PYRIDOSTIGMINE

- Symptomatic Treatment of Myasthenia Gravis
- Antidote for Neuromuscular Blocking Agents

Pyridostigmine is an anti-cholinesterase agent that is used for the symptomatic treatment of myasthenia gravis (MG) in dogs and cats and also as an antidote for certain neuromuscular blocking agents. The drug is not labeled for veterinary use.

PHARMACOLOGY

Pyridostigmine works by inhibiting the hydrolysis of acetylcholine (ACh) by competing as a substrate with ACh for the enzyme acetylcholinesterase. This combination is hydrolyzed slower than the ACh–enzyme combination, which in turn allows a buildup of ACh at the synapses. This buildup leads to increased cholinergic activity by allowing the ACh to remain in contact with the receptors for longer periods of time. This effect produces general cholinergic responses, including miosis, increased muscle tone of both skeletal and intestinal muscle, bradycardia, bronchial constriction, and secretion of saliva and sweat.

Pyridostigmine does not cross the blood–brain barrier at moderate doses but can cross it at excessive doses. This can cause central nervous system stimulation, which can later lead to central nervous system depression as well as respiratory depression, paralysis, and death.

INDICATIONS

In humans, pyridostigmine is used for symptomatic treatment of MG by improving muscle strength. It is also used as an antidote for nondepolarizing neuromuscular blockers, known as nerve gases. Although the product is not approved for use in animals, it is used to treat MG in dogs and sometimes in cats. It is thought to be more effective in treating acquired MG than the congenital form in animals.

CAUTIONS

Adverse Effects

The most common adverse reactions are cholinergic side effects, such as nausea, vomiting, diarrhea, increased peristalsis, miosis, excess salivation, stomach cramps, sweating (if possible in the animal species), lacrimation, bradycardia, bronchospasm, hypotension, and skin rash (due to the bromide component). Overdose can cause a cholinergic crisis, which could lead to death. Atropine injection should be available if the patient is hyperreactive.

Contraindications

The use of pyridostigmine is contraindicated in patients with mechanical obstruction of the intestinal or urinary tract or known hypersensitivity to pyridostigmine. If a patient has concurrent renal disease, a lower dosage may be required (although there are no guidelines for dose adjustment). The drug should be used with extreme caution in patients with epilepsy, bronchial asthma, bradycardia, hyperthyroidism, cardiac arrhythmias, or peptic ulcers.

Use in Pregnancy

Pyridostigmine is classified as a pregnancy category C drug, which means that either there are no controlled studies in women or that studies in animals have shown adverse effects on the fetus. The drug should be used in this circumstance only if the benefits outweigh the possible risks to the fetus. Little data exist regarding the use of pyridostigmine during pregnancy. Transient muscle weakness, however, has occurred in 10% to 20% of neonates whose mothers had received anticholinesterase agents, but similar
symptoms have occurred in infants whose mothers were not on treatment. Pyridostigmine may cause uterine irritability and induce preterm labor if used intravenously when the mother is near term.\(^2\)

**Acute Toxicity**

Acute toxicity of pyridostigmine can cause cholinergic crisis, resulting in nausea, vomiting, excess salivation, lacrimation, urination, defecation, increased bronchial secretions, miosis, bradycardia or tachycardia, cardiospasm, bronchospasm, hypotension, muscle cramps, blurred vision, weakness, or paralysis.\(^2\) Very high doses of the drug can cause agitation, confusion, hallucinations, or electrolyte abnormalities. Death may occur due to cardiac arrest or respiratory paralysis. Treatment for acute toxicity would include discontinuation of the pyridostigmine, maintenance of adequate respiration, and IV administration of 1 to 4 mg of atropine. The atropine may be repeated every 5 to 30 minutes as needed.\(^2\)

It can be difficult to determine whether the problem is the result of an exacerbation of MG (i.e., myasthenic crisis) or a cholinergic crisis. An edrophonium test can be used to distinguish between these disorders. This test can be conducted (if the patient has adequate respiration) by administering 1 mg of IV edrophonium and then monitoring the status of the patient. If the patient’s respiration is not impaired, a second dose of edrophonium is given, and it is assumed that the patient is in a myasthenic crisis. If the patient’s respiration weakens or does not improve considerably, this constitutes cholinergic crisis. At this point, the anticholinesterase agent should be withheld until the patient’s condition improves.\(^3\)

