TELAZINE

Tablets

Composition
Each tablet contains Trifluoperazine (as Hydrochloride) 10 mg

Action
Trifluoperazine is one of the phenothiazine class of compounds and as such has many pharmacodynamic effects which relate to its therapeutic actions and side effects. The most notable action of phenothiazines is antagonism at dopamine receptors in the CNS. It is hypothesized that this action in the limbic system and associated areas of cerebral cortex is the basis of the antipsychotic action of phenothiazines, whilst in the medullary chemoreceptor trigger zone it appears to be responsible for the antiemetic effect of these agents. In addition, dopamine antagonism in the basal ganglia appears to be involved in some of the extrapyramidal side-effects of phenothiazines, whilst blockage of the dopaminergic inhibition of prolactin release from the anterior pituitary gland is thought to lead to hyperprolactinaemia.

Other central actions of phenothiazines include sedation and inhibition of the function of the hypothalamic heat regulatory centre. Phenothiazines also lower the seizure threshold. Central actions of phenothiazines also affect the cardiovascular system, as does their antagonism of peripheral α - adrenergic receptors, which can cause hypotension.

Phenothiazines also have anti – muscarinic activity which causes certain side effects.

Trifluoperazine is one of the piperazine sub–class of phenothiazine drugs whose members have fewer sedative, antimuscarinic and hypotensive side – effects but more extrapyramidal side effects than other types of phenothiazines.

Pharmacokinetics
The pharmacokinetics for Trifluoperazine are typical of phenothiazines such as chlorpromazine. It is readily absorbed from the gastrointestinal tract with peak plasma levels being reached from 1.5 to 6.0 hours after ingestion. A high interindividual variation in bioavailability has been consistently reported. In the blood, Trifluoperazine is highly bound to plasma proteins. It probably penetrates the placental barrier and enters breast milk like chlorpromazine.

The elimination of Trifluoperazine from the blood is multiphasic with an α phase elimination half-life of about 3.6 hours and a terminal elimination half-life of about 22 hours. Several metabolites of Trifluoperazine have been identified, including an N-oxide, a sulphoxide and a 7-hydroxy derivative. The N-oxide is thought to be the main metabolite and possibly active. This and the sulphoxide metabolite are thought to be extensively metabolised pre-systemically (i.e. in the gut and/or liver), whilst the 7-hydroxy derivative appears to undergo no such metabolism.

Elimination occurs via bile and urine.

Indications
Trifluoperazine is a piperazine phenothiazine tranquilizer with potent antipsychotic, anxiolytic and anti-emetic activity, and a pharmacological profile of moderate sedative and hypotensive properties, and fairly pronounced tendency to cause extrapyramidal reactions.

Low Dosage
Trifluoperazine is indicated as an adjunct in the short term management of anxiety states, depressive symptoms secondary to anxiety, and agitation. It is also indicated in the symptomatic treatment of nausea and vomiting.

High Dosage
Trifluoperazine is indicated for the treatment of symptoms and prevention of relapse in schizophrenia and in other psychoses, especially of the paranoid type, but not in depressive psychoses. It may also

be used as an adjunct in the short term management of severe psychomotor agitation and of dangerously impulsive behavior, for example, mental sub-normality.

Contraindications

Do not use Trifluoperazine in comatose patients, particularly if associated with other central nervous system depressants, or in those with existing blood dyscrasias or known liver damage, or in those hypersensitive to the active ingredient or related compounds. Patients with uncontrolled cardiac decompensation should not be given Trifluoperazine.

Warnings

Tardive Dyskinesia

Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause Tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of Tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of Tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to neuroleptic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of Tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific

treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

An encephalopathic syndrome (characterized by weakness, lethargy, fever, tremulousness and confusion, extrapyramidal symptoms, leukocytosis, elevated serum enzymes, BUN and FBS) has occurred in a few patients treated with lithium plus a neuroleptic. In some instances, the syndrome was followed by irreversible brain damage. Because of a possible causal relationship between these events and the concomitant administration of lithium and neuroleptics, patients receiving such combined therapy should be monitored closely for early evidence of neurologic toxicity and treatment discontinued promptly if such signs appear. This encephalopathic syndrome may be similar to or the same as neuroleptic malignant syndrome (NMS).

