



University of Nebraska Medical Center
DigitalCommons@UNMC

[MD Theses](#)

[Special Collections](#)

5-1-1964

Treatment of cholinesterase inhibitor poisonings

James E. Ryan
University of Nebraska Medical Center

This manuscript is historical in nature and may not reflect current medical research and practice. Search [PubMed](#) for current research.

Follow this and additional works at: <https://digitalcommons.unmc.edu/mdtheses>

 Part of the [Medical Education Commons](#)

Recommended Citation

Ryan, James E., "Treatment of cholinesterase inhibitor poisonings" (1964). *MD Theses*. 51.
<https://digitalcommons.unmc.edu/mdtheses/51>

This Thesis is brought to you for free and open access by the Special Collections at DigitalCommons@UNMC. It has been accepted for inclusion in MD Theses by an authorized administrator of DigitalCommons@UNMC. For more information, please contact digitalcommons@unmc.edu.

TREATMENT OF CHOLINESTERASE INHIBITOR POISONINGS

James Edward Ryan

Submitted in Partial Fulfillment for the Degree of
Doctor of Medicine

College of Medicine, University of Nebraska

February 1, 1964

Omaha, Nebraska

TABLE OF CONTENTS

	Page
I. Introduction	1
II. Functions of Acetylcholine	4
III. Functions of Cholinesterase.	5
IV. Measurement of Cholinesterase.	7
V. Cholinesterase Inhibitors.	8
Signs and Symptoms	9
Laboratory Findings.	12
Pathology.	12
Mechanism of Death	12
Treatment.	14
VI. Atropine	17
Dosage of Atropine	19
Contraindications for Use of Atropine.	19
VII. 2-PAM.	20
Routes of Administration	22
Dosage	22
Side Effects	23
VIII. Treatment of Convulsions	23
IX. Contraindicated Drugs.	24
X. Prognosis.	24
XI. Mass Casualties.	24
XII. Summary.	30
XIII. Conclusion	35
XIV. Bibliography	

INTRODUCTION

Could you prevent the death of a person poisoned with a cholinesterase inhibiting agent? If you can answer this yes, then I ask you if you could successfully treat several patients at once with this poisoning? Our society in the near future may place this challenge upon you.

Maybe you answered "No" to both the above questions and ask, "What is a cholinesterase-inhibiting agent?"

In 1939 a German scientist by the name of Schrader was searching for a more effective insecticide and discovered "Nerve Gas", a cholinesterase-inhibiting agent. Since this discovery, many refinements have been made on this agent and now it can be used as the base for excellent insecticides and has potential use as a "war gas" against man.

My purpose in this paper is to present some of its military potential, medical uses, mode of action, present concepts in treatment, and some of the unusual problems that may present themselves to medical personnel in the event that this agent is used against large populations, either military or civilian.

World War I proved the effectiveness of chemical warfare. A difficult lesson learned must not be forgotten quickly. This lesson was given in April 1915 by the Germans when they released chlorine gas against the Allies in France. The effect of this type of warfare was profound and demoralizing, and the casualties were many.

The Germans developed a compound known as Tabun, a nerve gas and cholinesterase-inhibitive agent in World War II. At the close of the war a large German plant for the manufacture of Tabun was captured by the Russians and moved back to Russia. So we know that other countries can manufacture these agents.

Since World War I gas warfare has not been used, either because of International Rules of Warfare or the fear that the opponent may retaliate in kind if used against him. However, nuclear weapons with their vast devastating powers have been used in the past and are in future plans in certain cases. Therefore if these awesome weapons are under consideration for use, one must assume that chemical agents are under consideration for use.

Some of the reasons that cholinesterase-inhibiting agents may be used in future warfare are the following:

1. Not all countries in the world can afford financially to develop nuclear weapons, nor do they have the scientists to develop and perfect them.
2. Cholinesterase-inhibiting agents are easy to produce and there is an abundance of raw material. Any major military power could produce hundreds of tons of this agent per day.
3. Therefore it is possible that a small nation without nuclear weapons could wage war just as effectively in terms of death to the enemy, using cholinesterase-inhibiting agents, as their opponents could with nuclear weapons.

Recently L. J. LeRoux, vice president of the National Council for Scientific and Industrial Research, stated that South African scientists are working on "deadly gases" as a low cost military weapon that can cause massive devastation comparable to that from nuclear weapons. Cholinesterase-inhibiting agents also have these advantages:

1. They could be used in a way that identification of the aggressor would be impossible.
2. These agents are colorless, odorless and cause no irritation to the body that give warning of exposure until the patient has been seriously poisoned. Therefore identification of the agent or the attack may be too late.
3. Saboteurs could spread these agents against large cities or military bases with little chance of being detected.
4. These agents are at least twice as lethal as any previously known chemical agent. In fact one deep breath or a few droplets of this agent on skin may result in death. The time between exposure and death may be seconds.
5. It is conceivable that these agents can be delivered by aircraft or long range missiles.
6. These agents do not destroy property and once the area has been decontaminated, either through human efforts or nature's method of time and weather, the area may be occupied and its industry utilized.

The above introduction gives only a few of the reasons why this type of poisoning may be seen in the mass casualty situation in the future.

If you still aren't convinced that this type of poisoning may be a common one in the future and justifies your knowing how to treat this poisoning, then let us proceed to its use as an insecticide. The cholinesterase-inhibitor agents constitute the base of many of the commercial insecticides today. Certainly the insecticides aren't as lethal in small concentrations as the "war gases", but workers spraying fields can easily become dangerously contaminated with large doses of them. Contamination can take place either by inhalation, through the skin, or by ingestion. The knowledge of the possible routes of poisoning can lead the imagination to supply thousands of possible ways that people handling insecticides could accidentally be poisoned.

