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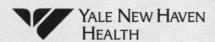
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When atropine and pralidoxime are used together, the signs of atropinization (flushing, mydriasis, tachycardia, dryness of the mouth and nose) may occur earlier than might be expected when atropine is used alone.

Protopam Chloride (pralidoxime chloride)

*For complete information on indications, please refer to Full Prescribing Information. Please see brief summary of Prescribing Information on the adjacent page.

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PROTOPAM Chloride

(pralidoxime chloride) for Injection

Chemical name: 2-formyl-1-methylpyridinium chloride oxime. Available in the United States as PROTOPAM Chloride, pralidoxime chloride is frequently retered to as 2-PAM Chloride.

Structural formula:

C,H,CIN,O M.W. 172.61
Pralidoxime chloride occurs as an odorless, white, nonhygroscopic, crystalline powder which is soluble in water. Stable in air, it melts between 215° and 225° C, with decomposition.

and 22° C. will decomposition. The specific activity of the drug resides in the 2-formyl-1-methylpyridinium ion and is independent of the particular salt employed. The chloride is pre-ferred because of physiologic compatibility, excellent water solubility at all temperatures, and high potency per gram, due to its low molecular weight. Prailizosime chloride is a cholinesterase reactivator.

Pratiopositie criticole is a chiomesterase reactive or infusion is prepared by cry-odesiccation. Each vial contains 1g of sterile pralidoxime chloride, and NaOH to adjust pH, to be reconstituted with 20 mL of Sterile Water for Injection. USP. The pH of the reconstituted solution is 3.5 to 4.5. Intramuscular or sub-cutaneous injection may be used when intravenous injection is not feasible.

CLINICAL PHARMACOLOGY

CLINICAL PHARMACO.OGY
The principal action of pralidoxime is to reactivate cholinesterase (mainly outside of the central nervous system) which has been inactivated by phosphorylation due to an organophosphate pesticide or related compound. The destruction of accumulated acetylcholine can then proceed, and neuromuscular junctions will again function normally. Pralidoxime also slows the process of 'aging' of phosphorylated cholinesterase to a nonreactivatable torm, and detoxifies certain organophosphates by direct chemical reaction. The drug has its most critical effect in relieving paralysis of the muscles of respiration. Because pralidoxime is less effective in relieving depression of the respiratory center, atropine is always required concomitantly to block the effect of accumulated acetylcholine at this site. Pralidoxime relieves muscarinic signs and symptoms, salivation, bronchospasm, etc., but this action is relatively unimportant since atropine is adequate for this purpose.

is relatively unimportant since atropine is adequate for this purpose. Prallidoxime is distributed throughout the extracellular water; it is not bound to plasma protein. The drug is rapidly excreted in the urine partly unchanged, and partly as a metabolite produced by the liver. Consequently, prallidoxime is relatively short acting, and repeated doses may be needed, especially where there is any evidence of continuing absorption of the poison.

The minimum therapeutic concentration of praifodyme in plasma is 4 μ_0/mL ; this level is reached in about 16 minutes after a single injection of 600 mg PROTOPAM Chloride. The apparent half-life of PROTOPAM Chloride is 74 to 77 minutes.

is 74 to 77 minutes.

It has been reported that the supplemental use of oxime cholinesterase reactivators (such as pralidoxime) reduces the incidence and severity of developmental defects in chick embryos exposed to such known teratogens as parathion, bidrin, carbachol, and neostigmine. This protective effect of the oximes was shown to be dose related.

INDICATIONS AND USAGE

PROTOPAM is indicated as an antidote: (1) in the treatment of poisoning due to those pesticides and chemicals of the organophosphate class which have anticholinesterase activity and (2) in the control of overdosage by anticholinesterase drugs used in the treatment of myasthenia gravis. The principal indications for the use of pralidoxime are muscle weakness and respiratory depression. In severe poisoning, respiratory depression may be due to muscle weakness.

CONTRAINDICATIONS

There are no known absolute contraindications for the use of PROTOPAM. Relative contraindications include known hypersensitivity to the drug and other situations in which the risk of its use clearly outweighs possible benefit (see PRECAUTIONS).

