PRESCRIBING INFORMATION
PRODUCT MONOGRAPH

SINEQUAN*

(Doxepin hydrochloride)

10 MG, 25 MG, 50 MG, 75 MG, 100 MG

ANTIDEPRESSANT AND ANXIOLYTIC

Aspri Pharma Canada Inc.
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ACTION

SINEQUAN (doxepin HCl) is a psychotropic agent with antidepressant and anxiolytic properties. It also has sedative and anticholinergic effects, and, in the higher dosage range, it produces peripheral adrenergic blocking effects. Studies of electroencephalograms in humans have shown decreases in amplitude, and amplitude variability, also, the delta, theta and 24-35 CPS activities increased.

INDICATIONS

The antidepressant and anxiolytic properties of SINEQUAN (doxepin HCl) have been found to be of value in the drug treatment of:

1. Psychoneurotic patients with anxiety and/or depressive reactions;

   Anxiety neurosis associated with somatic disorders;
   Alcoholic patients with anxiety and/or depression.

2. Psychotic depression, including manic-depressive illness (depressed type) and involutional melancholia.

CLINICAL USE

Controlled clinical trials have confirmed that SINEQUAN (doxepin HCl) is an effective psychotropic agent with antidepressant and anxiolytic properties. SINEQUAN has been found useful in alleviating manifest anxiety in neurotic patients including those with somatic disorders. It has also been found useful in patients with neurotic depression, including those with mixed anxiety and depression. Patients with endogenous or psychotic depression, including manic-depressive illness (depressed type), and involutional melancholia, have also been reported to respond favorably to SINEQUAN. As adjunctive medication, it appears to benefit some alcoholic patients with chronic anxiety and depressive reactions.

As with most psychotropic agents, some patients with these conditions who have failed to respond to other appropriate medication may benefit from treatment with SINEQUAN. In psychoneurotic patients the following symptoms have responded significantly to doxepin HCl: anxiety, tension, depressed mood, somatic concern, guilt feelings, insomnia, fear, apprehension, and worry. Its anxiolytic effect occurs promptly, while onset of the antidepressant effect is delayed and can usually be expected after 10 days or more of treatment.

CONTRAINDICATIONS

SINEQUAN (doxepin HCl) is contraindicated in individuals who have shown hypersensitivity to the drug or to other dibenzoxepine compounds.

It is not recommended for use in children since safety and efficacy in this age group have not been established.

Because of its anticholinergic activity SINEQUAN should not be administered to patients with a history of glaucoma, increased intraocular pressure or urinary retention.

Tricyclic agents are generally contraindicated during the acute recovery phase following myocardial infarction and in the presence of acute congestive heart failure, as well as in patients with a history of blood dyscrasias and severe liver disease.

SINEQUAN should not be administered concomitantly with MAO inhibitors, since such a combination may cause a syndrome of intensive sympathetic stimulation. Drugs of this type should be discontinued at least two weeks before instituting therapy with SINEQUAN.

WARNINGS

Tricyclic antidepressant drugs, particularly when given in high doses, can induce sinus tachycardia, changes in conduction time and arrhythmias. A few instances of unexpected death have been reported in patients with cardiovascular disorders. Myocardial infarction and stroke have also been reported with drugs of this class. Therefore, SINEQUAN (doxepin HCl) should be administered with extreme caution to patients with a history of cardiovascular disease, those with circulatory lability and elderly patients. In such cases, treatment should be initiated with low doses with progressive increases only if required and tolerated, and the patients should be under close surveillance at all dosage levels.

Since tricyclic agents are known to reduce the seizure threshold, SINEQUAN should be used with caution in patients with a history of convulsive disorders. Concurrent administration of ECT and SINEQUAN may be hazardous and, therefore, such treatment should be limited to patients for whom it is essential.

Close supervision is required when SINEQUAN is given to hyperthyroid patients or those receiving thyroid medication because of the possibility of cardiovascular toxicity. At doses above 150 mg/day, it may block the antihypertensive effect of guanethidine and related compounds.

Use in Pregnancy and Lactation - The safety of SINEQUAN during pregnancy and lactation has not been established and therefore, it should not be used in women of childbearing potential or nursing mothers, unless, in the opinion of the physician, the potential benefits to the patient outweigh the possible hazards to the fetus.