Cholinesterase-inhibiting agents are also used medically in the treatment of glaucoma, myasthenia gravis, and abdominal distention. Therefore prescribing or ingesting toxic doses in the treatment of the above medical problems could also lead to the same type poisoning.

FUNCTIONS OF ACETYLCHOLINE

The name of the type of poisoning suggests its action. Cholinesterase-inhibiting agents act as an irreversible inhibitor of the enzyme cholinesterase, allowing accumulation of large amounts of acetyl-

choline. Therefore one may look at the poisoning as an excess of acetylcholine. What is acetylcholine? What is its physiologic function?

Acetylcholine is a methylated quaternary ammonium salt found at nerve terminals in the neuromuscular motor end plate, at all autonomic preganglionic fibers, all parasympathetic postganglionic fibers and the sympathetic postganglionic fibers supplying sweat glands. Nerves that liberate an acetylcholine like transmitter are called cholinergic fibers.

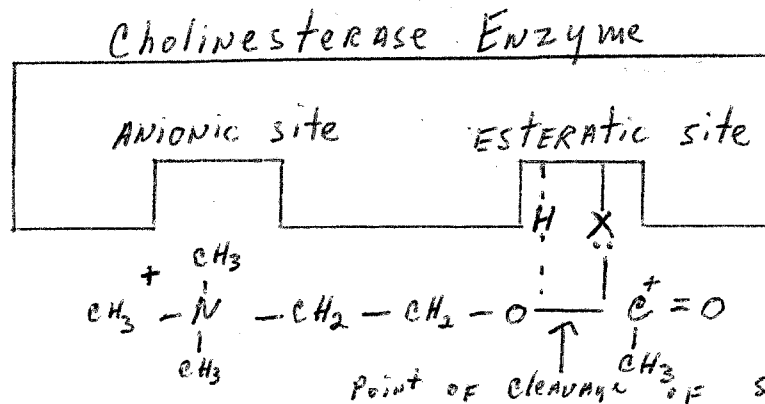
The nerve terminal contains many vesicles which are microscopic packets containing a constant number of acetylcholine molecules, roughly 1,000 to 10,000. An impulse traveling down a nerve fiber depolarizes the nerve terminal and releases the acetylcholine. The acetylcholine then diffuses across the small gap between the nerve ending and the motor end plate. The end plate has an acetylcholine receptor complex which increases the permeability of the end plate membrane to all ions. This leads to end plate depolarization. When the depolarization hits threshold levels an impulse is generated and the muscle contracts or the nerve impulse is transmitted on in the case of the ganglion fibers listed above that respond to acetylcholine. In summary acetylcholine is a chemical mediator necessary for the transmission of the nervous impulse.

FUNCTIONS OF CHOLINESTERASE

Acetylcholine is hydrolyzed almost instantly so that the synapse

is ready to transmit a physiologic impulse. If acetylcholine is allowed to accumulate there is an abnormal increase in function ranging from muscle fasciculations to paralysis. To prevent the repetitive firing of muscles, the acetylcholine is destroyed or actually hydrolyzed in a few milliseconds by an enzyme called acetylcholinesterase to choline and acetate.

This action can be represented by the following diagram from the Biochemistry text of Cantarow and Schepartz⁵:



Experiments show that the enzyme has two important binding sites.

An anionic site and "esteratic" site. The esteratic site is the site of hydrolysis and the one to consider here. When the acetylcholine and the enzyme combine acylation of site X occurs and the acyl group is transferred from the enzyme to a water molecule. The substrate end products are choline and acetate.

There are two general types of cholinesterase. The first is a true and very specific enzyme called acetylcholinesterase. In humans this is found in nervous tissue and in red blood cells, and has great functional importance in neurohumoral transmission in muscles

and glands.

The second type is a non-specific enzyme called pseudocholinesterase and is found in blood plasma. Pseudocholinesterase is regenerated in the liver and therefore is closely related to liver function. It is known that when the level of pseudocholinesterase is lowered by any cause it takes approximately 120 days to regenerate fully; therefore this enzyme reflects the rate of red blood cell replacement. As far as it is known pseudocholinesterase does not have any function in neurohumoral transmission. It does, however, break down procaine and succinylcholine.

MEASUREMENT OF CHOLINESTERASE

Much work has been done trying to find a suitable method of assaying cholinesterase levels. Temperature, pH of medium, salts and ionic strength of media influence the test. Most methods of assaying cholinesterase are based on the determination of the rate of disappearance of acetylcholine or the rate of formation of acetic acid from the hydrolysis of acetylcholine.

The most accurate and sensitive methods are the recording titrimetric and Warburg Manometric procedures in which the amount of acid is measured stoichiometrically.

The method of Michel is an electrometric method in which a change in pH is measured. This method is not as accurate as the aforementioned method, but it is suitable for assaying large numbers of samples.

A field method has been tried, using whole blood and bromothymol blue as a test based on matching the color of glass standards against the color of reaction mixtures. So far this method has been unsatisfactory because of lack of suitable normal standards.

Blood being sent away for analysis should be separated into cells and plasma. The samples should be refrigerated to 0 to 5° centigrade.

CHOLINESTERASE INHIBITORS

The cholinesterase inhibitors are rapidly absorbed with contact to the eyes, skin, respiratory tract, gastrointestinal tract leading to systemic manifestations of the poisoning.