WARNINGS
PROTOPAM is not effective in the treatment of poisoning due to phosphorus, inorganic phosphates, or organophosphates not having anticholinesterase activity.
PROTOPAM is not indicated as an antidote for intoxication by pesticides of the carbamate class since it may increase the toxicity of carbaryl.

PRECAUTIONS

General Pralidoxime has been very well tolerated in most cases, but it must be remembered that the desperate condition of the organophosphate-poisoned patient will generally mask such minor signs and symptoms as have been noted in normal subjects.

Intravenous administration of PROTOPAM should be carried out slowly and. Intravenous administration of PHO ID-PAM Should be carried out slowly and, preferably, by infusion, since certain side effects, such as tachycardia, laryngospasm, and muscle rigidity, have been attributed in a few cases to a toorapid rate of injection. (See DOSAGE AND ADMINISTRATION.)
PROTOPAM should be used with great caution in treating organophosphate overdosage in cases of myasthenia gravis since it may precipitate a myasthenic crisis.

them crisis.

Because pralidoxime is excreted in the urine, a decrease in renal function will result in increased blood levels of the drug. Thus, the dosage of pralidoxime should be reduced in the presence of renal insufficiency.

Should be reduced in the presence or retain insumicency.

Laboratory Tests

Treatment of organophosphate poisoning should be instituted without waiting for the results of laboratory tests. Red blood cell, plasma cholinesterase, and urinary paranitrophenol measurements (in the case of parathion exposure) may be helpful in confirming the diagnosis and following the course of the illness. A reduction in red blood cell cholinesterase concentration to below 50% of normal has been seen only with organophosphate ester poi-

soning. • Drug Interactions

Drug Interactions
When atropine and pralidoxime are used together, the signs of atropinization (flushing, mydrasis, tachycardia, dryness of the mouth and nose) may occur earlier than might be expected when atropine is used alone. This is especially true if the total dose of atropine has been large and the administration of pralidoxime has been delayed 2**
The following precautions should be kept in mind in the treatment of anti-cholinesterase poisoning, although they do not bear directly on the use of pralidoxime: since barbiturates are potentiated by the anticholinesterases, they should be used cautiously in the treatment of convulsions, morphine, theophylline, aminophylline, succinylcholine, reserpine, and phenothiazine-type tranquilizers should be avoided in patients with organophosphate poisoning.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Since pralidoxime chloride is indicated for short-term emergency use only, no investigations of its potential for carcinogenesis, mutagenesis, or impairment of fertility have been conducted by the manufacturer, or reported in the literature.

Pregnancy use servers operanancy and the proposed in the literature.

Premancy
TERATOGENIC EFFECTS-PREGNANCY CATEGORY C
Animal reproduction studies have not been conducted with pralidoxime. It is also not known whether pralidoxime can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Pralidoxime should be given to a pregnant woman only if clearly needed.

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when pralidoxime is administered to a nursing woman.

R only

Pediatric Use Safety and effectiveness in pediatric patients have not been established.

Clinical studies of PROTOPAM did not include sufficient numbers of subjects Clinical studies of PRUI OPAM 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 or other drug therapy.

ADVERSE REACTIONS
Forty to 60 minutes after intramuscular injection, mild to moderate pain may be experienced at the site of injection.

be experienced at the site of injection. Pratitoxime may cause blurred vision, diplopia and impaired accommodation, dizziness, headache, drowshiness, nausea, tachycardia, increased systolic and diastolic blood pressure, hyperventilation, and muscular weakness when given paretrally to normal volunteers who have not been exposed to anticholinesterase poisons. In patients, it is very difficult to differentiate the toxic effects produced by artopine or the organophosphate compounds from those of the drug. Elevations in SG0T and/or SGPT enzyme levels were observed in 1 of 6 normal volunteers given 1200 mg of pratidoxime chloride intramuscularly, and in 4 of 6 volunteers given 1800 mg intramuscularly. Levels returned to normal in about 2 weeks. Transient elevations in creatine phosphokinase were observed in all inormal volunteers given the drug. A single intramuscular injection of 330 mg in 1 mL in rabbits caused myonecrosis, inflammation, and hemorrhage.

