THE TREATMENT OF NERVE-GAS POISONING

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INTRODUCTION

The nerve gases are organic phosphorus compounds which possess the property of being potent inhibitors of cholinesterase. They were first synthesized and described by Gerhard Schrader who was searching at I.G. Farbenindustrie in Germany in the 1930s for new synthetic insecticides. During the last war large quantities of one of these compounds, ethyl NN-dimethylphosphoamidocyanidate (Tabun), were stored and ready for use by Germany, and other compounds, such as isopropylmethylphosphonofluoridate (Sarin) and 1-3:3-dimethyl-n-butyl 2-methylphosphonofluoridate (Soman), were being actively investigated.

A large amount of research on the physiological, pharmacological, and biochemical aspects of nerve-gas poisoning has now been reported and it seemed desirable to summarize for the service medical officer the pertinent aspects of the published results so that he can have a better understanding of the fundamental basis of suggested therapeutic procedures.

EFFECTS OF NERVE-GASES

These gases can enter the body through the respiratory tract, the eye or the skin, but, whatever the route of entry, all these compounds produce qualitatively similar toxic effects. A lethal dose of Sarin produces the following picture in the conscious animal. There is muscular fasciculation, followed by incoordination, violent convulsive movements, prostration, gasping respiratory movements and signs of "air hunger," engorgement of the veins and often micturition and defecation. Unconsciousness follows, respiration ceases, the heart slows and the pupils may contract. (Miosis always occurs early if the eyes are exposed directly to the drug.) Then the skin capillaries collapse and finally the heart ceases to beat.

At autopsy the picture is similar for each route of poisoning. The diaphragm is elevated, with the lungs usually collapsed and ischaemic although occasionally they are congested. There is spasm of the small intestine and the abdominal viscera, with peritoneal effusion, and the splanchnic veins are engorged with dark venous blood. The right heart is distended and the left ventricle is usually empty. Apart from the "venous" colour of the arterial blood, the brain is generally normal in appearance, but there are sometimes a few petechiae in the brain substance.

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The Treatment of Nerve-Gas Poisoning

The general picture in all the species studied (mouse, rat, guinea-pig, rabbit, cat, dog, monkey, sheep and goat) is characteristic of the asphyxial state and it is evident that failure of respiration is the predominant effect produced by the intoxication.

Impairment of ventilation can occur in three main ways, viz., by the production of bronchoconstriction, through neuromuscular block affecting the respiratory muscles, and because of central respiratory failure. The latter seems to be the predominant factor in most circumstances although the detailed picture varies with the gas used, the dosage administered, etc. (de Candole et al. 1953).

Respiration may also be embarrassed during nerve-gas poisoning by the profuse secretion of fluid from the bronchial and especially the salivary glands (Dirnhuber & Cullumbine, 1955). In the unconscious subject some of this fluid might be aspirated into the respiratory tract or, if positive pressure artificial ventilation were applied, might be forced down into the narrower airways and so contribute to blocking them, thus increasing the danger of asphyxia. The occurrence of this possibility is increased by the fact that the cough reflex is abolished in nerve-gas poisoning.

Although the major event in nerve-gas poisoning is the failure of respiration, these agents can cause marked effects on the cardiovascular system. A slowing of the heart with a reduction in cardiac output and a fall in the systemic blood pressure occurs. Accompanying these changes a rise in venous pressure and an initial fall, followed by a gradual return to normal, of the pulmonary arterial pressure are also seen.

BASIS OF THERAPY

Since the most important effect of the nerve gases is upon the respiratory system and since this and the major effects of the nerve gases are due to the accumulation of acetylcholine following upon the inhibition of cholinesterase, the problem of treatment of nerve-gas poisoning can be approached in several ways.

Obviously artificial ventilation may be required in order to maintain adequate tissue oxygenation. In addition, the actions of acetylcholine could be countered by, for example, atropine or a similarly acting substance. A more fundamental approach would be to reverse the inhibition of the cholinesterase, thus re-establishing normality to the affected physiological mechanisms. Finally, the nerve gas itself could be destroyed or detoxified in the body before it had the opportunity to inhibit cholinesterase.