Insecticides have a high acute toxicity but fortunately are not as toxic as the "war gases". So far the agriculture residues on food have not been a problem because the insecticides break down rapidly upon exposure to weathering. Animals whose food is contaminated with cholinesterase inhibiting agents do not store the agent in their bodies. The pharmacologic action of the cholinesterase inhibiting agents is that of inhibiting the enzyme cholinesterase. The excess acetylcholine that accumulates causes over-stimulation of the parasympathetic nervous system. Excessive secretion by the glands they innervate occurs. The action of excessive acetylcholine at the myoneural junction can lead to curare like flaccid paralysis. Therefore the cholinesterase-inhibiting agents

interfere with respiration by directly depressing the respiratory center, by paralyzing muscles of respiration, by causing excessive respiratory secretion and finally bronchoconstriction. Many authors state that the bronchoconstriction observed in animals exposed to these agents does not occur in man.

The level of cholinesterase in both man and animals can be gradually depressed without signs or symptoms; thus the action of these agents depends on both the degree and the rate of depression. A point might be made that it takes approximately 90% cholinesterase inhibition at the respiratory centers to cause respiratory failure. Thus, considering treatment, even a slight degree of cholinesterase reactivation at this critical site may relieve failure of respiratory movements.

SIGNS AND SYMPTOMS

The signs and symptoms of anticholinesterase poisonings may vary in severity, in rapidity of onset, in duration and in range, depending on the route and magnitude of exposure. Systemic poisonings lead to muscarine-like and nicotine-like effects. The nicotine-like effects are usually not seen until muscarine effects have reached moderate severity.

Optic effects

1. Miosis
2. Tearing
3. Conjunctival hyperemia

4. Pressure sensation behind eye
5. Headache
6. Funnel vision
7. Blurred vision

Respiratory effects

1. Increased respiratory tract secretions
2. Rhinorrhea
3. Nasal hyperemia
4. Tightness in chest
5. Wheezing
6. Dyspnea
7. Pulmonary edema
8. Cyanosis
9. Cheyne-Stokes breathing
10. Respiratory arrest

Gastrointestinal Tract

1. Salivation
2. Anorexia
3. Nausea
4. Vomiting
5. Abdominal cramps
6. Diarrhea
7. Involuntary defecation

Skeletal muscles

1. Weakness
2. Local fasciculations
3. Muscle twitching
4. Cramps
5. Paralysis

Skin

1. Increased sweating

Central Nervous System

1. Tension
2. Anxiety
3. Emotional lability
4. Insomnia
5. Excessive dreaming
6. Slurring of words
7. Depression
8. Confusion
9. Ataxia
10. Grand mal seizures
11. Coma
12. Loss of reflexes

Some authors believe that miosis is an early diagnostic sign, others feel that the "pin point" pupils should not be relied upon too much as an early sign. In general the "eye signs", rhinorrhea, increased respiratory secretion, tightness in chest, weakness,

sweating, abnormal cramps will be seen early or in less severe poisonings. Loss of reflexes, convulsions, coma, loss of sphincter control, such as involuntary defecation or urination are usually seen in advanced cases.

LABORATORY FINDINGS

Laboratory findings in anticholinesterase poisonings are decreased serum cholinesterase levels, leukocytosis and albuminuria. Frequently acetonuria, glycosuria and hemoconcentration are seen. In the absence of symptoms there is no electroencephalogram (EEG) changes. EKG may demonstrate various A-V blocks and bradycardia. The most reliable laboratory finding in making a diagnosis is the cholinesterase levels. The cholinesterase levels may be depressed considerably below normal before signs and symptoms appear.

Grob¹⁵ states that he has found evidence of only depressed cholinesterase levels. Grob could not find any alterations in the chemical constituents or formed elements of the blood and no change in the urine or renal or hepatic function.

PATHOLOGY

The gross or microscopic pathologic findings are not significant. Evidence of pulmonary or cerebral congestion or changes secondary to convulsions are often seen.

MECHANISM OF DEATH

The mechanism of death is due to respiratory failure. The respiratory failure is due to paralysis both centrally and peripherally.

The peripheral paralysis is brought about by muscle fatigue and the curare-like blocking of the myoneural junctions of the diaphragm and accessory muscles of respiration. This leads to profound anoxia. The anoxia at first stimulates the chemoreceptors to try to increase respiratory rate and correct the anoxia. Continued anoxia rapidly depresses the respiratory center.

Brown³ described an experiment which proves there is also a central respiratory failure due to cholinesterase inhibiting agents. This test was done with "sarin", one of the war gases. Sarin was injected intravenously and before the respiratory muscles were paralyzed as evidenced by the twitch height of muscles, respirations ceased. This occurred before anoxia or neuromuscular effects were demonstrated. The experimental animals were given a therapeutic injection of atropine and respiratory stimulant. The rapidity of respiratory failure after cholinesterase inhibiting agents were given and the equally rapid recovery after atropine injection seemed to leave little doubt about the central origin of respiratory failure in addition to peripheral failure to paralysis.

The profound anoxia and the increasing accumulation of acetylcholine in the nervous system leads to intermittent and then almost continuous grand mal seizures until flaccid paralysis supervenes.

The anoxia and acetylcholine affect the cardiovascular system. The anoxia at first initiates hypertension but if the anoxia is not improved the blood pressure completely falls leading to circulatory

collapse. A cholinergic effect of acetylcholine is bradycardia.

TREATMENT

Grob¹² gives this method of treating anticholinesterase poisonings. These are not necessarily the preferred order of treatment.

1. Remove from exposure
2. Decontaminate
3. Remove secretions
4. Maintain adequate airway
5. Apply artificial respiration if needed
6. Administer atropine
7. In severe cases administer oximes (2-PAM)
8. If convulsions present, treat with trimethadions (Tridione)

The patient should be removed from exposure. This step is not important with poisonings due to ingestion but it is vitally important when dealing with the "war nerve gases" or insecticides. If the patient is still absorbing poisons from the skin or lungs due to contamination of the environment he will become more toxic while you are treating him.

