

NEW ZEALAND DATA SHEET

ANTEN

Doxepin (as hydrochloride) capsules

10mg, 25mg & 50mg



Presentation

ANTEN (doxepin hydrochloride) is available in capsules of three strengths.

ANTEN 10 mg capsule: Capsule, Blue OP Body, Scarlet OP Cap, size 4. Contains a white powder.

ANTEN 25 mg capsule: Capsule, Flesh OP Body, Scarlet OP Cap, size 4. Contains a white powder.

ANTEN 50 mg capsule: Capsule, Flesh OP Body, Scarlet OP Cap, size 2. Contains a white powder.

Uses

Actions

Doxepin is a tricyclic antidepressant. The mechanism of action of doxepin is not definitely known. It is neither a central nervous stimulant nor a monoamine oxidase inhibitor. The current hypothesis is that the clinical effects are due, at least in part, to influences on the adrenergic activity at the synapses so that deactivation of noradrenaline by re-uptake into the nerve terminals is prevented. Animal studies suggest that doxepin hydrochloride does not appreciably antagonize the antihypertensive action of guanethidine. In animal studies anticholinergic, antiserotonin and antihistamine effects on smooth muscle have been demonstrated. At higher than usual clinical doses, noradrenaline response was potentiated in animals. This effect was not demonstrated in humans.

At clinical dosages up to 150 mg per day, doxepin can be given to man concomitantly with guanethidine and related compounds without blocking the antihypertensive effect. At dosages above 150 mg per day blocking of the antihypertensive effect of these compounds has been reported.

Pharmacokinetics

Doxepin is well absorbed from the gastrointestinal tract. Approximately 55-87% of orally administered doxepin undergoes first pass metabolism in the liver, forming the primary active metabolite, desmethyldoxepin.

In healthy volunteers, a single oral dose of 75mg resulted in peak plasma concentrations for doxepin ranging from 8.8 - 45.8 ng/ml (mean 26.1 ng/ml). Peak levels were reached between 2 and 4 hours (mean 2.9 hours) after administration. Peak levels for the primary metabolite desmethyldoxepin ranged from 4.8-14.5 ng/ml (mean 9.7 ng/ml) and were achieved between 2 and 10 hours after administration. The mean apparent volume of distribution for doxepin is approximately 20 L/kg. The protein binding for doxepin is approximately 76%.

In healthy volunteers, the plasma elimination half-life of doxepin ranged from 8 to 24 hours (mean 17 hours). The half-life of desmethyldoxepin ranged from 33-80 hours (mean 51 hours). Mean plasma clearance for doxepin is approximately 0.84 L/kg.hr. Paths of metabolism of doxepin include demethylation, N-oxidation, hydroxylation and glucuronide formation. Doxepin is excreted primarily in the urine, mainly as its metabolites, either free or in conjugate form.

Indications

Symptoms of depressive illness, especially where sedation is required.

Doxepin may be used with benefit where symptoms are of short or long duration prior to treatment and in patients with a wide range of intensity of illness.

As with other psychotherapeutic agents, the degree of response varies with each patient. In patients exhibiting a beneficial response, this may be seen within a few days of commencing therapy, while others may not respond for two weeks or longer.

Due to its excellent toleration, doxepin is particularly useful in ambulatory patients seen in general practice as well as in the treatment of hospitalised patients.

Dosage and Administration

The optimum oral dose depends on the severity of the condition and the individual patient's response. The dose varies from 30 – 300 mg daily. Doses up to 100 mg daily may be given on a divided or once daily schedule. Should doses over 100 mg daily be required, they should be administered in three divided doses daily. 100 mg is the maximum dose recommended at any one time. This dose may be given at bedtime.

For the majority of patients with moderate or severe symptoms, it is recommended that treatment commences with an initial dose of 75 mg daily. Many of these patients will respond satisfactorily at this dose level. For patients who do not, the dosage may be adjusted according to individual response. In more severely ill patients, it may be necessary to administer a dose of up to 300 mg, in three divided doses daily, to obtain a clinical response.

In patients where insomnia is a troublesome symptom, it is recommended that the total daily dose be divided so that a higher proportion is given for the evening dose; similarly, if drowsiness is experienced as a side effect of treatment, doxepin may be administered by this regimen, or the dosage may be reduced.

It is often possible, having once obtained a satisfactory therapeutic response, to reduce the dose for maintenance therapy.

The optimal antidepressant effect may not be evident for two to three weeks.

