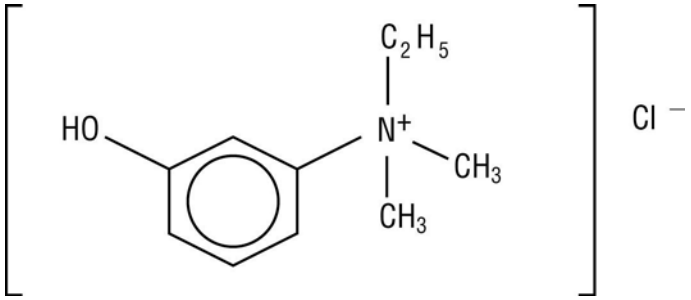
ENLON-PLUS (edrophonium chloride, USP and atropine sulfate, USP) Injection

Rx only

DESCRIPTION

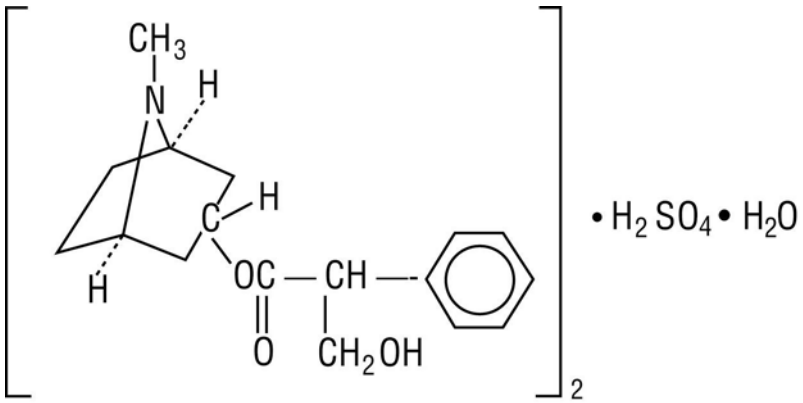
ENLON-PLUS (edrophonium chloride, USP and atropine sulfate, USP) Injection, for intravenous use, is a sterile, nonpyrogenic, nondepolarizing neuromuscular relaxant antagonist. ENLON-PLUS is a combination drug containing a rapid acting acetylcholinesterase inhibitor, edrophonium chloride, and an anticholinergic, atropine sulfate. Chemically, edrophonium chloride is ethyl (m-hydroxyphenyl) dimethylammonium chloride; its structural formula is:



Molecular Formula: $C_{10}H_{16}ClNO$

Molecular Weight: 201.70

Chemically, atropine sulfate is: endo-(±)-alpha-(hydroxymethyl)-8-methyl-8-azabicyclo [3.2.1]oct-3-yl benzeneacetate sulfate (2:1) monohydrate. Its structural formula is:



Molecular Formula: $(C_{17}H_{23}NO_3)_2 \cdot H_2SO_4 \cdot H_2O$

Molecular Weight: 694.84

ENLON-PLUS contains in each mL of sterile solution:

5 mL Ampuls: 10 mg edrophonium chloride and 0.14 mg atropine sulfate compounded with 2.0 mg sodium sulfite as a preservative and buffered with sodium citrate and citric acid. The pH range is 4.0-5.0.

15 mL Multidose Vials: 10 mg edrophonium chloride and 0.14 mg atropine sulfate compounded with 2.0 mg sodium sulfite and 4.5 mg phenol as a preservative and buffered with sodium citrate and citric acid. The pH range is 4.0-5.0.

CLINICAL PHARMACOLOGY

Pharmacodynamics

ENLON-PLUS (edrophonium chloride, USP and atropine sulfate, USP) Injection is a combination of an anticholinesterase agent, which antagonizes the action of nondepolarizing neuromuscular blocking drugs, and a parasympatholytic (anticholinergic) drug, which prevents the muscarinic effects caused by inhibition of acetylcholine breakdown by the anticholinesterase. Edrophonium chloride antagonizes the effect of nondepolarizing neuromuscular blocking agents primarily by inhibiting or inactivating acetylcholinesterase. By inactivating the acetylcholinesterase enzyme, acetylcholine is not hydrolyzed as rapidly by acetylcholinesterase and is thereby allowed to accumulate. The greater quantity of acetylcholine reaching the sites of nicotinic cholinergic postjunctional receptors improves transmission of impulses across the myoneural junction. The concomitant, unavoidable accumulation of acetylcholine at the sites of muscarinic cholinergic transmission occurring at the parasympathetic, postganglionic receptors of the autonomic nervous system, may cause **bradycardia, bronchoconstriction, increased secretions**, and other parasympathomimetic side effects. The magnitude of these muscarinic side effects can be expected to vary from patient to patient depending upon the amount of vagal nerve activity present. Atropine sulfate counteracts these side effects.