Medical judgment is as important in treating anticholinesterase poisonings as any other acute medical emergency. Decontamination should begin as soon as possible, however, one should not direct all the attention to decontamination when respiration has ceased. There are some unusual situations that must be considered here. Physicians must remember that these compounds are readily absorbed

through the skin and airways. Therefore attendants should remember to protect themselves from contamination. Non-military poisonings can probably be dealt with merely by wearing rubber gloves to prevent skin contamination. Volatile compounds can contaminate the atmosphere making special individual protection such as gas masks and protective clothing necessary.

Decontamination of gastrointestinal tract should be carried out by prompt induction of emesis. Durham and Hayes article 9 states that experiments have indicated that vomiting induced immediately or even $1\frac{1}{2}$ hours after ingestion is more effective than gastric lavage in removing poison. Induce vomiting and then give some neutral material such as water or milk and induce the vomiting again. Vomiting should never be induced if the patient is unconscious unless an endotracheal tube is inserted beforehand. If the patient is unconscious, or the vomiting profuse, gastric lavage may be done with 5% sodium bicarbonate.

All contaminated clothing must be removed as quickly as possible. Care must be taken to prevent contamination during the disposal of the clothes. The clothing should be buried rather than burned. Vapors released from burning contaminated materials could contaminate the surrounding atmosphere.

The patient should be washed with soap and lots of water. Care should be taken to avoid abrasion of the skin, for this would speed up absorption of the poison. Once the skin appears clear,

bathe with ethyl alcohol. Many insecticides and the oil based cholinesterase inhibitors are more soluble in alcohol than in water. The eyes absorb the anticholinesterase agents remarkably rapid. If they are suspected of being contaminated, irrigate them with physiologic saline or tap water.

The upper respiratory tract should be suctioned to remove secretions. Endotracheal intubation should be done as soon as possible. Intubation helps maintain an adequate airway and it certainly helps aspirating the thick mucus which might prove to be very difficult with a rubber catheter being passed alone down the trachea. A tracheostomy may be necessary but most authors agree that intubation is superior in that it can be done very rapidly, and the patient is not subjected to the hazards of tracheostomy. Most physicians agree that, if an airway must be maintained over twenty-four to forty-eight hours, a tracheostomy should be done; but response to specific therapy of anticholinesterase poisoning is so rapid usually that tracheostomy is not needed.

Artificial respiration must be given if respiration has either failed or is inadequate. A note of caution should be given on mouth-to-mouth respiration on a "nerve gas" casualty. The administrator could become a victim of the same lethal chemical agent. This author has not read any articles reporting poisoning to the administrator of mouth-to-mouth respiration of an insecticide type of cholinesterase-inhibiting agent.

A mechanical respirator with a non-rebreathing valve could be most ideal and one should be procured and maintained at the bedside even if the casualty does not need it immediately. The patient should be watched very closely for at least forty-eight hours for sudden respiratory arrest. Sudden respiratory arrests have been known to occur in the first forty-eight hours even though the patient appears to be responding well clinically.

ATROPINE

The administration of atropine is specific for anticholinesterase poisoning. The intravenous route is the preferred method of administration because the effects are seen within four minutes and are maximal in eight minutes. Atropine should be given as soon as possible.

Wills et al²³ states that atropine must be given within one minute of severe exposure to sarin, a nerve gas, if treatment is to be effective. The reason for this is that death occurs very rapidly, usually within a few minutes after severe exposure to sarin. This author has not read any articles in the review of literature that gives a time limit to the effectiveness of atropine in insecticide poisoning of the anticholinesterase type. One assumes atropine will be beneficial if given at any time during the course anticholinesterase poisonings, assuming the patient lives long enough after administration for the pharmacologic action to occur.

The point being, the atropine must be given within a few min-

utes in severe poisoning in order to save the patients life but can also be very helpful in mild to moderate poisonings if given for the first time several hours after exposure.

The antidote effect of atropine in anticholinesterase poisonings is not due to any action on, or neutralization of the anticholinesterase compound. Atropine merely serves to block certain actions of the excess acetylcholine accumulated. Atropine specifically blocks the muscarinic actions of acetylcholine such as glandular secretion, and slowing of the heart. It is also specific to reverse the effects of anticholinesterases in the central nervous system especially the central respiratory center. Atropine has absolutely no effects on the nicotine-like effect of excess acetylcholine. These effects are increased fatigability, generalized weakness, involuntary muscular twitching, muscle cramps, fasciculations and muscular paralysis.

Atropine will not prevent respiratory failure due to respiratory muscle paralysis nor will it restore strength to respiratory or pharangeal muscles.

The symptoms of atropine if administered to a normal subject are dryness of mouth, pharynx, a slight difficulty in swallowing, dilated pupils, dry flushed skin, blurry near vision, subjective feeling of warmth, slight tachycardia, mild drowsiness, slowness of memory and occasionally hallucinations.

DOSAGE OF ATROPINE

Most authors recommend two to four milligrams intravenous atropine to be given as soon as cyanosis is overcome. Atropine in doses of two milligrams given intravenously should be given at five to ten minute intervals until signs of over atropinization appear (see above symptoms of atropine) or until symptoms are relieved. Poisonings by anticholinesterase compounds increase the tolerance for atropine. A severely poisoned individual may take as many as forty milligrams or more before signs of over atropinization are produced. A mild degree of over atropinization should be maintained for twenty-four hours in a mild poisoning case, and forty-eight hours in a severe case. Over atropinization may be a little incapacitating but presents little challenge to life.

Atropine should not be administered for preventative purpose in persons who anticipate exposure to the "nerve gases" or contamination while working with various insecticides. The reason for this is that this may mask early symptoms, increase respiratory absorption of the anticholinesterase by inhibiting bronchial secretion, and in general allowing the person to expose himself to higher levels of poisoning without warning. Atropine itself may render a person unfit for his occupation.

