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APPENDICES

Pralidoxime Chloride

Chemistry

Pralidoxime chloride, (2-hydroxyiminomethyl-1-mthyl pyridinium chloride, 2-pyridine aldoxime methochloride; 2-PAM) is a quaternary ammonium oxime. The chemical formula is $C_7H_9ClN_2O$. This drug is a white to pale yellow, crystalline powder and is freely soluble in water. The reconstitution of this drug with sterile water for injection has a pH about 3.5 – 4.5 and the pKa is about 7.8-8. The molecular weight is 172.63. The solubility of pralidoxime in alcohol is 1 in 100 and in water is about 1 in 20 (solubility in water at 25°C is equal to 640 mg/ml).

Pharmacology

Pralidoxime chloride is the cholinesterase reactivator. The principle pharmacologic effect of pralidoxime is reactivation of cholinesterase, which has been recently inactivated by phosphorylation as the result of exposure to certain organophosphates. It is employed with atropine in the management of organophosphate poisonings. The organophosphate intoxication is resulted in the accumulation of acetylcholine at muscarinic, nicotinic and CNS synapses. The mechanism of action of the organophosphorus compound starts at the binding to cholinesterase, the enzyme is inactivated and can undergo three process:Endogenous hydrolysis of the phosphorylated enzyme; reactivation by a strong nucleophile, such as 2-PAM; and biochemical changes that make the phosphorylated molecule inactive ("aged")

These agents are powerful inhibitors of carboxylic esterase enzymes, including acetylcholinesterase and buturylcholinesterase. The organophosphate binds irreversibly to the esterase enzyme and then inactivated by phosphorylation. Pralidoxime removes the phosphoryl group from the active site of the inhibited enzyme by nucleophillic attack, regenerating active cholinesterase and forming an oxime complex Pralidoxime also detoxifies certain organophosphates by direct chemical reaction and probably also reacts directly with cholinesterase to protect it from inhibition. Pralidoxime must be administered before aging is completed, phosphorylated cholinesterase cannot be reactivated, and newly synthesized cholinesterase must replace the inhibited enzyme. Pralidoxime is not equally antagonistic to all anticholinesterases, partly because the time period required for aging of the inhibited enzyme

varies and depends on the specific organophosphate bound to the cholinesterase. Pralidoxime also reactivates cholinesterase which has been inactivated by carbamylation. However, carbamylated cholinesterase has a much faster rate of spontaneous reactivation than does phosphorylated cholinesterase. Pralidoxime also reactivates cholinesterase which has been inactivated by carbamylation. However, carbamylated cholinesterase which has a much faster rate of spontaneous reactivation than, does phosphorylated cholinesterase. Cholinesterase reactivation produced by pralidoxime occurs principally at the neuromuscular junction and results in reversal of anti-cholinesterase-induced paralysis of respiratory and other skeletal muscles. The drug also reactivates cholinesterase at autonomic effector sites and, to a lesser degree, within the CNS. Pralidoxime is effective against nicotinic manifestations of anticholinesterase poisoning (e.g., muscular twitching, fasciculation, cramps, weakness, pallor, tachycardia elevated blood pressure). The drug does not substantially influence muscarinic effects (e.g., bronchoconstriction, dyspnea, cough, increased bronchial secretion, nausea,vomiting, abdominal cramps, diarrhea, increased sweating, salivation, lacrimation, bradycardia, fall in blood pressure, miosis, blurred vision, urinaryfrequency, and incontinence). Therefore, pralidoxime is used in conjunction with atropine, which ameliorates muscarinic symptoms and directly blocks the effects of accumulation of excess acetylcholine at various sites including the respiratory center. Other reported pharmacologi effects of pralidoxime include depolarization at the neuromuscular junction, anticholinergic action, mild inhibition of cholinesterase, sympathomimetic effects, potentiation of thedepressor action of acetylcholine in nonatropinized animals, and potentiation of the pressor action of acetylcholine in atropinized animals. However, the contribution of these effects to the therapeutic action of the drug has not been established.

Mechanism of action

Reactivates cholinesterase that has been inactivated by phosphorylation due to exposure to organophosphate pesticides by displacing the enzyme from its receptor sites; most effective if given within 24 hours of exposure; has greater impact on reversing nicotinic effects versus muscarinic.

