may increase the risk of toxicity associated with dothiepin (see Interactions with Other Medicines).
- Patients should be advised to store the medicine securely, out of sight and reach of children.
- In cases of overdose, patients should seek IMMEDIATE MEDICAL ATTENTION (see OVERDOSAGE).

Clinical Worsening and Suicide Risk
The risk of suicide attempt is inherent in depression and may persist until significant remission occurs. This risk must be considered in all depressed patients.

Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored for clinical worsening and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality symptoms that may be precursors to worsening depression or suicidality, if these symptoms are severe, abrupt in onset, or were not part of the patient’s presenting symptoms. Patients with co-morbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

Pooled analyses of 24 short-term (4-16 weeks), placebo-controlled trials of nine antidepressant medicines (SSRIs and others) in 4400 children and adolescents with major depressive disorders (16 trials), obsessive compulsive disorder (4 trials), or other psychiatric disorders (4 trial) have revealed a greater risk of adverse events representing suicidal behaviour or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients treated with an antidepressant was 4%, compared with 2% of patients given placebo. There was considerable variation in risk among the antidepressants, but there was a tendency towards an increase for almost all antidepressants studied. The risk of suicidality was most consistently observed in the major depressive disorder trials, but there were signals of risk
arising from trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in these trials. It is unknown whether the suicidality risk in children and adolescents patients extends to use beyond several months. The nine antidepressant medicines in the pooled analyses included five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and four non-SSRIs (bupropion, mirtazapine, nefazodone, venlafaxine).

Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and paediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non psychiatric. Although a casual link between the emergence of such symptoms and either worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and non-psychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behaviour, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers.

Prescriptions for Prothiaden should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce risk of overdose.

Latent schizophrenia may be activated by dothiepin.

Psychotic manifestations, including mania and paranoid delusions, with or without associated hostility, may be exaggerated during treatment with tricyclic antidepressants.

**Screening Patients for Bipolar Disorder**
A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

**Electroconvulsive Therapy**
The hazards of ECT may be increased as the drug lowers the convulsive threshold.

**Elective surgery**
The drug should be withdrawn prior to surgery as anaesthetics given during tricyclic antidepressant therapy may increase the risk of arrhythmias and hypotension.

**Severe depression**
In patients with severe depression, the possibility of suicide using this drug exists and hence they
should be closely supervised during early therapy. These patients should not receive large quantities of the drug.

**Manic depressive psychosis**
The drug may provide a shift towards the manic phase.

**Monoamine oxidase inhibitors**
Do not prescribe dothiepin concurrently or within 14 days of MAOIs (see CONTRAINDICATIONS). After withdrawal of MAOIs, initiate therapy at low doses and gradually increase to the normal range.

**Cardiovascular disorders**
Prothiaden may increase the risk of cardiovascular toxicity (cardiac arrhythmias, conduction disorders, cardiac failure and circulatory collapse), especially in the elderly. Caution should be exercised in using Prothiaden in the elderly and in patients with suspected cardiovascular disease (see CONTRAINDICATIONS).

**Hyperthyroidism or patients being treated with thyroid hormone**
Closely supervise these patients as the drug may provoke cardiac arrhythmias or conduction defects.

**Glaucoma, prostatic hypertrophy, urinary retention and concurrent anticholinergic therapy**
Dothiepin has an anticholinergic action and can exacerbate glaucoma and urinary retention and potentiate anticholinergics

**Concurrent therapy with sympathomimetic drugs**
Tricyclic antidepressants have been reported to produce possible dangerous potentiation of the effects of sympathomimetic drugs.

**Renal or hepatic impairment**
Use with care as toxic blood levels may develop (see Dosage with impaired liver or renal function).

**Ophthalmological examination**
Eyes should be examined regularly for visual acuity and colour fields checked during prolonged therapy since the drug or its metabolites may accumulate in the pigmented area of the eye in experimental animals.

**Impairment of motor co-ordination**
Ability to drive or operate machinery may be impaired as alertness is decreased.

**Use in children and adolescents (< 18 years)**
The safety and efficacy of Prothiaden for the treatment of depression or other psychiatric disorders in children and adolescents aged less than 18 years has not been satisfactorily established. Prothiaden should not be used in this age group for the treatment of depression or other psychiatric disorders.
**Elderly patients**
Use with care as confusional states may occur.