PRECAUTIONS

Since drowsiness may occur with the use of this drug, patients should be advised against driving or engaging in activities requiring mental alertness and physical coordination until their response to the drug has been well established.

Patients should be warned that the effects of other drugs acting on the central nervous system, such as alcohol, barbiturates and other CNS depressants, may be potentiated by SINEQUAN.

The possibility of suicide in seriously depressed patients may remain until significant remission occurs. Such patients should be closely supervised throughout therapy and consideration should be given to the possible need for hospitalization. This type of patient should not have easy access to large quantities of SINEQUAN.

Tricyclic antidepressants may precipitate or aggravate psychotic manifestations in schizophrenic patients and hypomanic or manic episodes in manic-depressive patients. This may require a reduction of dosage, discontinuation of the drug, and/or administration of an antipsychotic agent.

Tricyclic antidepressants may also give rise to paralytic ileus, particularly in the elderly and in hospitalized patients. Therefore, appropriate measures should be taken if constipation occurs.

When SINEQUAN is given concomitantly with anticholinergic or sympathomimetic drugs, close supervision and careful adjustment of dosages are required.

SINEQUAN should be discontinued prior to elective surgery for as long as the clinical situation will allow.

SINEQUAN should be used with caution in patients with impaired liver function or with a history of hepatic damage or blood dyscrasias. Periodic blood counts and liver function tests should be performed when patients receive doxepin hydrochloride in large doses or over prolonged periods.

Drugs metabolized by cytochrome P450 (CYP) 2D6: SINEQUAN, like other tricyclic antidepressants (TCAs), is metabolized by CYP2D6. Inhibitors or substrates of CYP2D6 (i.e.quinidine, selective serotonin reuptake inhibitors [SSRIs]) may increase the plasma concentration of TCAs when administered concomitantly. The extent of interaction depends on

the variability of effect on CYP2D6 and the therapeutic index of the TCA. The clinical significance of this interaction with doxepin hydrochloride has not been systematically evaluated.

Cimetidine: Cimetidine has been reported to produce clinically significant fluctuations in steady-state serum concentrations of various tricyclic antidepressants. Serious anticholinergic symptoms (ie., 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 seen in patients receiving concurrent cimetidine therapy. Discontinuation of cimetidine has been reported to decrease established steady-state serum tricyclic antidepressant levels and compromise their therapeutic effects.

ADVERSE REACTIONS

Although some of the adverse reactions included in the following list have not been reported with SINEQUAN (doxepin HCl) pharmacological similarities among the tricyclic antidepressants require that each of the reactions be considered when prescribing SINEQUAN.

Behavioral - Drowsiness, fatigue, excitement, agitation, restlessness, insomnia, nightmares, hypomania, anxiety, confusion, disorientation, disturbed concentration, delusions, hallucinations, activation of latent psychosis.

Neurological - Seizures, alteration in EEG patterns, dizziness, tremors, extrapyramidal symptoms, numbness, tingling, paresthesias of the extremities, peripheral neuropathy, tinnitus, syndrome of inappropriate ADH (antidiuretic hormone) secretion, ataxia, tardive dyskinesia.

Cardiovascular - Hypotension, hypertension, tachycardia, palpitations. A quinidine-like effect and other reversible ECG changes such as flattening or inversion of T-waves, bundle branch block, depressed S-T segments, prolonged conduction time and asystole, arrhythmias, heart block, fibrillation, myocardial infarction, stroke and unexpected death in patients with cardiovascular disorders have been reported with other tricyclic antidepressants.

Autonomic - Dry mouth, blurred vision, disturbances of accommodation, mydriasis, constipation, nasal stuffiness, delayed micturition, sublingual adenitis, paralytic ileus, urinary retention, dilation of the urinary tract, precipitation of latent and aggravation of existing glaucoma, vertigo.

Endocrine - Increased or decreased libido, impotence, menstrual irregularity, testicular swelling, breast enlargement and galactorrhea in the female, gynecomastia in the male, elevation and lowering of blood sugar levels.

Allergic or Toxic - Pruritus, skin rash, photosensitization, edema, drug fever, leukopenia, urticaria, petechiae, obstructive jaundice and bone marrow depression, including agranulocytosis, eosinophilia, purpura and thrombocytopenia.

