PRODUCT MONOGRAPH

[Pr]TENSILON®

Edrophonium Chloride Injection, USP

10 mg/mL

Nondepolarizing Neuromuscular Antagonist

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ACTIONS AND CLINICAL PHARMACOLOGY

Edrophonium is a rapidly reversible anticholinesterase agent. The drug attaches briefly to acetylcholinesterase at the anionic site, thereby occluding the site of acetylcholine binding and inhibiting its hydrolysis. As a result, acetylcholine accumulates at cholinergic synapses and its effects are prolonged and exaggerated. Edrophonium therefore produces generalized cholinergic responses of short duration, including miosis, increased tonus of intestinal and skeletal musculature, constriction of bronchi and ureters, bradycardia, and stimulation of secretion by salivary and sweat glands. The vagal stimulation produced by edrophonium results in shortening of the effective refractory period of atrial muscle and depressed conduction through the atrioventricular (AV) node. In addition, edrophonium has a direct cholinomimetic effect on skeletal muscle, which is greater than that of most other anticholinesterase drugs.

Because of its quaternary ammonium structure, moderate doses of edrophonium do not cross the blood-brain barrier to produce CNS effects. Extremely high doses, however, produce CNS stimulation followed by CNS depression, in addition to a depolarizing neuromuscular blockade, and may result in respiratory depression, paralysis, and death.

PHARMACOKINETICS

Following parenteral administration, edrophonium has a more rapid onset and shorter duration of action than has neostigmine, pyridostigmine, or ambenonium. Following i.v. administration, the effects of edrophonium on skeletal muscle begin within 30-60 seconds

and last 5-10 minutes, although patients with myasthenia gravis receiving edrophonium for the first time have been reported to experience effects for up to 30 minutes. Cumulative effects have occurred after administration of small doses of edrophonium i.v. every 30 minutes for several doses. After i.m. injection, skeletal muscle effects begin in 2-10 minutes and last 5-30 minutes. Edrophonium is not hydrolyzed by cholinesterases, but its exact metabolic fate and mode of excretion have not been elucidated.

INDICATIONS

Myasthenia Gravis

Tensilon® (edrophonium) is usually the drug of choice for differential diagnosis of myasthenia gravis. Tensilon® may be especially useful in evaluating cranial muscle strength. The Tensilon® test for myasthenia gravis has been reported to clearly establish the diagnosis in 90-95 % of patients suspected of having the disease, including neonates. Tensilon® is also useful in adjusting the dosage of other anticholinesterase agents in patients with myasthenia gravis. Because of its short duration of action, edrophonium is not useful for maintenance therapy in myasthenia gravis.

The drug may also be used to differentiate cholinergic crisis from myasthenic crisis after a controlled airway has been established.

Tensilon® is also useful whenever a curare antagonist is needed to reverse the neuromuscular block produced by curare, tubocurarine, gallamine triethiodide or dimethyltubocurarine. It is **not** effective against decamethonium bromide and succinylcholine chloride. It may be used adjunctively in the treatment of respiratory depression caused by curare overdosage.

CONTRAINDICATIONS

Tensilon® is contraindicated in patients with known hypersensitivity to anticholinesterase agents. Patients who are hyperreactive to Tensilon® (edrophonium) experience a severe cholinergic reaction to the drug. Therefore, atropine sulfate injection should always be

readily available as an antagonist for the muscarinic effects of edrophonium. This cholinergic reaction, which produces muscle weakness and fasciculation in addition to muscarinic effects, may be falsely interpreted as a negative reaction to diagnostic testing for myasthenia gravis.

Tensilon® is contraindicated in patients with mechanical obstruction of the intestinal or urinary tract.

WARNINGS

Tensilon® should be used cautiously in patients with symptoms of myasthenic weakness who are also receiving anticholinesterase agents, since symptoms of anticholinesterase drug overdose (cholinergic crisis) and underdosage (myasthenic weakness) may be similar.

When Tensilon® is used to diagnose myasthenia gravis or to evaluate dosage of anticholinesterase therapy in the treatment of myasthenia gravis, it should be kept in mind that individual muscle groups may respond differently to the same dose of an anticholinesterase agent, producing weakness in one muscle group while increasing strength in another. The muscles of the neck and of chewing and swallowing are usually the first muscles weakened by overdose, followed by the muscles of the shoulder girdle and upper extremities, and finally the pelvic girdle and extraocular and leg muscles. Vital capacity should be routinely measured during testing for the diagnosis of myasthenia gravis and adequate facilities for cardiopulmonary resuscitation, cardiac monitoring, endotracheal intubation and assisting respiration should be available during Tensilon® administration, especially in digitalized patients.

