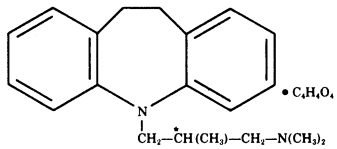
Surmontil®
(trimipramine maleate)

DESCRIPTION

Surmontil (trimipramine maleate) is 5-(3-dimethylamino-2-methylpropyl)-10,11-dihydro-5H-dibenz (b,f) azepine acid maleate (racemic form).



Molecular Formula: $C_{20}H_{26}N_2 \cdot C_4H_4O_4$ Molecular Weight: 410.5

Surmontil capsules contain trimipramine maleate equivalent to 25 mg, 50 mg, or 100 mg of trimipramine as the base. The inactive ingredients present are FD&C Blue 1, gelatin, lactose, magnesium stearate, and titanium dioxide. The 25 mg dosage strength also contains D&C Yellow 10 and FD&C Yellow 6; the 50 mg dosage strength also contains D&C Red 28, FD&C Red 40, and FD&C Yellow 6.

Trimipramine maleate is prepared as a racemic mixture which can be resolved into levorotatory and dextrorotatory isomers. The asymmetric center responsible for optical isomerism is marked in the formula by an asterisk. Trimipramine maleate is an almost odorless, white or slightly cream-colored, crystalline substance, melting at 140°-144° C. It is very slightly soluble in ether and water, is slightly soluble in ethyl alcohol and acetone, and freely soluble in chloroform and methanol at 20° C.

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CI 5187-1

CLINICAL PHARMACOLOGY

Surmontil is an antidepressant with an anxiety-reducing sedative component to its action. The mode of action of Surmontil on the central nervous system is not known. However, unlike amphetamine-type compounds it does not act primarily by stimulation of the central nervous system. It does not act by inhibition of the monoamine oxidase system.

INDICATIONS AND USAGE

Surmontil is indicated for the relief of symptoms of depression. Endogenous depression is more likely to be alleviated than other depressive states. In studies with neurotic outpatients, the drug appeared to be equivalent to amitriptyline in the less-depressed patients but somewhat less effective than amitriptyline in the more severely depressed patients. In hospitalized depressed patients, trimipramine and imipramine were equally effective in relieving depression.

CONTRAINDICATIONS

Surmontil is contraindicated in cases of known hypersensitivity to the drug. The possibility of cross-sensitivity to other dibenzazepine compounds should be kept in mind. Surmontil should not be given in conjunction with drugs of the monoamine oxidase inhibitor class (e.g., tranylcypromine, isocarboxazid or phenelzine sulfate). The concomitant use of monoamine oxidase inhibitors (MAOI) and tricyclic compounds similar to Surmontil has caused severe hyperpyretic reactions, convulsive crises, and death in some patients. At least two weeks should elapse after cessation of therapy with MAOI before instituting therapy with Surmontil. Initial dosage should be low and increased gradually with caution and careful observation of the patient. The drug is contraindicated during the acute recovery period after a myocardial infarction.

WARNINGS

General Consideration for Use

Extreme caution should be used when this drug is given to patients with any evidence of cardiovascular disease because of the possibility of conduction defects, arrhythmias, myocardial infarction, strokes, and tachycardia.

Caution is advised in patients with increased intraocular pressure, history of urinary retention, or history of narrow-angle glaucoma because of the drug's anticholinergic properties; hyperthyroid patients or those on thyroid medication because of the possibility of cardiovascular toxicity; patients with a history of seizure disorder, because this drug has been shown to lower the seizure threshold; patients receiving guanethidine or similar agents, since Surmontil may block the pharmacologic effects of these drugs.

Since the drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as operating an automobile or machinery, the patient should be cautioned accordingly.

PRECAUTIONS

General

The possibility of suicide is inherent in any severely depressed patient and persists until a significant remission occurs. When a patient with a serious suicidal potential is not hospitalized, the prescription should be for the smallest amount feasible.

In schizophrenic patients activation of the psychosis may occur and require reduction of dosage or the addition of a major tranquilizer to the therapeutic regime.

Manic or hypomanic episodes may occur in some patients, in particular those with cyclic-type disorders. In some cases therapy with Surmontil must be discontinued until the episode is relieved, after which therapy may be reinstituted at lower dosages if still required.

Concurrent administration of Surmontil and electroshock therapy may increase the hazards of therapy. Such treatment should be limited to those patients for whom it is essential. When possible, discontinue the drug for several days prior to elective surgery.

Surmontil should be used with caution in patients with impaired liver function.

Chronic animal studies showed occasional occurrence of hepatic congestion, fatty infiltration, or increased serum liver enzymes at the highest dose of 60 mg/kg/day.

Both elevation and lowering of blood sugar have been reported with tricyclic antidepressants.