Gastrointestinal - Nausea, epigastric distress, vomiting, flatulence, abdominal pain, diarrhea, peculiar taste, stomatitis.

Miscellaneous - Weakness, chills, flushing, headache, weight gain or loss, excessive appetite, anorexia, increased perspiration, urinary frequency, lacrimation, alopecia, parotid swelling, black tongue, hepatitis, exacerbation of asthma and hyperpyrexia (in association with chlorpromazine).

Withdrawal Symptoms - Abrupt cessation of treatment with tricyclic antidepressants after prolonged administration may produce nausea, headache and malaise. These symptoms are not indicative of addiction.

SYMPTOMS AND TREATMENT OF OVER DOSAGE

Symptoms - Excessive drowsiness leading to minor alterations of consciousness and even unresponsiveness could be an early indication of excessive dosage. However, overdosage with SINEQUAN (doxepin HCl) is more likely to be manifested by increased psychomotor agitation and convulsions leading to apnea and coma. The ECG changes (broadening of QRS and T-wave abnormalities) tend to be a late finding and are not always accompanied by cardiovascular hemodynamic changes.

Treatment - In general, treatment of overdosage should be symptomatic and supportive. Cardiac arrhythmias and CNS involvement pose the greatest threat with tricyclic antidepressant overdosage and may occur suddenly even when initial symptoms appear to be mild. Therefore, patients who may have ingested an overdosage of doxepin hydrochloride, particularly children, should be hospitalized and kept under close surveillance.

If the patient is conscious, induced emesis followed by gastric lavage, with appropriate precautions to prevent pulmonary aspiration, should be accomplished as soon as possible. Following lavage, activated charcoal may be administered to reduce absorption. An adequate airway should be established in comatose patients and assisted ventilation instituted, if necessary. The possibility of occurrence of seizures should be kept in mind. External stimulation should be minimized to reduce the tendency to convulsions. Convulsions, should

they occur, may respond to standard anticonvulsant therapy; however, barbiturates should be avoided since they may potentiate respiratory depression, particularly in children, and aggravate hypotension and coma.

ECG monitoring in an intensive care unit is recommended in all patients, particularly in the presence of ECG abnormalities, and should be maintained for several days after the cardiac rhythm has returned to normal. A patient who has ingested a toxic overdose of a tricyclic antidepressant may remain medically and psychiatrically unstable for several days due to sustained excessive drug levels. Unexpected cardiac deaths have occurred up to 6 days after overdosage with other antidepressants. The QRS interval of the electrocardiogram appears to be a reliable correlate of the severity of overdosage. If the QRS interval exceeds 100 milliseconds any time during the first 24 hours after overdosage, cardiac function should be continuously monitored for 5 or 6 days. Because of its effect on cardiac conduction, digitalis should be used only with caution. If rapid digitalization is required for the treatment of congestive heart failure, special care should be exercised in using the drug.

Shock should be treated with supportive measures such as intravenous fluids, oxygen and corticosteroids. Pressor agents, such as noradrenaline (but not adrenaline), are rarely indicated and should be given only after careful consideration and under continuous monitoring.

The slow intravenous administration of physostigmine salicylate has been reported to reverse most of the cardiovascular and CNS anticholinergic manifestations of tricyclic overdose. The recommended dosage in adults has been 1 to 2 mg in very slow intravenous injection. In children, the initial dosage should not exceed 0.5 mg and should be adjusted to age and response. Since physostigmine has a short duration of action, administration may have to be repeated at 30 to 60 minute intervals.

Deaths by deliberate or accidental overdosage have occurred with this class of drugs. Since the propensity for suicide is high in depressed patients, a suicide attempt by other means may occur during the recovery phase. The possibility of simultaneous ingestion of other drugs should also be considered.

DOSAGE AND ADMINISTRATION

An optimal daily dosage of SINEQUAN (doxepin HCl) depends on the condition which is being treated and the response of the individual.

Some patients respond promptly, others may not respond for 2 weeks or longer. An initial dosage of 25 mg t.i.d. is recommended in most patients. This dosage should be increased as required by 25 mg increments at appropriate intervals until a therapeutic response is obtained. The usual optimal dosage range is 100-150 mg per day. In some patients, up to 300 mg per day may be required, but there is rarely any benefit to be obtained by increasing this dosage.

In elderly patients it is advisable to proceed more cautiously with dosage increments and to initiate treatment with a lower dosage.