Adolescent Depression

Not recommended for use in adolescent patients 13-18 years of age for the treatment of depression, unless under the supervision of a specialist.

Use in the Elderly

In general, lower dosages are recommended. Where the presenting symptoms are mild in nature, it is advisable to initiate treatment at a dose of 10-50 mg daily. A satisfactory clinical response is obtained in many of these patients at a daily dose of 30-50 mg. The dosage may be adjusted according to the individual response.

Use in Hepatic Impairment

Dosage reduction may be required in patients with hepatic impairment.

Contraindications

- Doxepin is contraindicated for the treatment of depression in patients 12 years of age and under.
- Doxepin is contraindicated for the treatment of nocturnal enuresis.
- Hypersensitivity, mania, severe liver disease, lactation, glaucoma, tendency to urinary retention.

Warnings and Precautions

Clinical Worsening and Suicide Risk

Patients of any age with Major Depressive Disorder may experience worsening of their depression and/or the emergence of suicidal ideation and behaviour (suicidality), whether or not they are taking antidepressant

medications, and this risk may persist until significant remission occurs. Patients should be closely monitored, especially at the beginning of therapy or when the dose is changed, until such improvement occurs.

There has been a long-standing concern that some antidepressants may have a role in the emergence of suicidality in some patients. The possible risk of increased suicidality in patients applies to all classes of antidepressant medicines, as available data are not adequate to exclude this risk for any antidepressant. Therefore, consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms. Generally, when stopping an antidepressant, doses should be tapered rather than stopped abruptly.

The following symptoms, 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 causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and non-psychiatric disorders, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric and non-psychiatric disorders.

Mania and 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 any antidepressant alone may increase the likelihood of a mixed/manic episode in patients at risk for bipolar disorder. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder. It should be noted that doxepin is not approved for use in treating bipolar depression.

Information for Patients and Families

Patients and their families should be alerted about the need to monitor for the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, mania, worsening of depression, and suicidal ideation, especially early during antidepressant treatment. Such symptoms should be reported to the patient's doctor, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

The patient has the right to treatment meeting appropriate ethical and professional standards, and the patient needs to be fully informed with frank discussion of risk/benefit issues relating to the medicines efficacy and safety when used in the treatment regimen proposed.

The once-a-day dosage regimen of doxepin in patients with intercurrent illness or patients taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with anticholinergic effects.

Use with caution in patients with severe cardiovascular disease, including patients with heart block, cardiac arrhythmia and those who have experienced a recent myocardial infarction.

Use with caution in patients with hepatic and/or renal impairment.

Use with caution in patients with a history of epilepsy.

Impairment of Motor Coordination

Since drowsiness or motor incoordination may occur with the use of doxepin, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while taking this drug.

Patients should also be cautioned that their response to alcohol may be potentiated.

The possibility of development of withdrawal symptoms on abrupt cessation of treatment after prolonged doxepin treatment should be borne in mind.

Use in Geriatrics

The dose of doxepin in elderly patients should be adjusted carefully, based on the patient's condition. The use of doxepin on a once-a-day dosage regimen in geriatric patients should be adjusted carefully on the basis of the patient's condition. The elderly are particularly liable to experience toxic effects, especially agitation, confusion and postural hypotension. The initial dose should be increased with caution under close supervision. Half the normal maintenance dose may be sufficient to produce a satisfactory clinical response.

Use in Pregnancy (Category C)

Doxepin should only be used in pregnancy if considered necessary, taking into account the risks of untreated depression, and under the close supervision of a physician.

Epidemiological studies have suggested an increased risk of congenital abnormalities associated with use of tricyclic antidepressants, in pregnancy. There is evidence of interference with central monoamine neurotransmission in rats.

Neonates should be observed if maternal use of doxepin has continued into the later stages of pregnancy, particularly into the third trimester.

Neonates exposed to tricyclic antidepressants, late in the third trimester have showed drug withdrawal symptoms such as dyspnoea, lethargy, colic irritability, hypotension or hypertension and tremor or spasms.

Epidemiological data suggests that the use of tricyclic antidepressants in pregnancy may be associated with an increase in pre-term delivery.

Use in Lactation

Limited data indicate that doxepin and its active metabolite desmethyldoxepin, are excreted in breast milk. There has been a report of apnoea and drowsiness occurring in a nursing infant whose mother was taking doxepin. Because of potential for adverse side effects to the nursing infant, breast-feeding is not recommended during doxepin therapy.