Atropine has been recommended as the main item for drug therapy. It will prevent and reverse the muscarinic (e.g. miosis, bronchoconstriction) and the central effects (e.g. paralysis of the respiratory centre) of acetylcholine and of the nerve gases. Full atropinization must be achieved early and must be maintained, additional atropine being required when slowing of the heart suggests that further antagonism to nerve gas was required. Medical officers should therefore have no hesitation in giving repeated doses of atropine if the patient’s condition demands it. The nerve-gas casualty can receive relatively large doses of atropine.
since acetylcholine is accumulating in large quantities and is not being destroyed by cholinesterase.

It should be noted that atropine will not overcome the peripheral neuromuscular paralysis. This, however, seems to be temporary in nature and function gradually returns to the respiratory muscles in favourable cases. Another point to remember is that the depressed circulatory function may prevent the rapid and complete absorption and distribution of injected atropine to the cerebral and medullary centres.

It has been noted in animal experiments that the effectiveness of atropine varies in different species, with the particular nerve gas used, with the route by which the atropine or the nerve gas is administered, and with the dose of nerve gas applied. One of the main reasons for the variable efficacy may be that the relative importance of the three mechanisms contributing to respiratory embarrassment—bronchoconstriction, neuromuscular block, and central failure—varies between species, between nerve gases and with dosage (de Candole et al. 1953). Atropine does not affect the neuromuscular block and, therefore, in those circumstances where this is important, atropine will be less effective. It has been shown, for example, that the reason some fully-atropinized cats die from Sarin is the persistence of neuromuscular block in the respiratory muscles. Monkeys, in which the respiratory failure produced by nerve gases is mainly a central phenomenon, respond well to atropine.

Man, like the monkey but unlike the rabbit and the rat, also responds to small doses of atropine and so, if the picture of nerve-gas poisoning in man is similar to that in the monkey, reasonable doses of atropine may be effective in the therapy of poisoned men.

The dose of atropine sulphate for field use against nerve-gas poisoning must also be considered. Here it must be remembered that death may occur within a few minutes of exposure and early treatment is imperative. Therefore the individual service man must be made responsible for his own treatment. Unfortunately, since the early signs and symptoms of nerve-gas poisoning are vague, it is difficult to advise the service man when to give himself atropine so that this may be administered on suspicion and when no actual exposure has occurred. Since atropine itself has certain undesirable effects in the absence of acetylcholine or anti-cholinesterase poisoning, the dose of atropine which the individual service man can be allowed to use must be a compromise between the dose which is therapeutically desirable and that which can be safely administered to a non-intoxicated person.

Trials under temperate climatic conditions have shown that 2 mg. atropine sulphate is a reasonable amount to be recommended for injection by an individual and that higher doses may produce embarrassing effects such as dizziness, tiredness, difficulty in reading and dysuria, on troops with operational responsibilities (Cullumbine, McKee & Creasey, 1952).

In a warm environment, since atropine inhibits sweating, increases the heart rate and alters the rectal temperature, it would seriously affect the maintenance of body temperature. Therefore a study has been made of the
The Treatment of Nerve-Gas Poisoning

effect of atropine sulphate on the process of acclimatization to a hot, dry and a warm, moist environment (Cullumbine & Miles, 1953). It was found that 2 mg. atropine sulphate did temporarily disturb acclimatization, especially in the hot, dry environment, but that this effect was less marked as the period of acclimatization was prolonged.

Further trials with fully acclimatized troops showed that not many of them could tolerate 2 mg. atropine sulphate in either a hot, dry or a warm, moist climate. Resting men may remain efficient after this dosage although their eyesight may be affected. If exercise has to be taken, then there will be a general loss of efficiency and some subjects may collapse. If the exercise has to be done while exposed to the direct heat of the sun then a large proportion of the men may collapse and the military efficiency of the remainder will be negligible. These effects of atropine are very temporary and a collapsed man will quickly recover (in about an hour) if he is allowed to rest. This recovery will be hastened by sprinkling water on the skin to aid evaporative cooling.