Intravenous edrophonium chloride in doses of 0.5 to 1.0 mg/kg promptly antagonizes the effects of nondepolarizing muscle relaxants reaching the maximum antagonism within 1.2 minutes. A plateau of maximal antagonism is sustained for 70 minutes[1]. Intravenous atropine sulfate has an immediate effect on heart rate which reaches a peak in 2 to 16 minutes and lasts 170 minutes after an average 0.02 mg/kg dose.

Pharmacokinetics

Edrophonium Chloride

Edrophonium chloride given intravenously shows first order elimination in a two compartment open pharmacokinetic model[3]. Onset of reversal of muscle relaxant induced depression in twitch tension occurs within three minutes. Edrophonium is primarily renally excreted with 67% of the dose appearing in the urine[4]. Hepatic metabolism and biliary excretion have also been demonstrated in animals[4,8]. While infants and children have been shown to have a reduced plasma half-life and an increased clearance of edrophonium, doses in children are not significantly different from adults on a mg/kg basis although they are more variable in effect. Conversely, elderly subjects (>75 years old) have a prolonged plasma half-life and a reduced clearance. Studies have shown that in spite of these changes the onset and duration of action is unchanged in these patients.

Table of Pharmacokinetic Values for Edrophonium Chloride

Population	T1/2ß hr±S.D.	VD L/kg±S.D.	Cl mL/kg/min±S.D.	N	Ref.
Adults	1.8±0.6	1.1±0.2	9.6±2.7	10	3
Anephric Patients*†	3.4±1.0	0.68±0.13	2.7±1.4	6	4
Infants (3 wks-11 mos)	1.2±0.5	1.2±0.2	17.8±1.2	4	5
Children (1-6 yr)	1.6±0.5	1.2±0.7	14.2±7.3	4	5
Adults	‡0.9±0.3	1.1±0.6	13.3±5	5	6
Elderly* (over 75 yr)	‡1.4±0.3	0.6±0.1	5.1±1	5	6

T1/2ß = Elimination half-life
VD = Volume of distribution
Cl = Clearance
* No adjustments of edrophonium dosage are required because elimination of non-depolarizing muscle relaxants is similarly decreased.
† Values for anephric patients were calculated using a non-compartmental model.
‡ From a study using a different, less sensitive HPLC method and fitting C vs T data to a biexponential curve.

Atropine Sulfate

Atropine sulfate given intravenously shows first order elimination in a two compartment open model[7]. Approximately 57% of a dose of atropine appears in the urine as unchanged drug. Tropine is the primary hepatic metabolite of atropine and it accounts for approximately 30% of the dose[2]. Atropine is only 14±9% bound to plasma proteins[7]. Atropine clearance in children under 2 years old and in the elderly is decreased in relation to normal healthy adults.

Table of Pharmacokinetic Values for Atropine Sulfate

Population	T1/2ß hr±S.D.	VD L/kg±S.D.	Cl mL/kg/min±S.D.	N	Ref.
Adults	3.0±0.9	1.6±0.4	6.8±2.9	8	7
Children (0.08-10 yrs)	4.8±3.5	2.2±1.5	6.4±3.9	13	7
Elderly* (65-75 yrs)	10.0±7.3	1.8±1.2	2.9±1.9	10	7

T1/2ß = Elimination half-life
VD = Volume of distribution
Cl = Clearance
* No dose adjustment required because the cardiovascular effect of atropine is diminished in the elderly.

INDICATIONS AND USAGE

ENLON-PLUS (edrophonium chloride, USP and atropine sulfate, USP) Injection is recommended as a reversal agent or antagonist of nondepolarizing neuromuscular blocking agents. It is not effective against depolarizing neuromuscular blocking agents. It is also useful if used adjunctively in the treatment of respiratory depression caused by curare overdosage.

The appropriateness of the specific fixed ratio of edrophonium and atropine contained in ENLON-PLUS has not been evaluated in myasthenia gravis. Therefore, ENLON-PLUS is not recommended for use in the differential diagnosis of this condition.