When atropine and pralifoxime are used together, the signs of atropinization may occur earlier than might be expected when atropine is used alone. This

when alrophie and prailloxims are used togetiers, in esigns to a drophination may occur earlier tham might be expected when atropine is used alone. This is especially true if the total dose of atropine has been large and the administration of praildoxime has been delayed. "Excitement and manic behavior immediately following recovery of consciousness have been reported in several cases. However, similar behavior has occurred in cases of organophosphate poisoning that were not treated with praildoxime." "In the control of the c

DRUG ABUSE AND DEPENDENCEPralidoxime chloride is not subject to abuse and possesses no known potential for dependence.

OVERNOSAGE

Manifestations of Overdosage

Observed in normal subjects only: dizziness, blurred vision, diplopia, headache, impaired accommodation, nausea, slight tachycardia. In therapy it has been difficult to differentiate side effects due to the drug from those due to the effects of the poison.

Treatment of Overdosage
Artificial respiration and other supportive therapy should be administered as needed.
Acute Toxicity
IV – man TDLo: 14 mg/kg (toxic effects: CNS)

| V - man TDLo: 14 mg/kg (toxic e | V - rat LD_{sc}: 96 mg/kg | IM - rat LD_{sc}: 150 mg/kg | RAL - mouse LD_{sc}: 4100 mg/kg | V - mouse LD_{sc}: 155 mg/kg | V - mouse LD_{sc}: 90 mg/kg | IM - mouse LD_{sc}: 180 mg/kg | V - rabbit LD_{sc}: 95 mg/kg | IM - guinea pig LD_{sc}: 168 mg/kg

DOSAGE AND ADMINISTRATION
Organophosphate Poisoning
'Pralidoxime is most effective if administered immediately after poisoning. Praildoxime is most effective if administered immediately after poisoning, Generally, little is accomplished if the drug is given more than 36 hours after termination of exposure. When the poison has been ingested, however, exposure may continue for some time due to slow absorption from the lower bowel, and tatal relapses have been reported after initial improvement. Continued administration for several days may be useful in such patients. Close supervision of the patient is indicated for at least 48 to 72 hours. If dermal exposure has occurred, clothing should be removed and the hair and skin washed thoroughly with sodium bicarbonate or alcohol as soon as pos-sible. Diazepam may be given cautiously if convulsions are not controlled by atronier."

atropine."

Severe poisoning (coma, cyanosis, respiratory depression) requires intensive management. This includes the removal of secretions, airway management, the correction of acidosis, and hypoxemia. Atropine should be given as soon as possible after hypoxemia is improved. Atropine should not be given in the presence of significant hypoxia due to the risk of atropine-induced ventricular fibrillation. In adults, atropine may be given intravenous by in doses of 2 to 4 mg. This should be repeated at 5 to 10-minute intervals until full atropinization (secretions are inhibited) or signs of atropine toxicity appear (delirium, hyperthermia, muscle twitching). Some degree of atropinization should be maintained for at least 48 hours, and until any depressed blood cholinesterase activity is reversed. Morphine, theophylline, aminophylline, and succinylcholine are contraindicated. Tranquilizers of the reserpine or phenothiazine type are to be avoided.

Tranquilizers of the reservine or phenothiazine type are to be avoided.
After the effects of atropine become apparent, PROTOPAM (pralidoxime chloride) may be administered.

PROTOPAM Chloride Injection
Parenteral drup products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
Discard unused solution after a dose has been withdrawn.
In adults, inject an initial dose of 1 to 2 g of PROTOPAM, preferably as an infusion in 100 mL of saline, over a 15- to 30-minute period. If this is not practical or if pulmonary edema is present, the dose should be given slowly by intravenous injection as a 5 percent solution in water over not less than live minutes. After about an hour, a second dose of 1 to 2 g will be indicated if muscle weakness has not been relieved. Additional doses may be given cautiously if muscle weakness persists.

cautiously if muscle weakness persists.