The possibility that patients may develop brief or prolonged periods of refractoriness to anticholinesterase agents should be considered. During these periods, the patient should be monitored carefully and the need for respiratory assistance considered. Dosage of anticholinesterase agents should be reduced or therapy with the drugs withdrawn until responsiveness is restored.

Tensilon® should be used with caution in patients with bronchial asthma and those receiving a cardiac glycoside (see DRUG INTERACTIONS). Caution is advised in

patients with cardiac arrhythmias. Isolated instances of cardiac and respiratory arrest following administration of Tensilon® have been reported. It is postulated that these are vagotonic effects.

DRUG INTERACTIONS

Care should be given when administering this drug to patients with symptoms of myasthenic weakness who are also on anticholinesterase drugs. Since symptoms of anticholinesterase overdose (cholinergic crisis) may mimic underdosage (myasthenic weakness), their condition may be worsened by the use of this drug (see OVERDOSAGE section).

Tensilon® does not antagonize, and in fact may prolong, the phase I block of depolarizing muscle relaxants such as succinylcholine or decabethonium. Fully established phase II (desensitization) block can be transiently reversed by Tensilon®.

Tensilon® antagonizes the effects of nondepolarizing muscle relaxants (e.g., atracurium, gallamine, metocurine, pancuronium, tubocurarine, vecuronium), but the brief duration of action of edrophonium limits its therapeutic usefulness for this purpose.

Atropine antagonizes the muscarinic effects of Tensilon®, and this interaction is utilized to counteract the muscarinic symptoms of Tensilon® toxicity.

Digitalization may increase the sensitivity of the heart to Tensilon®. One patient receiving large amounts of digoxin experienced AV block and prolonged ventricular asystoly after being given edrophonium i.v. for diagnosis of a supraventricular tachyarrhythmia.

CARCINOGENESIS, MUTAGENESIS AND IMPAIRMENT OF FERTILITY

Carcinogenicity and mutagenicity studies have not been performed with Tensilon®. The effect of Tensilon® on fertility has not been investigated.

PREGNANCY

Teratogenic Effects: Animal reproduction studies have not been conducted with Tensilon®. However, Tensilon®, like other cholinesterase inhibitors, contains a quaternary ammonium structure and, therefore, would be expected to cross the placenta to only a limited extent. It is also not known whether Tensilon® can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity. Tensilon® should be given to a pregnant women only if clearly needed.

Non-teratogenic Effects: There are no adequate studies on the peri- or postnatal effects of edrophonium. Anticholinesterase drugs may cause uterine irritability and induce premature labor when given intravenously to pregnant women near term.

Nursing Mothers:

It is not known whether Tensilon® is excreted in human milk. If it is necessary to administer Tensilon® to a nursing mother, the infant should not be breastfed immediately following drug administration to the mother because of the potential for serious adverse reactions from Tensilon® in the nursing infant.

Pediatric Use:

Please refer to the DOSAGE and ADMINISTRATION section.

ADVERSE REACTIONS

Careful observation should be made for severe cholinergic reactions in the hyperreactive individual. The myasthenic patient in crisis who is being tested with Tensilon® (edrophonium chloride) should be observed for bradycardia or cardiac arrest and cholinergic reactions if an overdose is given. The following reactions common to anticholinesterase agents may occur, although not all of these reactions have been reported with the administration of Tensilon®, probably because of its short duration of action and limited indications:

Cardiac: arrhythmias (especially bradycardia), fall in cardiac output leading to hypotension.

Respiratory: increased tracheobronchial secretions, laryngospasm, bronchiolar constriction, paralysis of respiratory muscles, central respiratory paralysis.
Central Nervous System: convulsions, dysarthria, dysphonia, dysphagia.
Skeletal Muscles: fasciculations, weakness.
Gastrointestinal Tract: nausea, vomiting, abdominal cramps, increased salivary, gastric and intestinal secretions, increased peristalsis, diarrhea.
Genitourinary: increased urinary frequency and incontinence.
Ophthalmic: increased lacrimation, diplopia, pupillary constriction, spasm of accommodation, conjunctival hyperemia.
Miscellaneous: diaphoresis.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Manifestations: Tensilon® overdosage may induce cholinergic crisis, which is characterized by nausea, vomiting, diarrhea, excessive salivation and sweating, increased bronchial secretions, miosis, lacrimation, bradycardia or tachycardia, cardiospasm, bronchospasm, hypotension, incoordination, blurred vision, muscle cramps weakness, fasciculation, and paralysis. Death may result from cardiac arrest or respiratory paralysis and pulmonary edema. In patients with myasthenia gravis, in whom overdosage is most likely to occur, fasciculation and adverse parasympathomimetic effects may be mild or absent, making cholinergic crisis difficult to distinguish from myasthenic crisis.