CONTRAINDICATIONS FOR USE OF ATROPINE

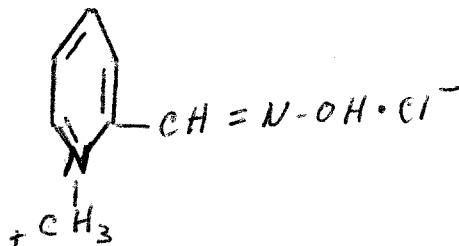
The use of atropine in anticholinesterase poisonings is contraindicated in one very important situation. This situation is the

anoxic patient. Granted it has been pointed out that atropine must be given as soon as possible if death is to be prevented in serious cases. However if the patient is cyanotic or anoxic this condition must be corrected by artificial respiration and oxygen first. It is known that atropine releases the heart from vagal control. The tachycardia that occurs leads to an increased work load on the cardiac muscle. The increased strain on the heart in face of severe anoxia will often lead to immediate ventricular fibrillation and death.

0.5% atropine ophthalmic solution may be locally applied to the eye to relieve the ocular symptoms produced by local absorption of anticholinesterase agents. Often systemic atropine does not relieve the miosis.

2-PAM

There has been much investigation in the past few years into agents that would reactivate cholinesterase. The most success appeared to be with the oximes. The most successful oxime appears to be 2-PAM chloride. This is 2-pyridine aldoxime methochloride. Its chemical structure is:



The specific activity of 2-PAM rests in the 2-formyl-1-methyl-

pridinium ion and is independent of the particular salt used. Chloride, iodide, methylsulfate and methane sulfonate salts have been used and tested. The chloride is preferred because of better water solubility at all temperature, a higher potency per gram and fewer side effects.

2-PAM chloride is capable of reversing the combination between a cholinesterase molecule and the inhibitor causing reactivation of cholinesterase. 2-PAM chloride does not replace the need for atropine in treatment of anticholinesterase poisonings because the oximes and atropines have different sites of action. It is preferable to use these two agents in combination and take advantage of the antidotal effects of both at their different sites of action. It is thought 2-PAM potentiates the action of atropine, and increases the signs of over atropinization. The mechanism of action for this may be due to 2-PAM reactivating the cholinesterase and removes the accumulated actylcholine, leaving the large doses of atropine to give an unopposed drug effect.

The mechanism of action of 2-PAM in regenerating the inhibited cholinesterase is thought to be due to direct combination with the phosphorus inhibited enzyme. 2-PAM aids or causes a reaction in which the phosphorus moiety is split off and hydrolyzed. 2-PAM residue appears to undergo a further reaction to regenerate the active enzyme. The important thing from a practical point is that 2-PAM has a greater affinity for the phosphorus moiety than does

the enzyme.

ROUTES OF ADMINISTRATION

2-PAM can be administered intravenously, intramuscularly, orally subcutaneously and has some penetration to the cornea when applied topically. The preferred route is intravenous administration because it is immediately dispersed throughout the extra cellular water and gives a high plasma level.

DOSAGE

The usual adult dose is 1000 milligrams initially and this can be injected directly in the vein at a rate not to exceed 500 milligrams per minute. The dose may also be mixed in 250 cc of saline and given over a thirty minute period. A second dose of 1000 milligrams of 2-PAM can be given one hour after initial dose if muscular weakness persists but caution should be used and facilities to maintain respiration should be in readiness for 2-PAM in high excessive doses is a weak anticholinesterase agent itself.

The dose for children is 25 to 50 milligrams per kilogram.

2-PAM is promptly and adequately absorbed orally. Marked drug effect is seen in thirty minutes and persists for approximately ten hours. The drug is probably not completely absorbed and some non excretory process are operated by this route so the dosages and dosage intervals are different in oral route.

One to four grams may be given orally on initial dose depending on severity of poisonings. Mild cases usually show full remission

in one hour when one to two grams are given orally. This dose may be repeated after three hours if necessary.

SIDE EFFECTS

The side effects of 2-PAM on normal subjects are dizziness, blurred vision, diplopia, headache, impaired accommodation, nausea, slight transient tachycardia. There are no demonstrable changes on blood pressures, EKG, respiration, urinalysis, liver function tests, bleeding or clotting times. No irritation at site of extravasation on intramuscular injection. In general 2-PAM appears to feature a low toxicity.

The time limit that 2-PAM must be administered after anticholinesterase poisoning, to be maximally effective is not known. It is felt that administration of 2-PAM thirty-six hours after exposure is not too beneficial.

TREATMENT OF CONVULSIONS

Patients with severe anticholinesterase poisonings may develop convulsions. If the convulsion interferes with artificial respiration and oxygen therapy, treat with trimethadione, one gram intravenously every fifteen minutes until controlled. Barbituates or ether may be given. The action of succinylcholine increases the effect of anticholinesterase agents, thus the use of this relaxant is contraindicated.

Care must be taken in administering barbituates, anticholinesterase poisoning sensitizes the medullary centers to depression by

barbituates.

CONTRAINDICATED DRUGS

Morphine, theophylline, aminophylline, are strictly contraindicated in these cases. Smoking should be forbidden as this increases the respiratory and gastrointestinal symptoms.

Tranquilizers should be used with great caution. Some of the phenothiazine derived tranquilizers are suspected to potentiate certain anticholinesterase agents.

PROGNOSIS

If death does not intervene, recovery from anticholinesterase poisonings is usually complete. However the cholinesterase level may remain low until regeneration restores normal level. Patients are very susceptible to even small exposures of anticholinesterase until this level is restored. This point should be seriously considered when further exposure is an occupational hazard.

Miosis and headaches are often the only residual effect and this is a minor one compared to the seriousness of this type of poisoning. They usually respond well to topical application of 0.5% atropine to the eyes.

