Tardive dyskinesia may appear in some patients on long-term therapy with antipsychotic drugs or may occur after therapy with these drugs has been discontinued. Antiparkinsonism agents do not alleviate some of the symptoms of tardive dyskinesia, and in some instances may aggravate them.

However, parkinsonism and tardive dyskinesia often coexist in patients receiving chronic neuroleptic treatment, and anticholinergic therapy with trihexyphenidyl may relieve some of these parkinsonian and tardive dyskinesia symptoms. Trihexyphenidyl is not recommended for use in patients with tardive dyskinesia unless they have concomitant Parkinson's disease.

Patients with arteriosclerosis or with a history of idiocy/syncrasy to other drugs may exhibit reactions of mental confusion, agitation, disturbance of behavior, or nausea and vomiting. Such patients should be allowed to develop a tolerance through the initial administration of a small dose and gradual increase in dose until an effective level is reached. If a severe reaction should occur, administration of the drug should be discontinued at a lower dosage. Psychiatric disturbances can result from indiscriminate use (leading to overdosage) to sustain continued euphoria. (See DRUG ABUSE AND DEPENDENCE).

Abrupt withdrawal of treatment for parkinsonism may result in acute exacerbation of parkinsonism symptoms; therefore, abrupt withdrawal should be avoided (See DOSAGE AND ADMINISTRATION).

Information for Patients

Trihexyphenidyl may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle. Patients should be cautioned about operating machinery, including automobiles, until they are reasonably certain that trihexyphenidyl therapy does not adversely affect their ability to engage in such activities. Because of increased sedative effects, patients should be cautioned to avoid the use of alcohol or other CNS depressants while taking trihexyphenidyl.

Since this medication may increase the susceptibility to heat stroke (gastrointestinal (GI) problems, fever, heat intolerance), use with caution in patients known to have intolerance to heat and in those with a history of gout, diabetes mellitus, and cardiovascular disease. Patients should be advised to report the occurrence of GI problems, fever, or heat intolerance promptly since paralytic ileus, hyperthermia, or heat stroke may occur. If GI upset occurs, trihexyphenidyl may be taken with food.

Patients should have close monitoring of intraocular pressure. (See WARNINGS).

Drug Interactions

Cannabimimetics, barbiturates, opiates, and alcohol may have additive effects with trihexyphenidyl, and thus, an abuse potential exists. Concurrent use of alcohol or other CNS depressants with trihexyphenidyl may cause increased sedative effects.

Monoamine oxidase inhibitors and tricyclic antidepressants possessing significant anticholinergic activity may intensify the anticholinergic effects of antidyskinetic agents because of the secondary anticholinergic activities of these medications. Prophylactic administration of anticholinergic agents, such as trihexyphenidyl, as a prevention of drug-induced parkinsonism during major surgery is not recommended. There may be an increased risk for the development of tardive dyskinesia during concomitant administration of anticholinergics and neuroleptics (See PRECAUTIONS, General).

The usual dose of either trihexyphenidyl or levodopa may be reduced during concurrent therapy, since concurrent administration may increase drug-induced involuntary movements (See DOSAGE AND ADMINISTRATION).

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity studies or adequate genotoxicity or fertility studies have been conducted for trihexyphenidyl.

Pregnancy

Teratogenic Effects

Pregnancy Category C

Animal reproduction studies to evaluate teratogenic and embryotoxic potential of the drug have not been conducted with trihexyphenidyl. It is also not known whether trihexyphenidyl can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Trihexyphenidyl should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when trihexyphenidyl is administered to a nursing woman.

As with other anticholinergics, trihexyphenidyl may cause suppression of lactation. Therefore, trihexyphenidyl should only be used if the expected benefit to the mother outweighs the potential risk to the infant.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established (See also ADVERSE REACTIONS).

Geriatric Use

Sensitivity to the actions of parasympathomimetic drugs may increase with age, particularly over the age of 60; therefore, elderly patients generally should be started on low doses of trihexyphenidyl and observed closely.