Drug Interactions

Cimetidine

There is evidence that cimetidine inhibits the elimination of tricyclic antidepressants. Downward adjustment of Surmontil dosage may be required if cimetidine therapy is initiated; upward adjustment if cimetidine therapy is discontinued.

Alcohol

Patients should be warned that the concomitant use of alcoholic beverages may be associated with exaggerated effects.

Catecholamines/Anticholinergics

It has been reported that tricyclic antidepressants can potentiate the effects of catecholamines. Similarly, atropinelike effects may be more pronounced in patients receiving anticholinergic therapy. Therefore, particular care should be exercised when it is necessary to administer tricyclic antidepressants with sympathomimetic amines, local decongestants, local anesthetics containing epinephrine, atropine or drugs with an anticholinergic effect. In resistant cases of depression in adults, a dose of 2.5 mg/kg/day may have to be exceeded. If a higher dose is needed, ECG monitoring should be maintained during the initiation of therapy and at appropriate intervals during stabilization of dose.

Drugs Metabolized by P450 2D6

The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the caucasian population (about 7-10% of caucasians are so called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African, and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA).

In addition, certain drugs inhibit the activity of the isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized 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). While all the selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine, sertraline, and paroxetine, inhibit P450 2D6, they may vary in the extent of inhibition. 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. Nevertheless, caution is indicated in the coadministration of TCAs with any of the SSRIs and also in switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA 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).

Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug. Furthermore, whenever one of these other drugs 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 going to be co-administered with another drug known to be an inhibitor of P450 2D6.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Semen studies in man (four schizophrenics and nine normal volunteers) revealed no significant changes in sperm morphology. It is recognized that drugs having a parasympathetic effect, including tricyclic antidepressants, may alter the ejaculatory response.

Chronic animal studies showed occasional evidence of degeneration of seminiferous tubules at the highest dose of 60 mg/kg/day.

Pregnancy

Teratogenic Effects—Pregnancy Category C

Surmontil has shown evidence of embryotoxicity and/or increased incidence

of major anomalies in rats or rabbits at doses 20 times the human dose. There are no adequate and well-controlled studies in pregnant women. Surmontil® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pediataric Use

This drug is not recommended for use in children, since safety and effectiveness in the pediatric age group have not been established.

ADVERSE REACTIONS

Note: The pharmacological similarities among the tricyclic antidepressants require that each of the reactions be considered when Surmontil is administered. Some of the adverse reactions included in this listing have not in fact been reported with Surmontil.

Cardiovascular
Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric
Confusional states (especially the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia and nightmares; hypomania; exacerbation of psychosis.

Neurological
Numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, alterations in EEG patterns; tinnitus; syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Anticholinergic
Dry mouth and, rarely, associated sublingual adenitis; blurred vision, disturbances of accommodation, mydriasis, constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract.

Allergic
Skin rash, petechiae, urticaria, itching, photosensitization, edema of face and tongue.

Hematologic
Bone-marrow depression including agranulocytosis, eosinophilia; purpura; thrombocytopenia. Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is evidence of pathological neutrophil depression.

Gastrointestinal
Nausea and vomiting, anorexia, epigastric distress, diarrhea, peculiar taste, stomatitis, abdominal cramps, black tongue.

Endocrine
Gynecomastia in the male; breast enlargement and galactorrhea in the female; increased or decreased libido, impotence; testicular swelling; elevation or depression of blood-sugar levels.

Other
Jaundice (simulating obstructive); altered liver function; weight gain or loss; perspiration; flushing; urinary frequency; drowsiness, dizziness, weakness, and fatigue; headache; parotid swelling; alopecia.

Withdrawal Symptoms
Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

DOSAGE AND ADMINISTRATION

Dosage should be initiated at a low level and increased gradually, noting carefully the clinical response and any evidence of intolerance.

Lower dosages are recommended for elderly patients and adolescents. Lower dosages are also recommended for outpatients as compared to hospitalized patients who will be under close supervision. It is not possible to prescribe a single dosage schedule of Surmontil that will be therapeutically effective in all patients. The physical psychodynamic factors contributing to depressive symptomatology are very complex; spontaneous remissions or exacerbations of depressive symptoms may occur with or without drug therapy. Consequently, the recommended dosage regimens are furnished as a guide which may be modified by factors such as the age of the patient, chronicity and severity of the disease, medical condition of the patient, and degree of psychotherapeutic support.

Most antidepressant drugs have a lag period of ten days to four weeks before a therapeutic response is noted. Increasing the dose will not shorten this period but rather increase the incidence of adverse reactions.

Usual Adult Dose

Outpatients and Office Patients—Initially, 75 mg/day in divided doses, increased to 150 mg/day. Dosages over 200 mg/day are not recommended. Maintenance therapy is in the range of 50 to 150 mg/day. For convenient therapy and to facilitate patient compliance, the total dosage requirement may be given at bedtime.