Adverse Effects

Note: Some of the side-effects noted below have not been specifically reported with doxepin use. However, due to the close pharmacological similarities amongst the tricyclics, the reactions should be considered when prescribing doxepin.

Anticholinergic Effects

Dry mouth, blurred vision, constipation and urinary retention have been reported. If they do not subside with continued therapy, or if they become severe, it may be necessary to reduce the dosage. Isolated cases of elevated intraocular pressure.

Central Nervous System Effects

Drowsiness is the most commonly noticed side-effect. This tends to disappear as therapy is continued. Insomnia and nightmares have also been reported. Other infrequently reported CNS side-effects are confusion, disorientation, agitation, hallucinations, numbness, paraesthesiae, ataxia, extrapyramidal symptoms, seizures, tardive dyskinesia, tremor, anxiety, nervousness and aggressive reaction. An NMS like syndrome has occurred in a patient with a history of depression with psychotic features treated with a lithium/doxepin combination.

Cardiovascular

Although doxepin carries less risk than other tricyclic antidepressants, caution should be observed in the treatment of patients with heart block or cardiac arrhythmias. Cardiovascular effects including hypotension, hypertension and tachycardia have been reported occasionally. Changes in ECG parameters (widening of the QRS and PR interval) very rarely.

Allergic

Skin rash, facial oedema, photosensitisation, pruritus and urticaria have occasionally occurred.

Haematological

Eosinophilia has been reported in a few patients. There have been occasional reports of bone marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia and purpura. Haemolytic anaemia.

Gastro-intestinal

Nausea, vomiting, indigestion, taste disturbances, diarrhoea, anorexia and aphthous stomatitis have been reported (see Anticholinergic Effects).

Endocrine

Raised or lowered libido, testicular swelling, gynaecomastia in males, enlargement of breasts and galactorrhoea in the female, raising or lowering of blood sugar levels and syndrome of inappropriate antidiuretic hormone secretion, have been reported following the administration of tricyclics.

Others

Dizziness, tinnitus, weight gain, sweating, chills, fatigue, weakness, flushing, jaundice, alopecia, headache, exacerbation of asthma and hyperpyrexia (in association with chlorpromazine) have been occasionally observed as adverse effects. Hepatitis, hepatic abnormalities, increased appetite rarely.

Psychotic manifestations, including mania and paranoid delusions may be exacerbated during treatment with tricyclic antidepressants.

Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and TCAs. The mechanism leading to this risk is unknown.

Withdrawal Symptoms

Withdrawal symptoms may occur on abrupt cessation of tricyclic antidepressant therapy and include nausea, headache, malaise, insomnia, irritability, and excessive perspiration. Withdrawal symptoms in neonates whose mothers received tricyclic antidepressants during the third trimester have also been reported and include respiratory depression, convulsions and 'jitteriness' (hyper-reflexia).

Interactions

MAO Inhibitors

Serious side effects and even death have been reported following the concomitant use of certain medicines with monoamine oxidase (MAO) inhibitors. Therefore, MAO inhibitors should be discontinued at least 2 weeks prior to the cautious initiation of therapy with doxepin. The exact length of time may vary and is dependent on the particular MAO inhibitor being used, the length of time it has been administered and the dosage involved.

Medicines Metabolised by Cytochrome P450 2D6

The biochemical activity of the cytochrome P450 metabolising isoenzyme 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7-10%). Such individuals are called poor metabolisers and may have higher than expected plasma concentrations of tricyclic antidepressants when given usual doses.

Cytochrome P450 2D6 Inhibitors

Normal metabolisers may resemble poor metabolisers when given compounds that inhibit cytochrome P450 2D6. The medicines that inhibit cytochrome P450 2D6 include some that are not metabolised by the enzyme (quinidine, cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines and the Type 1C antiarrhythmics propafenone and flecainide). Concomitant use of tricyclic antidepressants with medicines that inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant (TCA) or the other medicine. Whenever one of these other medicines is withdrawn from co-therapy, an increased dose of tricyclic antidepressant may be required. It is

desirable to monitor TCA plasma levels whenever a TCA is co-administrated with a known inhibitor of P450 2D6.

Hepatic Enzyme Inducers

Substances that activate the hepatic monooxygenase enzyme system (e.g. barbiturates, phenytoin, carbamazepine) may lower the plasma concentration of tricyclic antidepressants and also so reduce their effect. In addition, concomitant administration of a tricyclic antidepressant with phenytoin or carbamazepine may lead to elevated serum phenytoin or carbamazepine concentrations. If necessary, the doses of these medicines should be adjusted.