**Dependence and Withdrawal**
Dependency potential is unknown.

Abrupt withdrawal may produce headache, nausea, convulsions, insomnia, irritability, excessive perspiration and the possibility of thrombotic episodes. It is recommended that antidepressants be withdrawn gradually. Symptoms similar to insomnia, irritability and excessive perspiration in neonates whose mothers received tricyclic antidepressants during the third trimester also have been reported.

**Use in Pregnancy** (Category C)
Withdrawal symptoms in newborn infants have been reported with prolonged maternal use of this class of drugs. Tricyclic antidepressants have not been shown to be associated with an increased incidence of birth defects. However, there is evidence of interference with central monoamine neurotransmission in rats. Care should be taken that there are sound indications for the use of these antidepressants during pregnancy.

**Use in Lactation**
Small amounts of Prothiaden have been observed in breast milk and its possible effect on the child must be carefully considered if it is necessary to give the drug to nursing mothers.

**Interactions with other medicines**

*Alcohol:*
The effect of alcohol may be potentiated by dothiepin. One death has been associated with this combination.

*Other drugs:*
Barbiturates: The sedative effect may be potentiated.

*Tranquillisers and CNS depressants:*
The sedative effect may be potentiated.

*Guanethidine and other adrenergic neurone blocking drugs:*
The antihypertensive effect may be blocked by dothiepin.

*Sympathomimetics:*
The sympathomimetic effect may be dangerously potentiated by dothiepin.

*Monoamine oxidase inhibitors:*
A potentially lethal interaction can occur between MAOIs and tricyclic antidepressants (see CONTRAINDICATIONS and PRECAUTIONS).

*Anticholinergics:*
Dothiepin may potentiate their anticholinergic effects.
Antihistamines:
May be potentiated.

Food:
No information available.

Interference with clinical, laboratory and other tests:
No interference reported with laboratory tests.

Diuretics:
There is an increased risk of postural hypotension when tricyclic antidepressants are given with diuretics.

Antiepileptics
Tricyclic antidepressants may also antagonize the anticonvulsant effect of antiepileptics (convulsive threshold decreased).

ADVERSE EFFECTS

Occur in about 30% of patients and may be severe enough to discontinue the drug in 10% of patients.

More common reactions

Central nervous system, neuromuscular: Drowsiness, dizziness, tremor, extrapyramidal symptoms, confusional states, paraesthesia, alterations to EEG patterns, disorientation.

Anticholinergic: Dry mouth, urinary retention, sweating.

Cardiovascular: Hypotension, postural hypotension, tachycardia, arrhythmias, conduction defects, palpitations.

Endocrine: Increased or decreased libido in either sex.

Gastrointestinal: Nausea, vomiting, constipation.

Ocular: Disturbance of accommodation (blurred vision).

Several of the following reactions have not yet been reported with dothiepin but must be borne in mind because of its similarity to other antidepressants.

Less common reactions

Central nervous system, neuromuscular: Disturbed concentration, delusions, hallucinations, excitement, anxiety, hypomania, restlessness, insomnia, nightmares, peripheral neuropathy, ataxia, incoordination, seizures, fatigue, headaches.

Anticholinergic: Paralytic ileus.
Cardiovascular: Hypertension, myocardial infarction, heart block, stroke.

Endocrine: Males: Gynaecomastia, testicular swelling, impotence; Females: Galactorrhoea.

Gastrointestinal: Epigastric distress, abdominal cramps, stomatitis, black tongue, peculiar taste sensations, parotid swellings, diarrhoea.

Haematological: Bone marrow depression including agranulocytosis, thrombocytopenia, eosinophilia.

Hepatic: Cholestatic jaundice, hepatitis, altered liver function.

Allergic: Skin rash, urticaria, angioneurotic oedema, photosensitisation, skin blisters.

Other: Weight loss, urinary frequency, mydriasis. Increased appetite and weight gain have been reported but it is not known whether it is due to relief of depression or to the drug.

Adverse events have been reported during post-approval use of Prothiaden. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to Prothiaden exposure.