Despite the temporarily harmful effects produced by atropine in warm environments, 2 mg. atropine sulphate is still recommended as the first aid dose in all climates since it is considered that unnecessary atropinization is preferable to death from nerve-gas poisoning.

Because death occurs so rapidly in nerve-gas poisoning the first aid dose of atropine must be given quickly and with certainty and various self-injection devices have been suggested for this purpose. The intramuscular route of administration is recommended, chiefly on the grounds of ease and rapidity of injection, since the descending order of rapidity of action following administration by various routes is intravenous, subcutaneous, intramuscular and oral.

The efficacy of atropine will be enhanced if artificial ventilation is also applied to the poisoned animal. There are several reasons for this. Adequate oxygenation of the tissues will be maintained and, therefore, the important physiological mechanisms, such as the respiratory centre, will remain responsive to atropine. Thus it has been shown that atropine will only be effective in restoring respiration so long as the degree of asphyxia is not too great. Further, the neuromuscular block, which is unresponsive to atropine, appears to be a temporary phenomenon so that in the absence of asphyxia normal neuromuscular transmission will eventually return.

Moreover, in animals poisoned with nerve gases, atropine also causes acceleration of the heart rate and a momentary rise in blood pressure to a level exceeding its initial value. A fall in peripheral vascular resistance also occurs so long as the pulmonary ventilation is adequate. Without the latter, the blood pressure falls, the heart fails and an increase in peripheral resistance occurs. These effects are probably due to asphyxia because they can be reversed by adequate artificial ventilation. Thus the synergism between atropine and artificial ventilation is again demonstrated. This is because the various important physiological mechanisms are disturbed both by the accumulation of acetylcholine and the development of asphyxia. In addition the absorption of injected atropine may be hampered by local and general circulatory failure.
A positive pressure form of artificial ventilation is recommended because of the possible occurrence of an increased airway resistance due to bronchoconstriction. In man this increased resistance to breathing may be only moderate in degree and of short duration, but it would appear to be essential to avoid any element of asphyxia complicating the picture of nerve-gas poisoning.

Therefore, ordinary manual methods of artificial respiration may be ineffective since they will not overcome the bronchospasm. They may possibly aid, however, to prolong life until other therapeutic procedures can be applied. The Holger-Nielson, arm-lift back pressure, method would seem to be best of the manual methods. It gives adequate pulmonary ventilation, is easy to teach and to learn and can be carried out for a long time by a single operator. The Schafer, prone-pressure, method is unsatisfactory because it provides only a small tidal volume which in many cases is less than the respiratory dead-space. In addition, the ventilation is entirely in the range of the respiratory reserve and would be handicapped when this is reduced and also the ribs may be fractured by this method. The arm-lift, chest pressure, method of Sylvester has the serious disadvantage that the tongue is liable to fall back and occlude the air-way, and also the ribs may be fractured or the liver ruptured. With the hip-lift method of Emerson the tidal volume in some cases is less than the dead-space and the method is fatiguing. The hip-lift, back pressure, method gives a high pulmonary ventilation and can be performed if the arms are injured. The disadvantage is that it soon fatigues the operator especially if he is small and the victim is large. The hip-roll, back pressure, method is less fatiguing but it gives a smaller ventilation and is more difficult to teach and to learn. (Gordon et al. 1951a, b, c, d; Karpovich & Hale, 1951a, b; Whittenberger et al. 1951; Nims, et al. 1951).

