Pralidoxime chloride is an antidote used in treating acute organophosphate (OP) insecticide intoxication in dogs and cats. OP insecticides bind irreversibly to cholinesterase enzymes, causing phosphorylation of these enzymes and inhibiting their activity. The inhibited cholinesterases are unable to hydrolyze acetylcholine. Clinical signs result from excess accumulation of acetylcholine at smooth muscle myoneural junctions, within the exocrine and endocrine secretory systems (muscarinic receptors), at neuromuscular junctions of skeletal muscle and autonomic ganglia (nicotinic receptors), and within the central nervous system. OP intoxication is an emergency with a risk of death due to respiratory failure.

PHARMACOLOGY AND PHARMACOKINETICS

Pralidoxime is well absorbed after IM administration. In the blood, pralidoxime is not bound to plasma protein. Because of its positive charge (quaternary ammonium structure), pralidoxime does not cross the blood–brain barrier easily. In animal models, the minimum therapeutic concentration in plasma is 4 µg/ml. To maintain this concentration, 500 mg/hr of pralidoxime should be infused in an adult human. The high values (1.7 to 13.8 L/kg) for volume of distribution reflect good distribution of pralidoxime in tissues. The drug is rapidly excreted essentially unchanged and as metabolites in the urine. The elimination half-life of pralidoxime is 3.6 ± 0.8 hours. Because pralidoxime is relatively short acting, repeated doses or constant-rate infusion may be needed.

The principal action of pralidoxime is to reactivate cholinesterases outside the central nervous system that have been inactivated by phosphorylation. Pralidoxime contains an oxime group that has an extremely high affinity for the phosphorus atom in OP insecticides. Pralidoxime binds to OPs and strips them from cholinesterases. The oxime–OP complex is water soluble and rapidly excreted by the kidneys. Pralidoxime is most effective in regenerating the cholinesterases associated with neuromuscular junctions. Pralidoxime can also inactivate unbonded OP molecules by direct chemical reaction.

INDICATIONS

Pralidoxime is an effective antidote for acute OP insecticide toxicosis. It should be administered to animals exhibiting nicotinic signs (tachycardia, fasciculations, tremors, muscle weakness, paralytic signs, respiratory paralysis). Pralidoxime is effective in relieving paralysis of respiratory muscles. It is also used as an antagonist to treat an overdose of anticholinesterase drugs (e.g., neostigmine, pyridostigmine, edrophonium, ambenonium), which are used in treating myasthenia gravis in dogs.

CAUTIONS

Carbamate insecticides are also cholinesterase inhibitors. Although OPs and carbamates may cause clinically indistinguishable signs, pralidoxime therapy is contraindicated for carbamate intoxication. In animals, administration of pralidoxime has been related to worsening of signs in carbamate (i.e., aldicarb, carbaryl, carbofuran, methomyl) poisoning. However, in most cases of severe poisoning by an un-
known anticholinesterase agent, addition of pralidoxime to atropine therapy is beneficial.

**Adverse Reactions**

Pralidoxime is well tolerated by most animals. Rapid IV administration may cause sudden cardiac and respiratory arrest. After IM administration, pain may be noted at the site of injection.

**Use in Pregnancy**

Studies have shown that pralidoxime exerts teratogenic effects in animals.

**ACUTE TOXICITY**

The LD₅₀ of pralidoxime by IV administration is 96 mg/kg in rats and 115 mg/kg in mice. High doses bind calcium ions and cause muscle spasms.

**DRUG INTERACTIONS**

Although the following precautions do not apply directly to the use of pralidoxime, they should be considered when treating anticholinesterase poisoning. Theophylline, aminophylline, phenothiazine tranquilizers (acepromazine), and barbiturates should be avoided in animals with OP poisoning. Antibiotics, such as aminoglycosides (e.g., streptomycin, gentamicin), should also be avoided because they may have neuromuscular-blocking effects.

**DOSAGE AND ADMINISTRATION**

The dose for small animals is 50 mg/kg diluted in 10% glucose solution and administered by slow IV. Following severe poisoning, a second dose of pralidoxime may be given after 1 hour if muscle weakness has not been relieved. For small dogs and cats, pralidoxime may be administered either intraperitoneally or IM. Recovery with pralidoxime occurs gradually over 48 hours. The dose should be reduced in the presence of renal failure.

Pralidoxime must be given along with atropine. Before administration of pralidoxime, atropine is administered IV at a dose of 0.1 mg/kg followed by an additional 0.3 mg/kg IM. Mild atropinization (i.e., mydriasis, lack of salivation) should be maintained for at least 48 hours. Atropine acts as a pharmacologic antidote, antagonizing the peripheral (i.e., profuse salivation, vomiting, bronchial hypersecretion, diarrhea, frequent urination) and central (i.e., restlessness, convulsive seizures, coma) muscarinic effects of OPs. It is capable of crossing the blood–brain barrier. Pralidoxime and atropine administered together may act synergistically. Treatment should be initiated as early as possible. Administering anticholinesterase more than 48 hours after exposure is thought to allow “aging” of the OP–cholinesterase complex, rendering inactivation irreversible. If convulsions occur, they may be controlled with diazepam (0.2 to 2 mg/kg slow IV). OPs (e.g., diazinon, dichlorvos, parathion) that have high lipid solubility, which allows fat storage, can produce recurrent signs after therapy has been withdrawn.

Determining cholinesterase activity in erythrocytes (in dogs) and plasma (in cats) may be helpful in confirming the diagnosis of poisoning. Serial analysis of cholinesterase levels in erythrocytes can be used as a guide for continuing pralidoxime treatment.

Pralidoxime normalizes erythrocyte cholinesterase levels but has no effect on plasma cholinesterase levels. Severe OP insecticide poisoning requires aggressive treatment, including continuous cardiac monitoring (i.e., electrocardiography) and respiratory monitoring (i.e., oxygen therapy, ventilation). Supportive care includes the correction of acidosis (sodium bicarbonate) and hyperthermia.

Cats are generally more susceptible than dogs to OP insecticide poisoning. Lethargy and prolonged anorexia are common in cats. Parenteral fluids and nutritional support may be required for weeks in cats.

**PREPARATIONS**

Pralidoxime (Protopam, Fort Dodge Animal Health) is currently approved by the FDA for use in dogs and cats. Each vial contains 1 g of sterile pralidoxime chloride to be reconstituted with 20 ml of sterile water for injection to provide a solution containing 50 mg/ml. The pH of the reconstituted solution is 3.5 to 4.5.

**STORAGE AND HANDLING**

Pralidoxime powder should be stored below 25°C and protected from light. After reconstitution, the solution should be used within a few hours or discarded.
REFERENCES