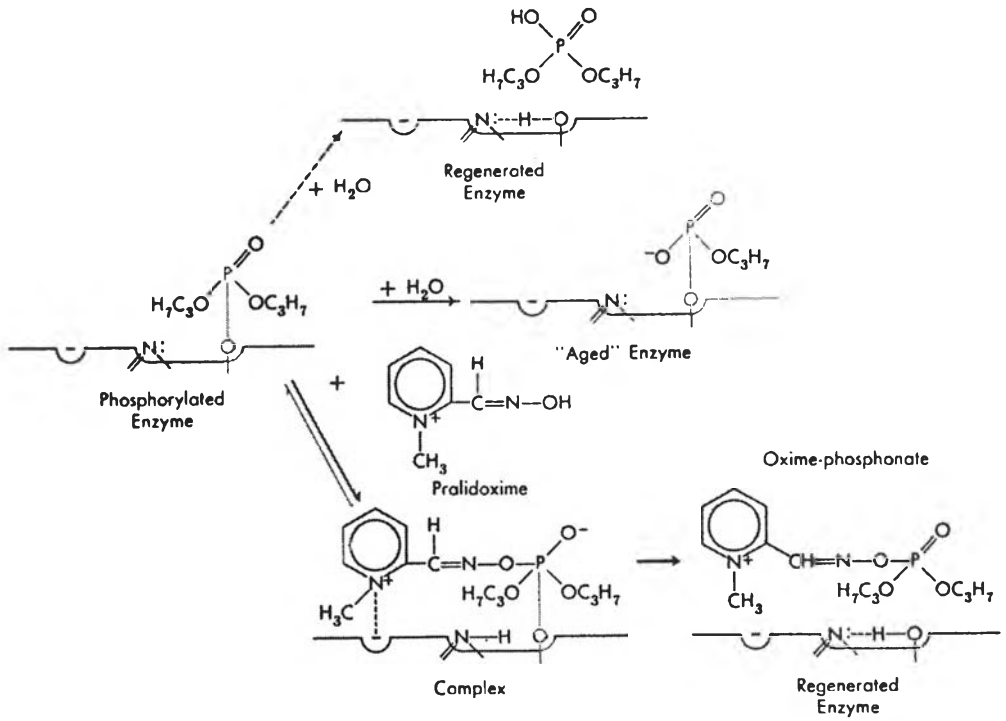

Figure 43 Reactivation of alkylphosphorylated acetylcholinesterase (AChE).

Following alkylphosphorylation of AChE by DFP(at left), spontaneous hydrolytic reactivation occurs at an insignificant rate (upper reaction), as indicated by the dashed arrow. "Aging" is the loss of one of the isopropoxy residue that occurs more rapidly than spontaneous hydrolysis; the product is very resistant to regeneration by pralidoxime. Pralidoxime (in lower reaction) combines with the anionic site by electrostatic attraction of its quarternary N atom, which orients the nucleophilic oxime group to react with the electrophilic P atom; the oxime-phosphonate is split off, leaving the regenerated enzyme.

Pharmacokinetics

Absorption

Absorption of pralidoxime chloride is variable and incomplete following oral administration. Based on results of animal studies, some authorities consider the minimum therapeutic plasma concentration of pralidoxime to be 4 ug/ml. Plasma concentrations are reached 2-3 hours after oral administration, 5-10 minutes after iv administration, and 10-20 minutes after im administration of pralidoxime chloride.

Distribution

Pralidoxime is distributed throughout the extracellular water. Because of its quaternary ammonium structure, the drug is not generally believed to enter the CNS, but recent animal studies and human clinical response observed by some investigators have raised some controversy on this point. Pralidoxime does not readily penetrate the cornea following systemic or topical administration. Pralidoxime is not appreciably bound to plasma proteins and crosses blood-brain barrier very slowly.

Elimination

The drug is believed to be metabolized in the liver. The half-life of pralidoxime in patients with normal renal function varies and has been reported to range from 0.8 – 2.7 hours. Pralidoxime is rapidly excreted in urine as unchanged drug as a metabolite. Approximately 80 – 90 % of an IV or IM dose of pralidoxime chloride is excreted unchange within 12 hours after administration.