Once a satisfactory therapeutic response has been obtained, it is generally possible to reduce the dosage and still maintain this effect.

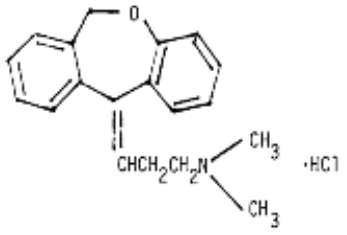
For maintenance therapy in depressed patients, the total daily dosage, up to 150 mg, may be given on a once-a-day schedule. This dosage should be established as described above and should preferably be given at bedtime. The 150 mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.

AVAILABILITY

SINEQUAN CAPSULES contain doxepin hydrochloride equivalent to 10, 25, 50, 75 and 100 mg of doxepin in bottles of 100.

CHEMISTRY AND PHARMACOLOGY

Doxepin HCl is designated chemically as N, N-dimethyl-3-(dibenz[*b,e*]oxepin -11(6H)-ylidene, propylamine hydrochloride and has the following structural formula:



Doxepin shares diverse pharmacological properties with related tricyclic antidepressants. It antagonizes the sedation caused by tetrabenazine and in combination with tetrabenazine causes a "jumping" syndrome in rats. Doxepin also significantly blocks and reverses reserpine-induced hypothermia in mice and potentiates and prolongs the stimulant action of amphetamine. It blocks the uptake of tritiated norepinephrine into rat heart and, in anesthetized cats, it potentiates and prolongs the pressor effect of norepinephrine, but reduces the pressor effect of epinephrine. The prolonged contraction of the nictitating membrane observed in the presence of doxepin may also result from the decreased uptake of norepinephrine.

Like other tricyclic drugs, doxepin decreases the electrical activity of the brain of monkeys, prolongs hexobarbital-induced sleep in mice and blocks conditioned avoidance behavior in rats, but does not suppress “conditioned emotional response”. At high, but non-lethal single doses in mice and dogs, doxepin produced several obvious symptoms of CNS depression.

Doxepin exerts a mydriatic effect in reserpinized mice and has a blocking effect on methacholine-induced mortality. These measures of peripheral anticholinergic action suggest that doxepin has a similar effect in this respect to imipramine, but a less pronounced effect than amitriptyline.

Doxepin exhibits a wide spectrum of spasmolytic activity on isolated guinea pig ileum and trachea, and on isolated rabbit aortic strips. Antagonism to histamine and serotonin is pronounced on the isolated guinea pig tissues, but the anticholinergic action is comparatively weak.

Doxepin reduces the perfusion pressure in the hind limb of the rabbit and also has a vasodilator effect in the dog. It produces EKG changes in the rabbit similar to those resulting from the quinidine-like action of other tricyclic drugs, increases the central venous pressure in rabbits, and has negative inotropic and chronotropic effects on the isolated guinea pig auricles. These effects support the inference that acute toxicity of doxepin at high doses may be due to cardiac insufficiency.

Doxepin exerts no significant antiemetic effect in dogs, anti-inflammatory action in rats, analgesic effect in mice, or anesthetic effect in the rabbit, and has no anticonvulsive properties. It has only a negligible effect on liver monoamine oxidase, does not influence the blood glucose concentration of fasted rats or inhibit aldehyde dehydrogenase in vitro, and no induction of drug metabolizing enzymes in dogs has been noted.

Metabolism - Drug metabolism studies with doxepin in rats and dogs reflect the fundamental similarity of its structure to that of related tricyclic psychotherapeutic agents. Doxepin is well absorbed after oral administration and rapidly appears in the blood. Repeated oral administration results in blood levels of doxepin and demethyl doxepin considerably higher than those attained after a single dose. The kidney is the major excretory organ, the urine containing a large proportion of the radioactivity administered.

In dogs, doxepin was rapidly distributed from the blood stream into other tissue compartments, and was also rapidly metabolized. Thus, concentrations of unchanged doxepin measured in the

blood were extremely low, and doxepin and demethyl doxepin constituted only about 2% of the total drug-related material present in the plasma. Plasma levels of doxepin and demethyl doxepin in the dog reached a maximum at approximately 1-3 hours following the administration of a single 100 mg dose, declined rapidly, and in one dog tested, was not measurable after 24 hours. In a multiple-dose study in dogs administered 100 mg daily for 5 days, plasma concentrations of doxepin and demethyl doxepin were also low, but, in 2 of 3 dogs, doxepin was still detectable in plasma 3 days after the last dose.