Treatment: In the treatment of Tensilon® overdosage, maintaining adequate respiration is of primary importance. Tracheotomy, bronchial aspiration, and postural drainage may be required to maintain an adequate airway; respiration can be assisted mechanically or with oxygen, if necessary. Cardiac function should be monitored until the patient's condition is stable. Appropriate measures for managing seizures and shock, if present, should also be instituted. Tensilon® should be discontinued immediately and 0.4 - 0.5 mg of atropine sulfate administered i.v. Additional doses of atropine may be given every 3-10 minutes as needed to control muscarinic symptoms, but because of the short duration of action of edrophonium, more than 2 mg is rarely required. If there are copious bronchial

secretions obstructing the airway, up to 1.2 mg of atropine sulfate may be given i.v. and repeated every 20 minutes until secretions are controlled. Atropine overdosage should be avoided as tenacious secretions and bronchial plugs may result. It should be kept in mind that, unlike muscarinic effects, the skeletal muscle effects and consequent respiratory paralysis that can occur following Tensilon® overdosage are not alleviated by atropine.

NOTE: The intravenous LD_{50} of Tensilon® in mice has been reported to be 9 mg/kg and 18.6 mg/kg.

DOSAGE AND ADMINISTRATION

Diagnosis of Myasthenia Gravis

In the diagnosis of myasthenia gravis, all anticholinesterase medications should be discontinued for **at least 8 hours** before administering Tensilon®. Placebo response should be determined before administering Tensilon® by measuring muscle strength before and after administration of atropine sulfate or sodium chloride injection; this may be particularly important in patients with mild weakness and those whose weakness is strongly influenced by emotional factors. Pre-injection and post-injection strength are usually most accurately measured in cranial musculature, which is less subject to variation in effect. Administration of atropine sulfate to prevent or reverse cholinergic reactions during Tensilon® testing usually is not necessary, but atropine should be readily available, especially for older patients.

For diagnosis of myasthenia gravis in adults, 10 mg of Tensilon® is drawn into a syringe and 2 mg of the drug is injected i.v. over 15-30 seconds. If a cholinergic reaction occurs, the test should be discontinued and 0.4-0.5 mg of atropine sulfate administered i.v.. If no response to Tensilon® occurs, the remaining 8 mg of the drug is given 45 seconds later; some patients (especially those who are overweight) may require larger doses. After 30 minutes, the test may be repeated if necessary.

Children weighing 34 kg or less may initially be given 1 mg of Tensilon® i.v. for diagnosis of myasthenia gravis; children weighing more than 34 kg may receive 2 mg

initially. If a cholinergic reaction occurs after this initial dose, the test should be discontinued and atropine sulfate administered i.v. If no response occurs after 45 seconds of the initial dose of Tensilon®, 1 mg of the drug may be given every 30-45 seconds up to a maximum cumulative dose of 5 mg for children weighing 34 kg or less, and up to 10 mg for heavier children. Alternatively, children may be given a total of 0.2 mg/kg or 6 mg/m^2 i.v.. One fifth of this dose should be given in one minute, and followed by the remainder if no response occurs within 45 seconds. Infants may be given a total dose of 0.5 mg i.v..

The usual adult i.m. dose of Tensilon® for the diagnosis of myasthenia gravis is 10 mg . If a cholinergic reaction occurs, 2 mg should be given i.m. 30 minutes later to rule out a false-negative reaction. Children weighing up to 34 kg may be given 2 mg i.m. for the diagnosis of myasthenia gravis, and children weighing more than 34 kg may receive 5 mg i.m.. Infants may receive 0.5 - 1.0 mg i.m. or subcutaneously.

Patients with myasthenia gravis show a dramatic, transient increase in muscle strength in response to i.v. Tensilon®, with less adverse muscarinic effects and fasciculation than is seen in nonmyasthenic patients; an increase in intraocular pressure of 2-5 mm Hg also occurs. All signs that would appear with the i.v. test also appear with the i.m. and subcutaneous tests, except that there is a delay of 2-10 minutes before a reaction is noted. Patients with other myopathies, such as polymyositis, muscular dystrophy, or “myasthenic syndrome”, may show a slight improvement in muscle strength after Tensilon®, but only patients with myasthenia gravis respond markedly to anticholinesterase administration.