Uses

Pralidoxime chloride is used concomitantly with atropine and supportive measures to reverse muscle paralysis associated with toxic exposure to organophosphate anticholinesterase pesticides and chemicals. Pralidoxime appears to be most effective when given within 24 hours after exposure and is usually not of value after 36-48 hours have elapsed. Pralidoxime and atropine were used together for more effective than either drug alone in the treatment of toxic exposure to organophosphate anticholinesterase compounds. The use of pralidoxime be considered in any life-threatening situation resulting from toxic exposure. Pralidoxime has been used for the management of overdosage of the drugs that carbamylate cholinesterase, such as ambenonium, neostigmine, and pyridostigmine, particularly in the treatment of cholinergic crisis in patients with myasthenia gravis. This drug may be useful in the treatment of tetanus, but further controlled studies are needed to determine if the drug, alone or in combination with tetanus antitoxin, is better than usual treatment regimen.

Dosage and Administration

Reconstitution and Administration

Pralidoxime chloride is usually administered IV, preferably as an infusion given over 15-30 minutes. It may also be administered by IM or subcutaneous injection. Pralidoxime chloride sterile powder for injection is reconstituted by adding 20 ml of sterile water for injection to the vial as containing 1 g of the drug to provide a solution containing approximately 50 mg/ml. Sterile water for injection containing preservatives should not be used to reconstitute pralidoxime chloride sterile powder for injection. Pralidoxime chloride solution should be used within a few hours. For IV infusion, the calculated dose of the reconstituted solution is furthered diluted to a volume of 100 ml with 0.9% sodium chloride injection.

Dosage

For the treatment of toxic exposure to organophosphate cholinesterase inhibitors, Pralidoxime therapy should be initiated at the same time as atropine. The usual initial parenteral dose of pralidoxime chloride is 1-2 g for adults, or 20-40 mg/kg for children. Dosage of pralidoxime chloride should be reduced in patients with renal insufficiency. The dose of pralidoxime chloride may be repeated in about 1 hour if muscle weakness has not been relieved. Some clinicians recommend continuous IV infusion of 500 mg of the drug per hour.

In some cases, especially after ingestion of the poison, the manufacturer recommends electrocardiographic monitoring because the anticholinesterase may cause heart block. Continued absorption of the anticholinesterase from pralidoxime may be needed every 3-8 hours. As in all cases of organophosphate poisoning, the patient should be observed closely for at least 24 hours.

Usual dosage

Poisoning : I.M., I.V. (use in conjunction with atropine):

Children: 25-50 mg/kg/dose infuse over 5-30 minutes; repeat in 1-2 hours if muscle weakness has not been relieved, then at 10 to 12 hour intervals if cholinergic signs recur.

Adults: 1-2 g; repeat in 1-2 hours if muscle weakness has not been relieved, then at 10- to 12- hour intervals if cholinergic signs recur.

Continuous dosing regimen: 4 mg/kg over 15 minutes followed by 3.2 mg/kg/hour for 3.75 hours; alternatively, the infusion rate may be as high as 500 mg/hour.

Mild organophosphate poisoning: Oral: initial: 1-3 g, repeat as needed in 5 hours.

Indications

1. Treatment of acute poisoning with organophosphate inhibitors of acetylcholinesterase

Exposure may result from accidents involving those involved in their manufacture or application; it may follow accidental ingestion by children or deliberate overdose in adults. These chemicals have also been developed as agents of warfare (nerve gas).

The patient presents with the combined muscarinic and nicotinic signs of acetylcholine accumulation caused by the antagonism of acetylcholinesterase activity. The muscarinic effects are nausea, vomiting, diarrhea, abdominal cramps, increased sweating, lacrimation, increased tracheobronchial secretion and salivation, meiosis and bradycardia. Nicotinic effects are skeletal muscle weakness, fasciculations, paralysis and central effect of confusion, dysphonia, seizure and coma. Mortality results from respiratory failure secondary to pulmonary edema, skeletal muscle paralysis and cardiorespiratory depression. In each case the general principle of treatment must be applied. These include the clearing of secretions and maintenance of an airwayand, when necessary, artificial ventilation of the patient. Steps to avoid the continuing absorption of the poison must be taken as appropriate; removal of contaminated clothing, washing of skin or irrigation of the eyes, gastric aspiration and lavage. Atropine sulfate must be administered to reduce the volume of secretions and maintain the potency of the airways. Doses (given intramuscularly or intravenously) are from 1 to 5 mg depending on the severity of symptoms, and may be repeated frequently (every 3-30 min.), the dose being titrated to stop salivation. It is advised to continue atropine for 24 hours or until symptoms no longer recur on its withdrawal.