Selective Serotonin Reuptake Inhibitors

The selective serotonin reuptake inhibitors (SSRIs), e.g. fluoxetine, sertraline and paroxetine, inhibit P450 2D6 and can elevate tricyclic antidepressant blood levels. The extent to which SSRI-TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Caution is indicated in the co-administration of tricyclic antidepressants with any of the SSRIs and in switching from one class to the other. Sufficient time must elapse before initiating tricyclic antidepressant treatment in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary).

Sympathomimetic Agents

The cardiovascular effect of sympathomimetic agents such as adrenaline, noradrenaline and amphetamine (as well as nasal drops and local anaesthetics containing sympathomimetics) may be potentiated by tricyclic antidepressants.

Anticholinergic Agents

Tricyclic antidepressants may have an additive anticholinergic effect when given in combination with anticholinergics or neuroleptics with an anticholinergic action (e.g. phenothiazines), hyperexcitation states or delirium may occur, as well as, attacks of glaucoma, urinary retention or paralytic ileus.

Cimetidine

Cimetidine has been reported to produce clinically significant fluctuations in steady-state serum concentrations of various tricyclic antidepressants. Serious anticholinergic symptoms (i.e. severe dry mouth, urinary retention and blurred vision) have been associated with elevations in the serum levels of tricyclic antidepressants when cimetidine therapy is initiated. Additionally, higher than expected tricyclic antidepressant levels have been observed when they are begun in patients already taking cimetidine. In patients who have been reported to be well controlled on tricyclic antidepressants while receiving concurrent cimetidine, discontinuation of cimetidine has been reported to decrease established steady-state tricyclic antidepressant levels and compromise their therapeutic effects.

Alcohol

It should be borne in mind that alcohol ingestion may increase the danger inherent in any intentional or unintentional doxepin overdose. This is especially important in patients who may use alcohol excessively.

Anaesthetics

Anaesthetics given during tricyclic or tetracyclic antidepressant therapy may increase the risk of arrhythmias and hypotension. If surgery is necessary, the anaesthetist should be informed that a patient is being so treated.

Antihypertensive Agents

Doxepin may decrease the antihypertensive effect of agents such as debrisoquine, bethanidine, guanethidine and possibly clonidine. It usually requires daily doses of doxepin in excess of 150 mg before any effect on the action of guanethidine is seen. It would be advisable to review all antihypertensive therapy during treatment with tricyclic antidepressants.

Thyroid Medication

The dose of thyroid hormone medication may need reducing if doxepin is being given concurrently.

Tolazamide

A case of severe hypoglycaemia 11 days after the addition of doxepin (75 mg/day) has been reported in a type II (non-insulin dependent) diabetic patient maintained on tolazamide (1 g/day).

Overdosage

Deaths may occur from overdosage with tricyclic antidepressants including doxepin, with the ingestion of 15 - 20 mg/kg or more being potentially fatal. Because of its rapid absorption and the onset of cardiac and central nervous system toxicity, the patient should be brought to hospital as soon as possible for immediate monitoring and treatment.

Multiple drug ingestion (including alcohol) is common in deliberate tricyclic antidepressant overdose. As the management is complex and changing, it is recommended that the physician contact the National Poisons Information Centre (0800 POISON or 0800 764 766) for current information on treatment.

Signs and Symptoms

Symptoms and signs at presentation depend upon the dose and the time since ingestion. The rapid absorption of TCAs can cause a patient with initially trivial symptoms to deteriorate and develop life threatening toxicity rapidly. Patients who are asymptomatic at 3 hours post ingestion do not normally develop major toxicity. Mild toxicity is commonly manifested by anticholinergic effects such as drowsiness, blurred vision and excessive dryness of mouth.

However, major toxicity can develop rapidly within 6 hours resulting in severe neurologic, anticholinergic and cardiovascular syndromes including: respiratory depression, mental status changes, delirium, convulsions, seizures, CNS depression (including coma), cardiac dysrhythmias (tachycardia is a common anticholinergic and early sympathomimetic effect, supraventricular and ventricular tachycardias, AV block, torsade de pointes and ventricular fibrillation), hypotension and ECG changes (such as QRS widening and QTc prolongation).

Other signs may also include: confusion, disturbed concentration, transient visual or auditory hallucinations, agitation, stupor, urinary retention (bladder atony), decreased gastrointestinal motility (paralytic ileus), hyperthermia or hypothermia, hyperpyrexia, dilated pupils, hyperreflexia, muscle rigidity and vomiting.