**DRUG INTERACTIONS**

Some drugs, such as aminoglycosides, certain antiarrhythmic agents, phenothiazine, methoxyflurane, muscle relaxants, and magnesium, may decrease the safety margin of neuromuscular transmission.\(^1,2,4\) These drugs may worsen preexisting nerve transmission disorders and should be used with extreme caution, weighing the risk versus the benefit in patients with MG. Using these drugs in combination with pyridostigmine may necessitate greater dosages of the pyridostigmine as well.\(^5\) Methylcellulose has been reported to completely inhibit the absorption of pyridostigmine.\(^5\) When corticosteroids are added to existing therapy, they may decrease the effect of the pyridostigmine by initially worsening the disease.\(^4\)

Anticholinesterase agents are often not effective long-term monotherapy for acquired MG because this condition is caused by an autoimmune response; therefore, immunosuppressive drugs are required to treat the underlying condition. One such study\(^6\) examined the use of azathioprine as adjunctive therapy in dogs with MG. The trial consisted of five dogs with acquired MG, four of which were concurrently treated with pyridostigmine. One dog died of a myasthenic crisis; however, four of the five dogs appeared to have a positive response to the combination of medications. The authors concluded that azathioprine could be an important adjunctive treatment in dogs with MG.\(^6\)

MG occurs in cats but not as frequently as in dogs. One study detailed the treatment of a 4-year-old cat with neuromuscular weakness and dysphonia. The cat was started on prednisone, which improved the condition slightly, but the weakness returned when the drug was discontinued. The cat was given a trial of neostigmine and was tentatively diagnosed with MG after showing signs of improvement. Pyridostigmine was given orally to the cat at a dose of 1 mg q12h and then increased to 2.4 mg q12h in combination with prednisone. This combination proved beneficial in the long-term management of the cat and is one example of why pyridostigmine is the treatment of choice in cats as well as dogs.\(^7,8\)

**Client Counseling Information**

- Pyridostigmine is used for the symptomatic treatment of myasthenia gravis in dogs and cats.
- Adverse effects, such as signs of excessive salivation, gastrointestinal disturbances (e.g., nausea, vomiting), weakness, or difficulty breathing, should be reported immediately to the veterinarian.
- The effects of the drug may be incomplete in some patients, and the medication may lose some of its effectiveness over weeks or months. As a result, supplementation with additional medications may be required.
- Spontaneous remission commonly occurs in dogs and requires changes in pharmacologic therapy; therefore, owners must be educated on the expected course of therapy and instructed to monitor their pets closely. The medication can be stopped if the animal is in remission; however, owners should be aware that the signs of the disease could recur at any time, and therapy would need to be reinitiated if that is the case.\(^9\)
- Do not double a dose to make up for missed doses. Too much of the medication can cause serious consequences.

**Dosage and Administration**

Pyridostigmine can be given orally, intramuscularly, or as a very slow intravenous injection.\(^2\) Oral bioavailability is estimated to be only about...
10%, and the oral doses are about 30 times less potent than parenteral doses. The oral route is the preferred route of administration, if tolerated. Because esophageal weakness that results from MG can make swallowing tablets more difficult, liquid formulations are usually easier for these patients to take. Reported dosages range and can be initiated from 0.2 to 2 mg/kg PO bid to tid to 1 to 3 mg/kg q8–12h PO and gradually increased. The dosage in cats should not exceed 0.25 mg/kg/day initially. The dose must be titrated to the individual needs of the animal and can vary day by day. For this reason, it may be difficult to find the optimal dose. Pyridostigmine should be administered before feeding for rapid absorption.

Compounding is not usually necessary due to the fact that the product is available in either tablet or liquid formulation. Also, because methylcellulose completely inactivates the drug, pyridostigmine cannot be compounded in any way with a product containing methylcellulose.

Patients should be routinely monitored for signs of cholinergic toxicity. Patients should also be monitored for efficacy of therapy, such as improvements in muscle strength or fatigability.

**PREPARATIONS**

No veterinary preparations of this drug are available, but there are several human preparations. Mestinon® (ICN Pharmaceuticals, Costa Mesa, CA) is available in 60-mg tablets in quantities of 100 and 500, 180-mg sustained-release tablets in a quantity of 30, 60 mg/5 ml syrup in 480-ml (16 oz) bottles, and a 5-mg/ml injection in 2-ml ampules and 5-ml vials (10 × 2-ml ampules).

**STORAGE AND HANDLING**

Pyridostigmine should be stored at room temperature, and the syrup should be protected from light.

**REFERENCES**

4. Shelton GD: Myasthenia gravis, article on vetmedcenter.com, accessed 12/19/01.