	Myasthenic[1]	Adequate[2]	Cholinergic[3]
Muscle Strength (ptosis, diplopia, dysphonia, dysphagia, dysarthria, respiration, limb strength)	increased	no change	decreased
Fasciculations (orbicularis oculi, facial muscles, limb muscles)	absent	present or absent	present or absent
Side reactions (lacrimation, diaphoresis, salivation, abdominal cramps, nausea, vomiting, diarrhea)	absent	minimal	severe

[1] **Myasthenic Response** - occurs in untreated myasthenics and may serve to establish diagnosis; in patients under treatment indicates that therapy is inadequate.

[2] **Adequate Response** - observed in treated patients when therapy stabilized; a typical response in normal individuals. In addition to this response in non-myasthenics, the phenomenon of forced lid closure is often observed in psychoneurotics.

[3] **Cholinergic Response** - seen in myasthenics who have been overtreated with anticholinerase drugs.

Assessment of Anticholinesterase Therapy

To assess the adequacy of therapy with other anticholinesterase agents in patients with myasthenia gravis, 1-2 mg of Tensilon® may be administered i.v., 1 hour after oral intake of the drug being used in treatment. A transient increase in muscle strength and subjective improvement without fasciculation or adverse muscarinic effects occur in patients who require additional anticholinesterase medication. If the patient is undertreated, the dosage of ambenoniu, pyridostigmine, or neostigmine should be gradually increased to the level at which an “adequate” or normal response to Tensilon® occurs. Decreased muscle strength, sometimes accompanied by fasciculation and severe muscarinic symptoms,

usually occurs in patients who have been overtreated with anticholinesterase medication. Occasionally, patients who are overtreated will show no response to Tensilon®; therefore, the possibility of inducing cholinergic crisis should be considered before increasing the dosage of anticholinesterase medication in patients with equivocal responses to Tensilon®. In myasthenic patients who are adequately treated, no change in muscle strength is seen after Tensilon®, and adverse effects, if they occur, are mild. During dosage adjustment, patients should be tested with Tensilon® every 1-3 days, because changes in oral dosage may take several days to show results.

Differentiation of Cholinergic and Myasthenic Crisis

Prior to administration of Tensilon® to differentiate cholinergic crisis from myasthenic crisis, controlled ventilation must be established immediately if the patient is apneic, to avoid cardiac arrest and irreversible CNS damage. Tensilon® should not be given until respiratory exchange is adequate. To perform the test to differentiate cholinergic crisis from myasthenic crisis, no more than 2 mg of Tensilon® should be in the syringe. Initially, 1 mg of the drug may be given i.v., and cardiac function carefully monitored. If the initial dose does not further impair the patient, the remaining 1 mg may be given 1 minute later. If the patient is experiencing **cholinergic crisis**, Tensilon® will cause increased oropharyngeal secretions and further weakness in the muscles of respiration. If the **crisis** is **myasthenic**, Tensilon® clearly improves respiration and the patient can be treated with longer acting i.v. anticholinesterase medication. If no clear improvement in respiration has occurred after 2 mg of Tensilon®, it is usually best to discontinue all anticholinesterase therapy and secure ventilation by tracheostomy with assisted respiration if needed.

Surgery

For reversal of the effects of nondepolarizing neuromuscular blocking agents after surgery, 10 mg of Tensilon® has been administered i.v. over 30-45 seconds and repeated every 5-10 minutes as needed, but no more than 40 mg total should be given. If large doses of Tensilon® (15 mg) are required, they should be preceded by 0.4-1.6 mg of atropine sulfate i.v., depending on the patient's age and weight. Because of its brief effect, Tensilon® should not be given prior to the administration of the neuromuscular blocking agent; it should be used at the time when its effect is needed. The effect of each dose of Tensilon® on respiration should be carefully observed before additional doses are given, and assisted ventilation should always be employed. The patient should be closely observed to be sure "recurarization" and respiratory depression do not occur. Full recovery may be delayed in the presence of extreme debilitation, hypokalemia, carcinomatosis, or with concomitant use of certain broad spectrum antibiotics (e.g., aminoglycosides) or anesthetic agents, notably ether. Satisfactory recovery of respiration and neuromuscular transmission must be assured before respiratory assistance is discontinued.