Hospitalized Patients—Initially, 100 mg/day in divided doses. This may be increased gradually in a few days to 200 mg/day, depending upon individual response and tolerance. If improvement does not occur in 2 to 3 weeks, the dose may be increased to the maximum recommended dose of 250 to 300 mg/day.

Adolescent and Geriatric Patients—Initially, a dose of 50 mg/day is recommended, with gradual increments up to 100 mg/day, depending upon patient response and tolerance.

Maintenance—Following remission, maintenance medication may be required for a longer period of time, at the lowest dose that will maintain remission. Maintenance therapy is preferably administered as a single dose at bedtime. To minimize relapse, maintenance therapy should be continued for about three months.

OVERDOSAGE*

Deaths may occur from overdosage with this class of drugs. 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 a poison control center for current information on treatment. Signs and symptoms of toxicity develop rapidly after tricyclic antidepressant overdose, therefore, hospital monitoring is required as soon as possible.

Manifestations

Critical manifestations of overdose include: cardiac dysrhythmias, severe hypotension, convulsions, and CNS depression, including coma. Changes in the electrocardiogram, particularly in QRS axis or width, are clinically significant indicators of tricyclic antidepressant toxicity.

Other signs of overdose may include: confusion, disturbed concentration, transient visual hallucinations, dilated pupils, agitation, hyperactive reflexes, stupor, drowsiness, muscle rigidity, vomiting, hypothermia, hyperpyrexia, or any of the symptoms listed under **ADVERSE REACTIONS**.

Management

General

Obtain an ECG and immediately initiate cardiac monitoring. Protect the patient's airway, establish an intravenous line and initiate gastric decontamination. A minimum of six hours of observation with cardiac monitoring and observation for signs of CNS or respiratory depression, hypotension, cardiac dysrhythmias and/or conduction blocks, and seizures is necessary. If signs of toxicity occur at any time during this period, extended monitoring is required. There are case reports of patients succumbing to fatal dysrhythmias late after overdose; these patients had clinical evidence of significant poisoning prior to death and most received inadequate gastrointestinal decontamination. Plasma drug levels may not reflect the severity of the poisoning. Therefore, monitoring of plasma drug levels alone should not guide management of the patient.

Gastrointestinal Decontamination

All patients suspected of tricyclic antidepressant overdose should receive gastrointestinal decontamination. This should include large volume gastric lavage followed by activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage. Emesis is contraindicated.

Cardiovascular

A maximal limb-lead QRS duration of ≥ 0.10 seconds has been associated with an increased incidence of seizures. A QRS duration of ≥ 0.16 seconds has been associated with an increased incidence of ventricular dysrhythmias. Intravenous sodium bicarbonate should be used to maintain the serum pH in the range of 7.45 to 7.55. If the pH response is inadequate, hyperventilation may also be used. Concomitant use of hyperventilation and sodium bicarbonate should be done with extreme caution, with frequent pH monitoring. A pH > 7.60 or a pCO_2 < 20 mm Hg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium or phenytoin. Type 1A and 1C antiarrhythmics are generally contraindicated (e.g., quinidine, disopyramide, and procainamide).

In rare instances, hemoperfusion may be beneficial in acute refractory cardiovascular instability in patients with acute toxicity. However, hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis generally have been reported as ineffective in tricyclic antidepressant poisoning.

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 these are ineffective, other anticonvulsants (e.g., phenobarbital, phenytoin). Physostigmine is not recommended except to treat life-threatening symptoms that have been unresponsive to other therapies, and then only in consultation with a poison control center.

Psychiatric Follow-up

Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase.

Psychiatric referral may be appropriate.

Pediatric Management

The principles of management of child and adult overdosages are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

**Poisindex® Toxicologic Management.*
Topic: Antidepressants, Tricyclic
Micromedex Inc. Vol.85.

HOW SUPPLIED

Surmontil® (trimipramine maleate) Capsules are available in the following dosage strengths:

25 mg, NDC 0008-4132, opaque blue and yellow capsule marked "WYETH" and "4132", in bottles of 100 capsules.

50 mg, NDC 0008-4133, opaque blue and orange capsule marked "WYETH" and "4133", in bottles of 100 capsules.

100 mg, NDC 0008-4158, opaque blue and white capsule marked "WYETH" and "4158", in bottles of 100 capsules.

Store at room temperature, approximately 25°C (77°F).

Keep bottles tightly closed.

Dispense in a tight container.

Protect capsules packaged in blister strips from moisture.

The appearance of these capsules is a trademark of Wyeth-Ayerst Laboratories.

by arrangement with Rhone-Poulenc Rorer France

Wyeth Laboratories Inc.
A Wyeth-Ayerst Company
Philadelphia, PA 19101
CI 5187-1 Issued February 17, 1999 Printed in USA