Trihexyphenidyl has been shown to cause some cognitive dysfunctions in the elderly, including confusion and memory impairment. (See ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Minor side effects, such as dryness of the mouth, blurred vision, dizziness, mild nausea or nervousness, will be experienced by 30 to 50 percent of all patients. These sensations, however, are much less troublesome with trihexyphenidyl than with belladonna alkaloids and are usually less disturbing than unalleviated parkinsonism. Such side reactions tend to become less pronounced, and even to disappear, as treatment continues. Even before these reactions have remitted spontaneously, they may often be controlled by careful adjustment of dosage, amount of drug, or interval between doses.

Isolated instances of supportive parotid secondary to excessive dryness of the mouth, skin rashes, dilatation of the colon, paralytic ileus, and certain psychiatric manifestations such as delusions, hallucinations, and paranoia, all of which may occur with any of the anticholinergic drugs, have been reported rarely with trihexyphenidyl. Potential side effects associated with the use of any antipsychotic drugs, including trihexyphenidyl, include cognitive dysfunctions, including confusion and memory impairment; constipation; drowsiness, urinary hesitancy or retention, tachycardia, dilation of the pupil, increased intraocular pressure, choreiform movements, weakness, vomiting, and headache. Exacerbation of parkinsonism with abrupt treatment withdrawal has been reported. Neuroleptic malignant syndrome with abrupt treatment withdrawal has been reported rarely (See WARNINGS, Neuroleptic Malignant Syndrome).

The occurrence of angle-closure glaucoma in patients receiving trihexyphenidyl has been reported (blindness has been reported in some cases). Paradoxical sinus bradycardia, dry skin, and cyclopia have been reported.

In addition to adverse events seen in adults, the following adverse reactions have been reported in the literature in pediatric patients: hyperkinesia, psychosis, forgetfulness, weight loss, restlessness, chorea, and sleep alterations.

DRUG ABUSE AND DEPENDENCE

Although trihexyphenidyl is not classified as a controlled substance, the possibility of abuse should be borne in mind due to its stimulant and euphoriant properties.

OVERDOSAGE

The mean oral LD₅₀ of trihexyphenidyl has been reported to be 365 mg/kg. (range, 35 to 3700 mg/kg) in mice and 1660 mg/kg (1420 to 1940 mg/kg) in rats. At a dose of 40 mg/kg, dogs have exhibited emesis, restlessness followed by drowsiness, equilibrium disturbances, and mydriasis. In humans, doses up to 300 mg (5 mg/kg) have been ingested without fatality or serious sequelae. However, rare cases of death associated with trihexyphenidyl overdosages taken in conjunction with other CNS-depressant agents have been reported and in patients with a compromised respiratory condition. Trihexyphenidyl blood concentrations associated with the fatalities ranged from 0.03 to 0.80 mg/l.

Signs and Symptoms

Overdose with trihexyphenidyl produces typical central symptoms of atropine intoxication (the central anticholinergic syndrome). Correct diagnosis depends upon recognition of the peripheral signs of atropine intoxication, including dilated pupils; warm, dry skin; facial flushing; decreased secretions of the mouth, pharynx, nose, and bronchii; foul-smelling breath; elevated temperature; tachycardia, cardiac arrhythmias; decreased bowel sounds; urinary retention. Neuropsychiatric signs such as delirium, disorientation, anxiety, hallucinations, illusions, confusion, incoherence, agitation, hyperactivity, ataxia, lip smacking and tasting movements, loss of memory, paranoia, combativeness, and seizures may be seen. The condition can progress to stupor, coma, paralysis, cardiovascular and respiratory arrest, and death.

Treatment

Treatment of acute overdose involves symptomatic and supportive therapy. Gastric lavage or other methods to limit absorption should be instituted if a small dose of trihexyphenidyl or a short-acting barbiturate may be administered if CNS excitation is observed. Phenothiazines are contraindicated because the toxicity may be intensified by their antimuscarinic action, causing coma. Respiratory support, artificial ventilation or vasopressor agents may be required. Hyperpyrexia must be reversed, fluid volume replaced and acid-base balance maintained. Urinary catheterization may be necessary. It is not known if trihexyphenidyl is dialyzable.