CONTRAINDICATIONS

ENLON-PLUS (edrophonium chloride, USP and atropine sulfate, USP) Injection is not to be used in patients with known hypersensitivity to either of the components, or in patients with intestinal or urinary obstruction of mechanical type. Atropine sulfate is contraindicated in the presence of acute glaucoma, adhesions (synechiae) between the iris and lens of the eye, and pyloric stenosis.

WARNINGS

ENLON-PLUS (edrophonium chloride, USP and atropine sulfate, USP) Injection should be used with caution in patients with bronchial asthma or cardiac arrhythmias. Cardiac arrest has been reported to occur in digitalized patients as well as in jaundiced subjects receiving cholinesterase inhibitors. In patients with cardiovascular disease, given anesthesia with narcotic and nitrous oxide without a potent inhalational agent, there is increased risk for clinically significant bradycardia. In patients receiving beta-adrenergic blocking agents there is increased risk for excessive bradycardia from unopposed parasympathetic vagal tone. Such patients should receive atropine sulfate alone prior to ENLON-PLUS. Isolated instances of respiratory arrest have also been reported following the administration of edrophonium chloride. Additional atropine sulfate (1 mg) should be available for immediate use to

counteract severe cholinergic reaction which may occur in hypersensitive individuals when ENLON-PLUS is used.

ENLON-PLUS contains sodium sulfite, 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 nonasthmatic people.

There is a potential for tissue irritation by extravascular injection.

PRECAUTIONS

General

As with any antagonist of nondepolarizing muscle relaxants, adequate recovery of voluntary respiration and neuromuscular transmission must be obtained prior to the discontinuation of respiratory assistance. Should a patient develop “anticholinesterase insensitivity” for brief or prolonged periods, the patient should be carefully monitored and the dosage of anticholinesterase drugs reduced or withheld until the patient again becomes sensitive to them. Use with caution in patients with prostatic hypertrophy and in debilitated patients with chronic lung disease.

When used in therapeutic doses, atropine can cause dryness of the mouth. This effect is additive when the product is administered with other drugs that can cause dryness of the mouth.

Since atropine sulfate slows gastric emptying and gastrointestinal motility, it may interfere with the absorption of other medications. The effect of atropine on dryness of the mouth may be increased if it is given with other drugs that have anticholinergic action (tricyclic antidepressants, antipsychotics, some antihistamines, and antiparkinsonism drugs).

Drug Interactions

ENLON-PLUS (edrophonium chloride, USP and atropine sulfate, USP) Injection should not be administered prior to the administration of any nondepolarizing muscle relaxants. It should be administered with caution to patients with symptoms of myasthenic weakness who are also on anticholinesterase drugs. Anticholinesterase overdosage (cholinergic crisis) symptoms may mimic underdosage (myasthenic weakness), so the use of this drug may worsen the condition of these patients (see **OVERDOSAGE** section for treatment).

Narcotic analgesics, except when combined with potent inhaled anesthetics, appear to potentiate the effect of edrophonium on the sinus node and conduction system, increasing both the frequency and duration of bradycardia. In patients with cardiovascular disease, given anesthesia with narcotic and

nitrous oxide without a potent inhalational agent, there is increased risk for clinically significant bradycardia. In patients receiving beta-adrenergic blocking agents there is increased risk for excessive bradycardia from unopposed parasympathetic vagal tone. Such patients should receive atropine sulfate alone prior to ENLON-PLUS.

Compared to muscle relaxants with some vagolytic activity, muscle relaxants with no vagolytic effects, i.e. vecuronium, may be associated with a slightly higher incidence of vagotonic effects such as bradycardia and first-degree heart block when reversed with ENLON-PLUS.

Pregnancy Category C

Animal reproduction studies have not been conducted with ENLON-PLUS. It is also not known whether ENLON-PLUS can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ENLON-PLUS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of ENLON-PLUS on the mother and fetus, on the duration of labor or delivery, in the possibility that a forceps delivery or other intervention or resuscitation of the newborn will be necessary, is not known. The effect of the combination drug on the later growth, development and functional maturation of the child is also unknown.

Nursing Mothers

The safety of ENLON-PLUS during lactation in humans has not been established.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Pediatric patients may have increased vagal tone. The effect of fixed ratios of edrophonium and atropine on heart rate in such patients has not been evaluated.