Although numerous metabolites of doxepin were detected in the liver and urine of rats and dogs, only doxepin and demethyl doxepin were found in the rat brain, and the normal ratio of cis to trans isomers was still present in this tissue. Metabolic transformations of doxepin included demethylation, N-oxidation, hydroxylation and glucuronide formation. The major metabolites in the rat appeared to be hydroxy doxepin and its glucuronide. Unchanged doxepin, doxepin-N-oxide and the glucuronide of hydroxy doxepin predominated in the dog. Appreciable amounts of polar metabolites, not extractable into methylene chloride even after glucuronidase treatment, were also present in rat and dog urine.

In the rat, doxepin and its metabolites were found in all tissues examined, but, were rapidly cleared except from the pigmented eye. When 2 mg of labelled doxepin was administered intraperitoneally to Long-Evans hooded rats, high concentrations were noted initially in liver, kidney, stomach and lung tissue, but these concentrations declined rapidly. Radioactivity in the blood and brain was very low, but appreciable and long-lasting levels were noted in the pigmented eyes of hooded rats. A comparison of radioactivity in pigmented eyes and eyes of albino rats (where radioactivity is rapidly removed) indicates that melanin is involved in this accumulation. This expected affinity for melanin is also reflected in in vitro studies with beef eyeball melanin.

TOXICOLOGY

Acute Toxicity in Adult Mice and Rats:

	LD_{50} Dose mg/kg	
	I.V.	ORAL
Mice	14.6 to 19.6	148 to 178
Rats	12.7 to 18.8	346 to 460

Subacute Toxicity - An oral 30 days subacute toxicity study with doxepin was performed on mongrel dogs at levels of 25 and 50 mg/kg/day. Hematology, clinical chemistry and urinalysis showed no abnormalities. There was no mortality in these animals during this period. At the 25 mg/kg level mild emesis and sedation were observed. At the 50 mg/kg level mild emesis, increased heart rate, miosis, sedation and twitching were observed. Similar studies at the same dosage level in rodents showed no mortality.

Chronic Toxicity - Canine toxicity studies at levels of 25 and 50 mg/kg/day for 12 months showed no histopathological changes attributable to the drug. The dogs exhibited slight emesis, ptosis, sedation and twitching. These dose levels are approximately 15 to 35 times the initial recommended dosage in man. Long term chronic feeding of doxepin to rats led to depression of growth rate at doses above 50 mg/kg/day. Fatty metamorphosis of the liver was observed in male rats after 7 to 12 months of feeding doxepin at 100 mg/kg/day. Studies in hooded rats indicate that doxepin displays the expected affinity for pigmented eye areas, but in vitro studies show it has much less affinity for melanin than the phenothiazine drugs.

REPRODUCTIVE STUDIES

Male and female Charles River C-D albino rats were treated with doxepin at dosage levels of 25, 5 and 0 mg/kg/day. When both male and female rats were treated for 14 days prior to mating, the number of implantation sites and average litter size were similar to controls. When female rats were treated for 14 days and mated with males treated for 7 months, conception rates were lower, average litter size was smaller, and the percentage of males copulating was less, at the 25 mg/kg/day dosage level. A comparative reproductive study of male and female rats treated with doxepin at 25 mg/kg/day (females for 14 days, and males for 9 months prior to mating) and mated

with untreated members of the opposite sex resulted in comparable numbers of average implantation sites and resorptions per litter.

However, the matings with treating males resulted in reduced conception rates. These males appeared to be less sexually aggressive than the untreated males. No gross external, visceral or skeletal abnormalities were noted in the offspring of Charles River C-D albino rats or of New Zealand White rabbits treated with doxepin at dosage levels of 25, 5 and 0 mg/kg/day.

Perinatal and postnatal studies in Charles River C-D albino rats treated with doxepin at 25, 5 and 0 mg/kg/day from the 14th day of gestation through lactation and weaning, and in macaca monkeys treated at 18 mg and 6 mg/kg/day from 6 to 56 days prior to conception through to parturition, produced no adverse effects in the developing fetus or neonate.

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