MASS CASUALTIES

If the cholinesterase-inhibiting agents are ever used as a "war gas" it would present many problems. Many of these problems are similar to those in all wars, some are new.

The problems are to initiate treatment quickly, decontaminate,

have as few sites as possible giving treatment and thus reduce problems of supply, to keep from contaminating all of the medical station, get maximum use out of equipment, and finally to set up a system where the lowest number of medical personnel can maintain the largest possible number of casualties.

Clinically the problem of separating the types of injury, determining the seriousness of injury and routing the patient to properly equipped medical station to care for a given injury is a basic problem of triage.

There could be a high number of casualties in a short period of time. These casualties could be in different states of incapacity. One of the first problems is to make a diagnosis of anticholinesterase poisonings. Good military intelligence forewarning of attack is of great importance. A good rule may be to consider all attacks on the United States to include "nerve warfare" until proven otherwise. Certainly whenever the first proven case of anticholinesterase poisoning is found the information should be sent to all medical facilities in the area. A definite plan of communication should be made because speed is of utmost importance. A disaster plan covering nerve gas attacks should be initiated in such a way that administration and communication are given the highest consideration. Mass panic and confusion could be one of the greatest dangers to nerve gas attack. Well trained medical teams can handle many seriously poisoned patients at once if they

know immediately what type of poisoning has occurred.

People respond amazingly well in stressful conditions that have not been experienced before if they have good leadership and have given consideration to a proposed plan of action. All terrifying situations panic people and reduce judgment. It is easy to understand that a plan is needed to get work properly directed and organized. Leadership must be assumed at all levels. Leadership is most effective when key command personnel understand the situation and know what needs to be done.

Determining the seriousness of anticholinesterase poisoning of a given individual in a mass casualty situation is complicated by lack of time and an over burdened laboratory. Eye signs are reputedly no good. Serum anticholinesterase levels can't be run on hundreds to thousands in time to be effective.

Cyanosis, respiratory arrest, coma, convulsions or flaccid paralysis are definite signs of serious poisoning and demand that vigorous and immediate treatment be given.

All patients should enter only one entrance and quickly be screened. It is very important to quickly designate and limit the contaminated area. A certain number of Doctors, Nurses and other medical personnel will be casualties due to initial attack, placing an added burden on those remaining. The remaining staff must take immediate steps to protect themselves from contamination from the patients. The screening station personnel should be protected with

gas masks, chemically impregnated or rubber impermeable suits and rubber gloves.

Assuming that all patients are nerve gas casualties only, which greatly reduces the screening problems, the following system may be used. The first screen by a doctor taking only seconds per patient could separate the critically poisoned patients using the signs stated above as criteria, from the lesser poisoned ones. The patients showing signs of poisoning but still capable of walking and breathing unassisted at the moment at least, could form a line where several nurses could quickly administer I.V. atropine or 2-PAM if necessary. This procedure hopefully taking only seconds per patient if the nurses are constantly resupplied so they do nothing but administer atropine. The use of signs or of one individual leading a group of ten to twenty people could lead these patients to an area where they could remove all their clothing. The men could be separated from the women if facilities permit. These people could be led to showers where they decontaminate themselves with soap and water, taking extra care to thoroughly wash the hair and fingernails. Again one person could supervise the shower to supply soap, give instructions and keep the patients moving. The patient being decontaminated could be given clothing and moved into another part of the medical aid station that is not contaminated. The group could then use the "buddy system" to observe on another and report any difficulty in breathing. A smaller medical team could then treat

this large group because hopefully they aren't as seriously poisoned and maybe only I.V. atropine is necessary. If they become seriously poisoned they should be transferred to maximum care section immediately where personnel and equipment is available.

Returning to the first screening station let us follow the handling of a seriously poisoned patient. These patients should be separated from the less serious patients and be directed toward intensive care. The next station and very close by, should have a doctor and nurse acting as a team. The doctor can insert an endotracheal tube quickly, suction out the respiratory tract and evaluate the patient further. The nurse would immediately give I.V. atropine and 2-PAM. It must be remembered that atropine cannot be given while cyanosis is present. The patient should then be quickly moved to a permanent high intensive care station freeing the second station to take care of another patient.

The third station is also an intermediate station being set up to administer drugs, O₂, and suction. All personnel should be protected against contamination. The purpose of this station is to decontaminate the patient and still maintain him. This station needs to be staffed by many more personnel so decontamination can be done quickly to a patient who cannot help himself.

The fourth station, the uncontaminated high intensive care area, should be arranged in groups of four. The patients could be arranged in a small square with their heads together. A centrally

located suction machine could then be used to keep the airways open without moving the machine much. Large mass casualty situations may require expanding the number to more than four. One person could keep a number of airways open using this technique. A certain amount of sterile technique would have to be overlooked as a sterile tube could not be placed down each individual as the suction machine is being used. When the time and situation permits antibiotics could be given, if needed, to treat resultant respiratory infection.

The time element as in all poisonings is very important but this problem compounds the seriousness of the disaster if thousands, if not hundreds of thousands are affected at the same time. Exposed people need help immediately and may not get to medical aid stations in time. Existing rescue services is not the answer. They would either be quickly swamped with work and could not get to aid all needing help or the rescue teams themselves might be poisoned.

Equipment and drug requirements may be another source of failure to adequately handle mass casualties. Most 200 bed hospitals probably have less than ten artificial respirators. Endotracheal tubes are probably more abundant but would fall short of hundreds that may be needed all at once.

According to Dr. Charles W. Steele, speaking before the ninth annual U. S. Civil Defense Counsel Conference at Minneapolis in

September, 1960, "if all the atropine available to civilian defense authorities were distributed among physicians, each physician would have about 6 doses or less than the amount needed for one severe case of poisoning."