Too-rapid administration may result in temporary worsening of cholinergic manifestations, injection rate should not exceed 200 mg/minute. If intravenous administration is not feasible, intramuscular or subcultaneous injection should be used.

In severe cases, especially after ingestion of the poison, it may be desirable to monitor the effect of therapy electrocardiographically because of the possibility of heart block due to the anticholinesterase. Where the poison has been ingested, it is particularly important to take into account the likelihood of continuing absorption from the lower bowel since this constitutes new exposure. In such cases, additional doses of PROTOPAM (pralidoxima) may be needed every three to eight hours. In effect, the patient should be "titrated with PROTOPAM as long as signs of poisoning recur. As in all cases of organophosphate poisoning, care should be taken to keep the patient under observation for at least 24 hours.

It convulsions interfere with respiration, they may be controlled by the slow intravenous injection of diazepam, up to 20 mg in adults.

Anticholinesterase Overdosage

Intravenous injection of dazepam, up to 20 mg in adults.

Anticholinesterase Overdosage
As an antagonist to such anticholinesterases as neostigmine, pyridostigmine, and ambenonium, which are used in the treatment of myasthenia gravis, PROTOPAM may be given in a dosage of 1 to 2 g intravenously followed by increments of 250 mg every five minutes.

HOW SUPPLIED

HOW SUPPLIED

NDC 69977-141-01-Hospital Package: This contains six 20 mL vials of 1 g
each of sterile PROTOPAM Chloride (pralidoxime chloride) white to off-white
porous cake", without diluent or syringe. Solution may be prepared by
adding 20 mL of Sterile Water for Injection, USP These are single-dose vials
for intravenous injection or for intravenous infusion after further dilution
with physiologic saline. Intramuscular or subcutaneous injection may be
used when intravenous injection is not feasible. *When necessary, sodium hydroxide is added during processing to adjust the pH.

Storage Store at 20°-25°C (68°-77°F), excursions permitted to 15°-30°C (59°-86°F) (see USP Controlled Room Temperature).

ANIMAL PHARMACOLOGY AND TOXICOLOGY

The following table lists chemical and trade or generic names of pesticides, chemicals, and drugs against which PROTOPAM (usually administered in conjunction with atropine) has been found to have antilotal activity on the basis of animal experiments. All compounds listed are organophosphates having anticholinesterase activity. A great many additional substances are in industrial use but have been omitted because of lack of specific information.

AAT-see PARATHION AAT SEE PARATHION
ALKRON®—See PARATHION
ALKRON®—See PARATHION
AMERICAN CYANAMID 3422—see PARATHION
AMITON—diethyl-5-(2-diethylaminoethyl)phosphorothiolate
ANTHIO®—see FORMOTHION
APHAMITE—see PARATHION
APHAMITE—see PARATHION

APHAMITE-see PARATHION
ARMIN-ethyl-4-nitrophenylethylphosphonate
AZINPHOS-METHYL-dimethyl-5-[(4-oxo-1,2,3,-benzotriazin-3(4 H)-ylmethyl] phosphorodithioate
MORPHOTHION-dimethyl-5-2-keto-2-(N-morpholy)ethylphosphorodithioate
NEGUVON*-see TRICHLOROFON
NIRAN*-see PARATHION
NIRAN*-see PARATHION
O.O-DIETHYL-0-p-NITROPHENYL PHOSPHOROTHIOATE-see PARATHION
O.O-DIETHYL-0-p-NITROPHENYL PHOSPHATE-see PARATHION
OR 1191-see PHOSPHAMIDON
OR 1591-see PHOSPHAMIDON
OR 1591-see PUNDY PHOS