Management and Treatment

Where the dose taken is known to be low (< 5 mg/kg) and manifested only by mild symptoms, ECG monitoring, supportive therapy, and observation for signs of CNS or respiratory depression and cardiovascular effects for at least 6 hours may be all that is necessary. If signs of toxicity occur at any time during this period, extended monitoring is recommended.

Severe toxicity must be suspected if overdosage is unknown, complicated by intake of alcohol or multiple drugs, or when symptoms have deteriorated. A maximal limb-lead QRS duration of ≥ 0.10 seconds may be the best indication.

Management should include cardiac monitoring to detect ECG abnormalities, establishing an intravenous line (normal saline) and securing the patient's airway. Activated charcoal may reduce absorption of doxepin if given within 1-2 hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube ensuring that the airway is protected. Emesis is not indicated since rapid neurologic and haemodynamic deterioration may occur.

Cardiovascular:

CV effects may be reversed by use of intravenous hypertonic sodium bicarbonate to maintain the serum pH at 7.45 – 7.55. If the pH response is inadequate, hyperventilation may also be used, but extreme caution must be taken if conducted concomitantly so that pH > 7.60 or a $pCO_2 < 20$ mm Hg is avoided.

All class 1a and 1c antiarrhythmic medicines are contraindicated, whilst class b medicines may exacerbate arrhythmias and the sodium channel blockade.

In rare instances, haemoperfusion may be beneficial in acute refractory cardiovascular instability in patients with acute toxicity. However, haemodialysis, peritoneal dialysis, exchange transfusions and forced diuresis are of little benefit due to high tissue and protein binding of doxepin.

Cardiovascular effects may persist beyond 48 hours.

CNS:

In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration. Seizures should be controlled with benzodiazepines or if ineffective, by anticonvulsants (e.g. phenobarbitone, phenytoin). Because of its potentially fatal adverse effects, physostigmine is not recommended except to treat life-threatening symptoms that have been unresponsive to other therapies. Physostigmine should only be used in consultation with the National Poisons Information Centre.

Neurologic effects may persist for 24 to 48 hours.

Follow-up:

Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase, therefore psychiatric referral may be appropriate.

Pharmaceutical Precautions

Store below 25°C.

Medicine Classification

Prescription Medicine.

Package Quantities

ANTEN 10: Blister packs of 100 capsules.

ANTEN 25: Blister packs of 100 capsules.

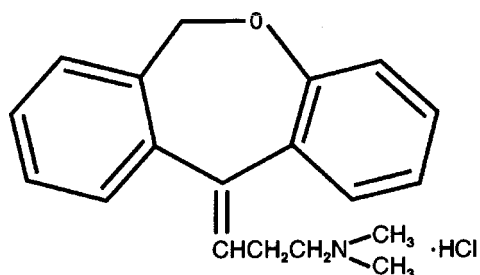
ANTEN 50: Blister packs of 100 capsules.

Further Information

Ingredients

Active:

ANTEN contains the tricyclic antidepressant, doxepin hydrochloride. The structural formula is:



C₁₉H₂₁NO.HCl, MW 316 CAS number 1229-29-4

Doxepin hydrochloride is a dibenzoxepin derivative, and consists of a mixture of the *cis* and *trans* isomers in a constant ratio (82 - 85% *trans*: 15-18% *cis*). It is a white crystalline solid, readily soluble in water, lower alcohols and chloroform. Chemically, it is 11-[3-dimethylaminopropylidene]-6H-dibenz[b,e]oxepin hydrochloride.

Each ANTEN 10 mg capsule contains 11.31 mg of the active ingredient, doxepin hydrochloride, equivalent to 10 mg doxepin.

Each ANTEN 25 mg capsule contains 28.27 mg of the active ingredient, doxepin hydrochloride, equivalent to 25 mg doxepin.

Each ANTEN 50 mg capsule contains 56.54 mg of the active ingredient, doxepin hydrochloride, equivalent to 50 mg doxepin.

Excipients:

Each capsule contains lactose, maize starch, colloidal silicon dioxide, magnesium stearate. The capsule shell consists of gelatine and the colorants titanium dioxide, erythrosine, red iron oxide (10 mg & 25 mg), yellow iron oxide (10 mg & 50 mg), brilliant blue FCF (10 mg) and sunset yellow FCF (50 mg).

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