A mechanical device is therefore needed to supply the required positive pressure. A continuous positive pressure in the lungs of more than 14 mm. of mercury impairs venous return, but an intermittent positive pressure seems to distribute the blood effectively and it is said to reduce the transfer gradient and to increase the arterial oxygen tension, possibly by promoting more uniform ventilation of the alveoli. Therefore, a manually operated apparatus, such as a bellows resuscitator or a mask-to-mask device, is being considered for field use. Such an apparatus could be easily carried by stretcher-bearers, is simple and quick to apply and use and can be applied to trapped or injured personnel since only the face is needed. It is not fatiguing to use, offers protection from the contaminated atmosphere and will indicate when respiratory obstruction occurs.

Other approaches to the problem of therapy for nerve-gas poisoning are, as stated, an attempt to destroy the nerve gas before it can react with the cholinesterase and an effort to reverse the cholinesterase-nerve-gas combination. Recently two groups of compounds—the oximes and the derivatives of hydroxamic acid—have been found which are capable of doing both those things (Childs et al. 1955).

In general the hydroxamic acids are quicker reactors with or destroyers of Sarin than the oximes while the latter are the more potent reactivators in vitro of Sarin-inhibited cholinesterase. (Tabun-inhibited cholinesterase cannot be
The Treatment of Nerve-Gas Poisoning

easily reactivated.) In addition there is evidence that some of the oximes will reverse in vitro, but to a less extent in vivo, the neuromuscular block caused by Sarin and that this reversal appears to be due to reactivation of the inhibited cholinesterase at the neuromuscular junction (Holmes & Robins, 1955).

Unfortunately many of these compounds, and particularly the oximes, have toxic actions of their own so that only small doses can be given to the whole animal. However, even these limited doses do show some prophylactic and therapeutic effectiveness in Sarin-poisoned animals. They are even more effective when used in conjunction with atropine. This synergism was to be expected since atropine does not affect the neuromuscular block but the oximes may.

It is perhaps too early to define the exact position of the oximes (or the hydroxamic acids) in the therapy of nerve-gas poisoning. Atropine is established as the Mark I therapy. Oximes could be given either as substitutes or as adjuncts or prophylactically. Their best role must be the subject for further research. There is no doubt, however, that for most practical purposes an effective therapy is available. With atropine, artificial ventilation and oximes available, adequate treatment of the degree of intoxication likely to be received in the field should be possible. This treatment will, nevertheless, have to be given rapidly since death from nerve gas occurs in a matter of minutes.

CONCLUSIONS

The nerve gases are organo-phosphorus compounds which inhibit cholinesterase and so allow acetylcholine to accumulate in the tissues.

Death from nerve-gas poisoning is due to respiratory failure.

Atropine is an effective therapy since it will prevent many of the actions of acetylcholine.

Positive pressure artificial ventilation will augment the effectiveness of atropine in severe cases of poisoning.

Certain oximes and hydroxamic acids will reactivate the inhibited cholinesterase and also hasten destruction of the nerve gas. They show promise of being useful adjuncts to atropine for therapy.

REFERENCES

THE USE OF SODIUM GENTISATE IN ACUTE RHEUMATIC FEVER

BY

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Sodium gentisate is a drug of particular value in the treatment of acute rheumatic fever, but its use is certainly not as widespread as its efficiency would seem to justify. It was therefore decided to carry out a small pilot trial employing the two more commonly used drugs, aspirin and sodium salicylate, and sodium gentisate. Whereas the results of this trial are not statistically significant, they are of decided interest in demonstrating how the latter drug compares with the two former drugs in the treatment of acute rheumatism.

Three groups of patients were used, each group consisting of three cases of acute rheumatic fever. The cases were not selected in any way as to first or subsequent attacks, presence of clinical carditis, or length of history, etc., but were just treated with one of the three drugs as they came into hospital. Brief case histories of these patients are given below.

GROUP I—ASPIRIN THERAPY

Case 1

B. V., aged 18, was admitted to hospital with a two-day history of acute pain and swelling in his right knee, followed one day later by pain in his left knee. For one week prior to these symptoms he had a "cold in the head." There was nothing relevant in his past history.

Examination revealed a temperature of 100°F, limitation of movement in both knees with an effusion in the right knee, and a soft, blowing, apical systolic murmur.