OR 1191-see PHOSPHAMIDON
OS 1836-see VINVLPHOS
OXYDEMETONMETHYL-dimethyl-S-2-(ethylsulfinyl) ethyl phosphorothiolate
PARADXON-diethyl (4-nitrophenyl) phosphate
PARATHION ridethyl (4-nitrophenyl) phosphorothionate
PENPHOS-see PARATHION
PHENCAPTON-diethyl-S-(2.5-dichlorophenyl/mercaptomethyl) phosphorodithioate
PHOSPRIN-see MEVINPHOS
PHOS-KIL-see PARATHION

PHOSDRIN*—see MEVINPHOS
PHOS-RIM.=see PARATHION
PHOSPHAMIDON-1-chloro-1-diethy/carbamoy/-1-propen-2-y/-dimethy/phosphate
PHOSPHOLINE: IODIDE*—see echothiophate iodide
PHOSPHORIMONICACID. OO-DIETHYI.-O-p-NITROPHEMYL ESTER—see PARATHION
PLANTHION*—see PARATHION
OUELETOX—see FENTHION
RUELENE**—4-tert-buryl-2-chlorophenylmethyl-N-methylphosphoroamidate
SHRUL OS 1836—see VINVLPHOS
SHELL 2046—see MEVINPHOS
SHELL 2046—see ME

VINYLPHOS-diethyl-2-chloro-vinylphosphate PROTOPAM (pralidoxime chloride) appears to be ineffective, or marginally effective, against poisoning by: CIODRIN® (alpha-methylbenzyl-3-[dimethoxyphosphinyloxy]-ciscrotonate)

DIMEFOX (tetramethylphosphorodiamidic fluoride)

DIMETHOATE (dimethyl-S-IN-methylcarbamov/methyllphosphorodithioate) METHYL DIAZINON (dimethyl-[2-isopropyl-4-methylpyrimidyl]-phospho-

METHYL PHENCAPTON (dimethyl-S-[2.5-dichlorophenylmercaptomethyl]phosphorodithioate)
PHORATE (diethyl-S-ethylmercaptomethylphosphorodithioate)

SCHRADAN (octamethylpyrophosphoramide)

WEPSYN® (5-amino-1-[bis-(dimethylamino) phosphinyl]-3-phenyl-1,2,4-triazole). The use of PROTOPAM should, nevertheless, be considered in any life-threat-ening situation resulting from poisoning by these compounds, since the lim-ited and arbitrary conditions of pharmacologic screening do not always accu-rately reflect the usefulness of PROTOPAM in the clinical situation.

CLINICAL STUDIES

The use of PROTOPAM (pralidoxime) has been reported in the treatment of human cases of poisoning by the following substances:

Methylparathion Diazinon Mevinphos Dichlorvos (DDVP) with chlordane Parathion Disulfoton Parathion and Mevinphos EPN Phosphamidon Isofluronhate Sarin Malathion Metasystox I* and Fenthion Methyldemeton

Of these cases, over 100 were due to parathion, about a dozen each to malathion, diazinon, and mevinphos, and a few to each of the other compounds.

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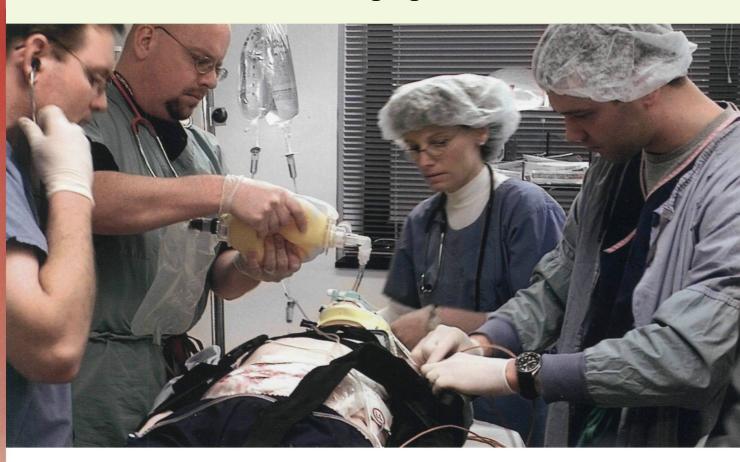




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