Patients who have demonstrated a hypersensitivity reaction (e.g., blood dyscrasias, jaundice) with a phenothiazine should not be re-exposed to any phenothiazine, including Trifluoperazine HCl, unless in the judgment of the physician the potential benefits of treatment outweigh the possible hazard.

Trifluoperazine HCl Concentrate contains sodium bisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

Trifluoperazine HCl may impair mental and/or physical abilities, especially during the first few days of therapy. Therefore, caution patients about activities requiring alertness (e.g., operating vehicles or machinery).
If agents such as sedatives, narcotics, anesthetics, tranquilizers or alcohol are used either simultaneously or successively with the drug, the possibility of an undesirable additive depressant effect should be considered.

Pregnancy
Category C
Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Nursing Mothers
There is evidence that phenothiazines are excreted in the breast milk of nursing mothers. Because of the potential for serious adverse reactions in nursing infants from Trifluoperazine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Adverse Reactions
The adverse reaction include drowsiness, dryness of the mouth, pallor of the skin, postural hypotension, weakness, lowering of body temperature (occasionally pyrexia), tachycardia, arrhythmias, agitation, insomnia, depression or sometimes agitation, photosensitivity and skin rashes.

Sensitivity reactions include urticaria, photosensitization and on occasions exfoliative dermatitis. Trifluoperazine may alter endocrine function. Patients have experienced amenorrhea galactorrhoea, gynecomastia, and mass gain and there have been reports of raised serum-cholesterol concentrations.

Extrapyramidal dysfunction with symptoms such as akathisia dystonia and Parkinsonism may occur. Muscles of the face and shoulder girdle maybe selectively involved. Spasm of the neck muscles, extensor rigidity of the back muscles, carpopedal spasm, oculogyric crises, trismus, and swallowing difficulty may be observed. Excitement and increased suggestibility are occasionally encountered. The extrapyramidal symptoms are reversible and usually subside within 24 to 48 hours after lowering dosage or temporarily discontinuing the drug, or by simultaneous administration of an anti-Parkinsonian drug. However, persistent Tardive dyskinesia has occurred and may be irreversible.

Other side effects include temporary stimulation or jitteriness, transient drowsiness dizziness, muscular weakness, anorexia, dryness of the mouth, rash, lactation and blurred vision, jaundice, allergic purpura, agranulocytosis, leucopenia, and thrombocytopenia have been reported occasionally.

If sore throat, fever, and weakness develop, the drug should be withdrawn immediately and white blood cell and differential counts should be made. If evidence of bilirubinuria and icterus appear, the drug should likewise be discontinued, and liver function tests should be made.

Precautions

General

Given the likelihood that some patients exposed chronically to neuroleptics will develop Tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk. The decision to inform patients and/or their guardians must obviously take into account the clinical circumstances and the competency of the patient to understand the information provided.

Thrombocytopenia and anemia have been reported in patients receiving the drug. Agranulocytosis and pancytopenia have also been reported-warn patients to report the sudden appearance of sore throat or other signs of infection. If white blood cell and differential counts indicate cellular depression, stop treatment and start antibiotic and other suitable therapy.

Jaundice of the cholestatic type of hepatitis or liver damage has been reported. If fever with grippe-like symptoms occurs, appropriate liver studies should be conducted. If tests indicate an abnormality, stop treatment.

One result of therapy may be an increase in mental and physical activity.
For example, a few patients with angina pectoris have complained of increased pain while taking the drug. Therefore, angina patients should be observed carefully and, if an unfavorable response is noted, the drug should be withdrawn.