Robert A. Lehman, the Vice President and Research Director of Campbell Pharmaceuticals, Inc., 121 East 24th Street, New York 10, New York, states the 2-PAM (Protopam Chloride) will be available for general distribution by his company around January 1964. Presently this drug is available on a research basis only.

The drug shortage is evident, however. Stockpiling the drug might not solve the problem as the time necessary to distribute the drug from supply areas might for all practical purposes nullify the usefulness of the drug.

Today the most basic protection against the nerve gases is to have good military intelligence to warn of imminent attack and completely evacuate the area.

Presently 2-PAM chloride is being considered for use as a prophylactic agent to protect against nerve gases. Studies aren't complete on its prophylactic use. The success of 2-PAM as a definite therapeutic agent in poisoned cases leaves hope that it may also be used as a pre-exposure protecting agent.

SUMMARY

The cholinesterase inhibiting agents considered here are organic phosphorus compounds which irreversibly bind the enzyme

cholinesterase. This action blocks the hydrolysis of acetylcholine and acetylcholine is allowed to accumulate. Excessive acetylcholine at the myoneural junction decreases its function and can lead to flaccid paralysis. The accumulated acetylcholine also over stimulates the parasympathetic nervous system causing excessive secretions by the glands they innervate. This type poisoning manifests muscarine-like and nicotine-like effects. The muscarine-like effects include nausea, vomiting, diarrhea, excessive salivation, sweating and dyspnea. The nicotinic-like effects are muscular weakness, fasciculations, cramps and finally paralysis. The mechanism of death is due to respiratory failure. Treatment involves maintaining respiration and directing medical attention towards breaking down the cholinesterase block which is irreversible without drug intervention. Oximes such as 2-PAM (2-pyridine-aldoxime-methochloride) are specific in action of reactivating the enzyme cholinesterase and reacting chemically with the anticholinesterase agent. Atropine therapy is also specific for symptomatic control of excessive glandular secretion caused by the accumulated acetylcholine.

Common sources of anticholinesterase poisoning are from insecticides such as parathion, matathion, chlorthion, phorate and other organic phosphorus compounds. The military war gases, the "nerve gases", such as sarin (isopropylmethylphosphonofluoridate) are very potent anticholinesterase agents. The treatment is the same for

all the above agents.

Treatment of a severe case of anticholinesterase poisoning with coma, cyanosis or respiratory distress present.

1. Maintain Airway

A. Endotracheal intubation.

B. Suction airway.

2. Artificial respiration

A. Use a positive pressure method of artificial respiration because of possible respiratory muscle paralysis and a restricted airway.

B. If a mechanical respirator is not used, then watch patient very closely for sudden respiratory arrest.

C. Cyanosis must be corrected before atropine can be administered otherwise there is great possibility of inducing ventricular fibrillation.

3. Atropine Administration

A. Adults:

1. Give 2 to 4 mg atropine intravenously.

2. Repeat dosage at 5 to 10 minute intervals until signs of atropinization appear.

3. A mild degree of atropinization should be maintained for 48 hours. (Dry, flushed skin, tachycardia.)

B. Children

1. 1 mg per square meter surface area.

4. 2-PAM Chloride therapy (2-Pyridine-Aldoxime-Methochloride).

A. Adults.

1. 1000 mg 2-PAM intravenously at a rate not to exceed 500 mg per minute.
2. The above dose may be repeated in one hour if muscle weakness has not been relieved. Additional doses may be given if muscular weakness persists, however, caution must be used because 2-PAM is a weak anticholinesterase agent itself.
3. 2-PAM can be given orally, intramuscularly, or subcutaneously if intravenous method is not feasible.

B. Children.

1. The dosage of 2-PAM is 25 to 50 mg per kg.

C. 2-PAM may be obtained from Campbell Pharmaceuticals, Inc.,
121 East 24th Street, New York 10, New York.

5. Decontaminate Patient.

- A. Medical personnel should protect themselves against contamination by wearing rubber gloves.
- B. Remove patients clothing and wash skin with soap and water.
- C. Then wash with alcohol since many anticholinesterase are more soluble in alcohol than in water.
- D. Wash eyes with physiologic saline or tap water.
- E. If ingestion has occurred induce emesis or give gastric lavage with 5% sodium bicarbonate.

6. Convulsions.

- A. If convulsions occur treat with one gram Trimethadione (Tridione) intravenously every 15 minutes until controlled. Barbituates or ether may be used with caution.

7. Contraindicated Drugs.

- A. Morphine, theophylline, aminophylline, succinylcholine and phenothiazine derived tranquilizers are contraindicated.
- B. Smoking should be forbidden as this increases respiratory and gastrointestinal symptoms.

8. Observe Patient.

- A. The patient should be observed for at least 24 hours after symptoms have subsided because fatal relapses can occur due to continuing absorption of the poison or the dissipation of the effect of the antidote.

9. Mild Cases of Poisoning.

- A. Mild cases demonstrating only headaches, blurred vision and mild muscarinic signs can be treated by decontaminating the patient and giving 1000 to 2000 mg 2-PAM chloride orally in a single dose. This treatment usually gives full remission of symptoms in one hour. The patient must be kept under medical supervision for at least 24 hours. If 2-PAM is not available, mild cases can often be controlled by atropine therapy alone. Remember that 2-PAM

is specific for reversing the cholinesterase inhibitor and that atropine can only block the parasympathetic activity.

CONCLUSION

The anticholinesterases are the basis of many insecticides and of nerve gas warfare. The potential and hazards of these agents are not well known. Severe poisoning by either agent could cause death in minutes. Nerve gas has the potential to kill 80% of the population in a several thousand square mile area. The seriousness can be compared to the well heralded atomic warfare potential that can destroy 50% of the population over a few hundred square mile area. Much education, planning and preparation for protection against atomic war by the public has occurred in the past 15 years. Very little has been said about nerve warfare.