DOSAGE AND ADMINISTRATION

Dosing schedule should be individualized. The initial dose should be low and then increased gradually, especially in patients over 60 years of age.

Whether trihexyphenidyl may be best given before or after meals should be determined by the way the patient reacts. Postprandial parkinsonism is more likely to occur after meals; therefore, trihexyphenidyl may prefer to take it after meals and may, in addition, require smaller amounts of atropine which, under such circumstances, is sometimes an effective adjuvant. If trihexyphenidyl tends to dry the mouth excessively, it may be better to take it before meals than after meals because it causes nausea. If taken after meals, the throat sometimes induced can be allayed by mint candies, chewing gum or water.

Abrupt withdrawal of treatment for parkinsonism may result in acute exacerbation of parkinsonism symptoms; therefore, abrupt withdrawal should be avoided.
Abrupt withdrawal of treatment may result in neuroleptic malignant syndrome (NMS) (See WARNINGS).

**Idiopathic Parkinsonism**
As initial therapy for parkinsonism, 1 mg of trihexyphenidyl hydrochloride may be administered the first day. The dose may then be increased by 2 mg increments at intervals of three to five days, until a total of 6 to 10 mg is given daily. The total daily dose will depend upon what is found to be the optimal level. Many patients derive maximum benefit from this daily total of 6 to 10 mg, but some patients, chiefly those in the postencephalitic group, may require a total daily dose of 12 to 15 mg.

**Drug-Induced Parkinsonism**
The size and frequency of the trihexyphenidyl dose needed to control extrapyramidal reactions to commonly employed tranquilizers, notably the phenothiazines, thioxanthenes, and butyrophenones, must be determined empirically. The total daily dosage usually ranges between 5 and 15 mg although, in some cases, these reactions have been satisfactorily controlled with as little as 1 mg daily. It may be advisable to commence therapy with a single 1 mg dose. If the extrapyramidal manifestations are not controlled in a few hours, the subsequent doses may be progressively increased until satisfactory control is achieved. Satisfactory control may sometimes be more rapidly achieved by temporarily reducing the dosage of the tranquilizer when instituting trihexyphenidyl therapy and then adjusting the dosage of both drugs until the desired ataractic effect is retained without onset of extrapyramidal reactions. It is sometimes possible to maintain the patient on a reduced trihexyphenidyl dosage after the reactions have remained under control for several days. Instances have been reported in which these reactions have remained in remission for long periods after trihexyphenidyl therapy was discontinued.

**Concomitant Use with Levodopa**
When trihexyphenidyl is used concomitantly with levodopa, the usual dose of each may need to be reduced. Careful adjustment is necessary, depending on side effects and degree of symptom control. A trihexyphenidyl dosage of 3 to 6 mg daily, in divided doses, is usually adequate.

**Concomitant Use with Other Parasympathetic Inhibitors**
Trihexyphenidyl may be substituted, in whole or in part, for other parasympathetic inhibitors. The usual technique is partial substitution initially, with progressive reduction in the other medication as the dose of trihexyphenidyl is increased.

The total daily intake of trihexyphenidyl hydrochloride oral solution USP is tolerated best if divided into 3 doses and taken at mealtimes. High doses (>10 mg daily) may be divided into 4 parts, with 3 doses administered at mealtimes and the fourth at bedtime.

**HOW SUPPLIED**
Trihexyphenidyl Hydrochloride Oral Solution, containing trihexyphenidyl hydrochloride 2 mg per 5 mL, is a clear, colorless lime-peppermint flavored liquid supplied in 473 mL (16 fl. oz) bottles, NDC 61748-054-16. Dispense in a tight, light-resistant container with a child-resistant closure.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

**DO NOT FREEZE.**

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