Although the hypotensive activity of Trifluoperazine is minor, patients with impaired cardiovascular systems should not receive large doses of Trifluoperazine. As Trifluoperazine may potentiate the action of antihypotensive agents, as well as that of general anaesthetics, hypnotics, alcohol, and other central nervous system depressants, caution should be observed in concomitant use of any of these drugs with Trifluoperazine. If use of a vasopressor should be necessary to counteract hypotension induced by an antihypertensive drug given simultaneously, epinephrine should not be employed because Trifluoperazine may reverse its action and cause profound hypotension; levarterenol however, may be given.

Since certain phenothiazines have been reported to produce retinopathy, the drug should be discontinued if ophthalmoscopic examination or visual field studies should demonstrate retinal changes. An antiemetic action of Trifluoperazine HCl may mask the signs and symptoms of toxicity or over dosage of other drugs and may obscure the diagnosis and treatment of other conditions such as intestinal obstruction, brain tumor, and Reye's syndrome.

With prolonged administration at high dosages, the possibility of cumulative effects, with sudden onset of severe central nervous system or vasomotor symptoms, should be kept in mind.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately 1/3 of human breast cancers are prolactin-dependent in vitro, a factor of potential importance if the prescribing of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhoea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Chromosomal aberrations in spermatocytes and abnormal sperm have been demonstrated in rodents treated with certain neuroleptics. Because phenothiazines may interfere with thermoregulatory mechanisms, use with caution in persons who will be exposed to extreme heat.
As with all drugs that exert an anticholinergic effect, and/or cause mydriasis, Trifluoperazine should be used with caution in patients with glaucoma.

Long-Term Therapy
To lessen the likelihood of adverse reactions related to cumulative drug effect, patients with a history of long-term therapy with Trifluoperazine HCl and/or other neuroleptics should be evaluated periodically to decide whether the maintenance dosage could be lowered or drug therapy discontinued.

Drug Interactions
Phenothiazines may diminish the effect of oral anticoagulants. Phenothiazines can produce alpha-adrenergic blockade.
Concomitant administration of propranolol with phenothiazines results in increased plasma levels of both drugs.

Antihypertensive effects of guanethidine and related compounds may be counteracted when phenothiazines are used concurrently.
Thiazide diuretics may accentuate the orthostatic hypotension that may occur with phenothiazines.

Phenothiazines may lower the convulsive threshold; dosage adjustments of anticonvulsants may be necessary. Potentiation of anticonvulsant effects does not occur. However, it has been reported that phenothiazines may interfere with the metabolism of Phenytoin and thus precipitate Phenytoin toxicity.

Drugs that lower the seizure threshold, including phenothiazine derivatives, should not be used with Amipaque. As with other phenothiazine derivatives, Trifluoperazine HCl should be discontinued at least 48 hours before myelography, should not be resumed for at least 24 hours post procedure and should not be used for the control of nausea and vomiting occurring either prior to myelography or post procedure with Amipaque.
The presence of phenothiazines may produce false-positive phenylketonuria (PKU) test results.

Dosage and Administration
The recommended starting dose for physically fit adults is 5mg twice a day; after a week this may be increased to 15mg a day. If necessary, further increases of 5mg may be made at three day intervals, but not more often. When satisfactory control has been achieved, dosage should be reduced gradually until an effective maintenance level has been established. As with all major tranquilizers, clinical improvement may not be evident for several weeks after starting treatment, and there may also be delay before recurrence of symptoms after stopping treatment. Gradual withdrawal from high dosage treatment is advisable.

Elderly
Reduce starting dose in elderly and frail patients by at least half.

Over Dosage
Signs and symptoms will be predominantly extrapyramidal; hypotension may occur. Treatment consists of gastric lavage together with supportive and symptomatic measures. Do not induce vomiting. Extrapyramidal symptoms may be treated with an anticholinergic antiparkinsonism drug. Treat hypotension with fluid replacement; if severe or persistent, noradrenaline may be considered. Adrenaline is contra-indicated.

Presentation
Box of 20 tablets