Geriatric Use

Clinical studies of ENLON-PLUS did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range,

reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Cardiovascular

Arrhythmias Frequency >10%: junctional rhythm, bradycardia, tachycardia; Frequency 3-10%: first and second degree A-V block, P Wave changes, atrial premature contractions; Frequency 1-3%: third degree A-V block, ventricular premature contractions; Frequency less than 1%: 3 second R-R interval.

Of the patients who experienced any arrhythmias, 85% had the onset within two minutes, 74% no longer had any arrhythmias after 10 minutes. Arrhythmias related to increased vagal tone, bradycardia, second and third degree heart block respond to treatment with 0.2-0.4 mg of atropine I.V. (Bigeminy or ventricular ectopy may be treated with lidocaine 50 mg I.V.).

Adverse experiences reported for anticholinesterase agents such as edrophonium chloride, but not observed in the 235 patients studied with ENLON-PLUS (edrophonium chloride, USP and atropine sulfate, USP) Injection:

Cardiovascular

Nonspecific EKG changes, fall in cardiac output leading to hypotension;

Respiratory

Increased tracheobronchial secretions, laryngospasm, bronchiolar constriction and respiratory muscle paralysis;

Neurologic

Convulsions, dysarthria, dysphonia, and dysphagia;

Gastrointestinal

Nausea, vomiting, increased peristalsis, increased gastric and intestinal secretions, diarrhea, abdominal cramps;

Musculoskeletal

Weakness and fasciculations;

Miscellaneous

Increased urinary frequency, diaphoresis, increased lacrimation, pupillary constriction, diplopia, and conjunctival hyperemia.

Untoward reactions to atropine sulfate generally are dose-related. Individual tolerance varies greatly but systemic doses of 0.5 to 10 mg are likely to produce the following effects, which were not observed in the 235 patients treated with ENLON-PLUS:

Neurologic

Speech disturbances and restlessness with asthenia;

Dermatologic

Flushed, dry skin, formation of a scarlatiniform rash;

Miscellaneous

Dryness of the nose and mouth, thirst, blurred vision, photophobia, slight mydriasis. Atropine may produce fever through inhibition of heat loss by evaporation.

OVERDOSAGE

Muscarinic symptoms (nausea, vomiting, diarrhea, sweating, increased bronchial and salivary secretions and bradycardia) may appear with overdosage (cholinergic crisis) of ENLON-PLUS (edrophonium chloride, USP and atropine sulfate, USP) Injection, but may be managed by the use of additional atropine sulfate. Obstruction of the airway by bronchial secretions can arise and may be managed with suction (especially if tracheostomy has been performed).

Should edrophonium chloride overdosage occur:

1. Maintain respiratory exchange.

2. Monitor cardiac function.

Appropriate measures should be taken if convulsions occur or shock is present.

Principal manifestations of overdosage (poisoning) with atropine sulfate are delirium, tachycardia and fever. In the treatment of atropine poisoning, respiratory assistance and symptomatic support are indicated. Death is usually due to paralysis of the medullary centers.

In the clinical studies performed with ENLON-PLUS, there were no reported overdoses and therefore no clinical information is available regarding overdosing with ENLON-PLUS.

DOSAGE AND ADMINISTRATION

Dosages of ENLON-PLUS (edrophonium chloride, USP and atropine sulfate, USP) Injection range from 0.05-0.1 mL/kg given slowly over 45 seconds to 1 minute at a point of at least 5% recovery of twitch response to neuromuscular stimulation (95% block). The dosage delivered is 0.5-1.0 mg/kg of edrophonium chloride and 0.007-0.014 mg/kg of atropine sulfate. A total dosage of 1.0 mg/kg of edrophonium chloride should rarely be exceeded. Response should be monitored carefully and assisted or controlled ventilation secured. Satisfactory reversal permits adequate voluntary respiration and neuromuscular transmission (as tested with a peripheral nerve stimulator). Recurarization has not been reported after satisfactory reversal has been attained.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

HOW SUPPLIED

NDC 10019-180-05	5 mL ampuls, boxes of 10
NDC 10019-195-15	15 mL multidose vials

Storage

ENLON-PLUS (edrophonium chloride, USP and atropine sulfate, USP) Injection should be stored between 15º-26ºC (59º-78ºF).

Baxter

Manufactured for
Baxter Healthcare Corporation
Deerfield, IL 60015 USA
by: Taylor Pharmaceuticals
Decatur, IL 62525

For Product Inquiry 1 800 ANA DRUG (1-800-262-3784)

Regulatory MLT-XXX

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