Pralidoxime should be administered as soon as possible in severe cases to reverse the nicotinic effects of poisoning, in particular the problem of skeletal muscle paralysis which can lead to respiratory arrest in the fully atropinized patient. The drug combination of pralidoxime and atropine is complementary and superior to either use alone. Pralidoxime may be

given in doses of 1-2 g either by intramuscular injection or by slow intravenous infusion as a 5 % solution in water for injection at rates of 100-300 mg/min. (not exceeding 500 mg/min.), or as an infusion in 100 ml saline over 15-30 min. The suggested dose for children is 20-40 mg/kg body weight.

Second of third doses may be administered at intervals of 1 hour if indicated by the persistence of muscular weakness. When the facility is available it is desirable to monitor the effects of treatment by determinations of cholinesterase levels. These are measured as pseudo-cholinesterase levels in the plasma and, more appropriately, as red blood cell cholinesterase levels.

If pralidoxime is not administered within 24-48 hours of exposure to the poison, its beneficial action tends to disappear as a result of the aging process which, as mentioned above, results in the irreversible binding of the organophosphate to acetylcholinesterase. However, clinical benefit may result from the administration of pralidoxime as late as 2-5 days after the toxic exposure, probably as a result of prolonged absorption of toxin from the gastrointestinal tract. In a reported case of poisoning with a fat-soluble organophosphate, symptoms were reported at up to 30 days after poisoning, both atropine and pralidoxime being continued to that time.

2. Prophylaxis of organophosphate poisoning

It has been suggested that pralidoxime has a role in the prophylaxis of organophosphate poisoning. While it can be effective in maintaining acetylcholinesterase activity, as has been shown, this role is indicated only under exceptional circumstances. It is usually possible, and certainly preferable, to take adequate steps to avoid contamination in those at risk of exposure.

Long-term sequelae consisting of neuromuscular weakness occasionally follow poisoning with organophosphates. It has been suggested that the chance of this occurring may be reduced by the early use of pralidoxime but there is no significant supportive evidence for this actually occurring in humans.

Adverse reactions

Potentially life-threatening effects

Adverse effect are usually regarded as being mild and have been difficult to ascribe to pralidoxime as distinct from the toxicity of the poison being dealt with and from the adverse effects of the concurrently administered atropine. No potentially life-threatening effects of pralidoxime have been identified.

Manic behavior and excitement, occurring on recovery of consciousness, have been reported in several cases.

Symptomatic adverse effects

When given parenterally to normal volunteers, symptoms of heaviness of the eyes, blurred vision, and difficulty in accommodation have been noted. Stinging at the injection site occurred after intramuscular injection and looseness of the stools after oral administration. The following suspected adverse reaction has been associated with the use of pralidoxime in the treatment of organophosphate poisoning: dizziness, blurred vision, diplopia and impair accommodation, headache, drowsiness, nausea, tachycardia, hyperventilation and muscular weakness.

Drug interaction

The mechanism of action involves drug interaction with the organophosphate, as has been described. Unwanted interactions are generally not severe and are uncommon

Potentially hazardous interactions

Interaction may occur with the following drugs which should be avoided when pralidoxime is given, morphine, theophylline, aminophylline, succhinylcholine, reserpine and phenothaiazine-like tranquilizers.

Other significant interactions

Atropine: When given together with atropine, pralidoxime may be expected to result in the signs of atropinization occurring earlier than would be found with atropine alone.

Potentially useful interactions

Barbiturates: These drugs may be used to control convulsions in organophosphate toxicity. Their action is potentiate by pralidoxime.

VITA

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