This author feels that many physicians don't understand the problems in the treatment of anticholinesterase poisonings. This lack of knowledge may cause the delay in treatment while the Doctor is getting this information. The delay may lead to death in a seriously poisoned patient.

Mass casualty poisonings such as those that could occur with use of the "nerve gases" could find the nation unprepared medically. The increased use of insecticides may present more poisonings by these agents in the future. The drugs necessary of specific treatment aren't generally present in most centers in either type or

amount. 2-PAM is available only for research use. Atropine, a common drug, is normally used in very small quantities. How many hospitals or clinics could supply the amount of atropine necessary to treat several patients requiring 40 mg a day for each patient? Immediate lack of mechanical respirators, endotracheal tubes and protective clothing adds to the medical state of unpreparedness to prevent mass homicide in nerve gas warfare.

The only sound solution to this problem is to develop a prophylactic drug protecting against anticholinesterase poisoning and the production and distribution of the drug making it available for immediate use. 2-PAM appears to have the most promise to meet these demands but a more active research program and national concern of this problem is necessary. A prophylactic drug could lend itself to a national program similar to that carried out with the oral polio vaccines. The drug could be distributed to the population so that it would be ready for immediate use in the event of imminent exposure. A smaller scale program could prevent industrial poisonings to labors working with insecticides.

BIBLIOGRAPHY

1. Askew, B. M., Oximes and Hydroxamic Acids as Antidotes in Anticholinesterase Poisoning, *Brit. J. Pharmacol.* 11:417, 1956.
2. Askew, B. M., Oximes and Atropine in Sarin Poisoning, *Brit. J. Pharmacol.* 12:340, 1957.
3. Brown, R. V. and others, Pyridine-2-Aldoxime-Methiodide in the Treatment of Sarin and Tabun Poisoning, with notes on its Pharmacology. *J. Pharmacol. Exp. Ther.* 120:276, 1957.
4. Callaway, S. and Davis, D. R., The Association of Blood Cholinesterase Levels with the Susceptibility of Animals to Sarin and Ethyl Pyrophosphate Poisoning, *Brit. J. Pharmacol.* 12:382, 1957.
5. Cantarow, Abraham and Schepartz, Benard, *Biochemistry* 2nd. ed. W. B. Saunders Company, Philadelphia, 1958. p. 629-33.
6. Cohen, E. M. and Wiersinga, H., Oximes in the Treatment of Nerve Gas Poisonings, I. *Acta Physiol. Pharmacol. Neerl.* 9:276, 1960.
7. Crozier, D., Civilian Medical Problems In the Defense Against Chemical and Biological Weapons, *Arizona Med.*, 18:142-50, May 1961.
8. Dultz, L. and others, Studies on a Group of Oximes as Therapeutic Compounds in Sarin Poisoning, *J. Pharmacol. Exp. Ther.* 119:522, 1957.
9. Durham, W. F. and Hayes, W. J. Jr., Organic Phosphorus Poisoning and its reference to Modes of Action and Compounds that reactivate Inhibited Cholinesterase, *Arch. Environ. Health (Chic)* 5:21-47, July 1962.
10. Frazier, R. E., Chemical Warfare another Serious Hazard, *Minn. Med.* 44:283-5, July 1961.
11. Freeman, G. and Epstein, M. A., Therapeutic Factors in Survival after Lethal Cholinesterase Inhibition by Phosphorus Insecticides, *New Engl. J. Med.* 253:266, 1955.
12. Grob, D. and Johns, R. J., Treatment of Anticholinesterase Intoxication with Oximes, *J. A. M. A.* 166:1855, 1958.

13. Grob, D. and Johns, R. J., Use of Oximes in the Treatment of Intoxication by Anticholinesterase Compounds in Normal Subjects, *Amer. J. Med.* 24:497, 1958.
14. Grob, D. and Harvey, A. M., The Effects and Treatment of Nerve Gas Poisoning, *Amer. J. Med.* 14:52, 1953.
15. Hobbiger, F., Protection Against the Lethal Effects of Organophosphates by Pyridine-2-Aldoxime Methiodide, *Brit. J. Pharmacol.* 12:438, 1957.
16. Holmes, R. and Robins, E. L., The Reversal by Oximes of Neuromuscular Blocks Produced by Anticholinesterases, *Brit. J. Pharmacol.* 10:490, 1955.
17. Loomis, T. A., The Effect of an Aldoxime on Acute Sarin Poisoning, *J. Pharmacol. Exp. Ther.* 118:123, 1956.
18. Namba, T. and Hiraki, K., PAM Therapy for Alkylphosphate Poisoning, *J. A. M. A.* 166:1834, April 12, 1958.
19. Read, W. T. and Combes, M. A., A New Specific Antidote for Organic Phosphate Ester Poisoning, *Pediatrics* 28:950, Dec. 1961.
20. Searle, V. C., The Chemical Warfare Threat, *Arizona Med.* 18:26-31, Jan. 1961.
21. Sim, V. M., Medical Aspects of Chemical Warfare, *J. A. M. A.* 175:1, 1961.
22. Way, J. L., Treatment of Poisonings due to Alkylphosphate Cholinesterase Inhibitors, *Wisconsin Med. J.* 62:157, March 1963.
23. Wills, J. H. and others, Pyridine-2-Aldoxime Methiodide and Poisoning by Anticholinesterases, *Science* 125-743, 1957.
24. Wilson, I. B., Designing of a New Drug with Antidotal Properties Against the Nerve Gas Sarin, *Biochim. Biophys. Acta*, 27:196, 1958.
25. Wood, J. R., Medical Problems in Chemical Warfare, *J. A. M. A.* 144:606, 1950.