Table 1: Additional Adverse Reactions from Postmarketing Surveillance

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity reactions</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>Endocrine side effects</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Hyponatremia</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Movement disorders</td>
</tr>
<tr>
<td>Investigations</td>
<td>Increased intraocular pressure, changes in blood sugar levels</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Dyspepsia</td>
</tr>
</tbody>
</table>

DOSAGE AND ADMINISTRATION

The main dose should be taken at night as it may produce drowsiness.

Note: When a satisfactory response has been obtained, dosage should be reduced to the smallest amount necessary to maintain relief of the symptoms of depression. Plasma levels will reach steady state 10 to 14 days after each up or down adjustment.

Adults: Commence with 25 mg three times daily for one to two weeks. If response is inadequate, the daily dosage should be increased by 25 to 50 mg at intervals of one to two weeks. The daily dose should not exceed 200 mg.

When an effective dose has been established, up to 150 mg of the daily dose may be given as a single nighttime dose.
Children and adolescents (< 18 years): The safety and efficacy of Prothiaden for the treatment of depression or other psychiatric disorders in children and adolescents aged less than 18 years has not been satisfactorily established. Prothiaden should not be used in this age group for the treatment of depression or other psychiatric disorders.

Elderly: Use adult dosage with care particularly in patients with impaired liver or renal function (see below) or cardiovascular disorders (see PRECAUTIONS).

With impaired liver or renal function: Dothiepin is contraindicated in hepatic failure.

Use with caution and reduce the dosage in patients with impaired liver or renal function since toxic blood levels may develop. Dothiepin is extensively metabolised by the liver, is thought to undergo enterohepatic circulation and its metabolites are excreted in the urine.

OVERDOSAGE

The onset of toxicity occurs within 4 – 6 hours.

Patients ingesting >5mg/kg should seek immediate medical attention.

All children ingesting Prothiaden should be assessed by a physician.

Symptoms:
The toxicity of tricyclic antidepressants is attributed mostly to their anticholinergic effects, which produce dry mouth, blurred vision, mydriasis, paralytic ileus and urinary retention.

Common CNS symptoms are agitation, delirium, ataxia, hyperpyrexia, convulsions, respiratory depression, coma, unconsciousness, muscle twitching, hyperreflexia, hypothermia, visual hallucinations and respiratory or metabolic alkalosis.

Cardiovascular symptoms include cyanosis, hypotension, shock, sinus tachycardia and cardiac arrhythmias, which are often the major cause of death.

Individual response varies, e.g. death has resulted from overdosage with 0.75 to 1 g of dothiepin (30 to 40 capsules) but recovery has occurred after as much as 2 g (80 capsules).

Serious overdosage with tricyclic antidepressants in children occurs more easily with a relatively small total dosage because the dose per weight ratio is higher.

Management:
- A clear airway and adequate ventilation should be ensured. Hypoxia and acid-based imbalances should be corrected by assisted ventilation and intravenous sodium bicarbonate as appropriate.
- Do not give flumazenil to reverse benzodiazepine toxicity in mixed overdoses.
- The use of activated charcoal should be considered as a preferred initial means of reducing absorption in patients presenting within 2 hours of ingestion.
- Blood pressure, pulse and cardiac rhythm should be monitored for at least 6 hours after ingestion.
- Arrhythmias are best treated by correcting hypoxia and acid-base disturbances. Specialist
poisons advice should be sought before using any anti-arrhythmic agents as these may exacerbate the arrhythmia.
- In cases of cardiac arrest, persist with prolonged CPR (for at least 1 hour).
- Convulsions should be controlled with intravenous diazepam or lorazepam.
- Due to their respiratory depressant effects, barbiturates should be avoided especially if the patient is thought to have been on MAOIs or if barbiturates have been taken in association with the antidepressant in the overdose.

For advice on the management of overdose please contact the Poisons Information Centre. In Australia please call 13 11 26.

PRESENTATION AND STORAGE CONDITIONS

Capsules, 25 mg (brown/red, marked P and 25 other end): 50's
Tablets, 75 mg (red, marked P75): 30's

NAME AND ADDRESS OF THE SPONSOR

Abbott Australasia Pty Ltd
32-34 Lord Street
Botany NSW 2019
Australia

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine - S4

Date of TGA Approval: 18 September 1995

Date of Most Recent Amendment: 20 June 2008

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