A 10-mg dose of edrophonium chloride has been given i.v. to determine the phase of nondepolarizing neuromuscular block; only fully established phase II (desensitization) block can be reversed by edrophonium chloride.

PHARMACEUTICAL INFORMATION

Proper Name: Edrophonium Chloride

Chemical Name: (1) Benzenaminium, *N*-ethyl-3-hydroxy-*N*,*N*-dimethyl-ammonium chloride

(2) Ethyl(*m*-hydroxyphenyl)dimethylammonium chloride

Chemical Formula: $C_{10}H_{16}ClN0$

Structural Formula:

Molecular Weight: 201.70

Description: Edrophonium chloride is a synthetic quaternary ammonium parasympathomimetic (cholinergic) agent. It occurs as a bitter tasting, white, crystalline powder and has approximate solubilities of 2 g/mL in water and 200 mg/mL in alcohol at 25^{o} C. Edrophonium chloride injection has a pH of 5-5.8.

COMPOSITION

Tensilon® (edrophonium chloride) parenteral injection 10 mg/mL contains:

- Edrophonium chloride
- Citric Acid, monohydrate
- Phenol
- Sodium Citrate
- Sodium Sulfite, Anhydrous

AVAILABILITY

Tensilon® (edrophonium chloride) 10 mg/mL is available in multidose vials of 10 mL in packs of 10 vials.

PHARMACOLOGY

Edrophonium chloride is poorly absorbed from the conjunctiva, skin, and lungs, since its permanent charge renders it relatively insoluble in lipids. Similarly, much larger doses are required for oral administration than for parenteral injection, hence it is not used orally. The metabolic pathway for edrophonium has not been elucidated, but it is known that the

drug is not subject to hydrolysis by cholinesterases. The mean half-life of elimination is 110 minutes and renal excretion accounts for approximately 70 per cent of the elimination of the drug.

In animal studies (mice), the neuromuscular transmission anticurare dose was found to be 0.2 mg/kg, the denervated muscle effective dose was 10 μg, and the intestinal motility effective concentration was 2×10^{-5} g/cc. A dose of 0.1 mg/kg administered intravenously produced a very rapid stimulation of the intact intestine of the cat, followed quickly by relaxation. Edrophonium potentiated the depressor effects of acetylcholine in the dog for about fifteen minutes, but the depressor response to vagus stimulation was not potentiated. The neuromuscular transmission activity of edrophonium, as antagonist to tubocurarine paralysis of the sciatic nerve tibial muscle preparation in cats, showed rapid onset and a short duration of action (within 10 minutes). Potentiation of the twitch tension was also a rapid action of short duration. The safety margin of edrophonium was eight-fold, as measured by the spread between the potentiating dose and the curarizing dose. This effect is due to a direct depolarizing action at the neuromuscular junction and the ability to potentiate acetylcholine directly.

TOXICITY

The acute toxicity of edrophonium chloride in animal species is summarized in the following table:

Acute Toxicity LD_{50} (mg/kg)

Animal Species	**Route**			
	i.p.	**i.v.**	**s.c.**	**oral**
Mice	37±2.6	9.0±1.0	130±4.0	600±126
Rabbits		28.5±7.0		
Dogs		15.0±1.0		

Chronic Toxicity

Edrophonium chloride was administered i.v. at a dose level of 0.5 mg/kg to 3 rabbits and 1.0 mg/kg to 4 rabbits, 5 days a week for 13 weeks. Blood counts were taken before beginning treatment, after 6 weeks and again after 13 weeks of treatment. The data showed no abnormal changes in red and white cell counts, hemoglobin levels, differential counts or in clotting time. The compound was well-tolerated by the rabbit. No evidence of toxic effects on growth was apparent. At autopsy no gross pathological changes were found.

Edrophonium was administered i.v. to dogs 5 days per week for 13 weeks. The treatment schedules were as follows: 0.05 mg/kg (3 dogs); 0.25 mg/kg (3 dogs); 0.5 mg/kg (3 dogs); and edrophonium 0.5 mg/kg plus atropine 0.25 mg/kg (3 dogs). Six dogs were kept as controls. The variations in weight and in hematology were similar in the treated and control dogs. Two dogs treated with 0.5 mg/kg of edrophonium and one control dog died. The dogs treated with 0.05 mg/kg and 0.25 mg/kg showed no ill effects. The dogs treated with 0.5 mg/kg of edrophonium plus 0.25 mg/kg of atropine showed no ill effects.