4. Organophosphorus Compounds

Uses
Numerous organophosphorus pesticides of varying toxicity are used extensively in agriculture and horticulture (including glasshouse crops) mainly as emulsifiable concentrates or wettable powder formulations for making up into liquid sprays, but also as granules for soil application. A limited number are also available as fogging formulations, smokes or impregnated resin strip preparations for use indoors.

Routes of Absorption
Absorption may take place via the skin or by inhalation.

Pharmacology
The acute toxicity, speed and duration of effect vary greatly from one organophosphate to another but they all have the same basic mode of toxic action, namely the depression of cholinesterase activity in blood, brain and most other tissues. This effect allows acetylcholine to accumulate at the autonomic and some central synapses, and at the autonomic post-ganglionic and skeletal efferent nerve endings thus blocking the transmission of nerve impulses.

Toxic Effects
The toxic effects are similar to those of a cholinergic drug such as neostigmine, but tend to be much more prolonged, lasting for a day or two rather than a few hours. Successive hours or days of unsafe use may cause progressive depletion of cholinesterase reserves until toxic effects occur. Their onset and severity depend mainly on the speed and degree of cholinesterase depression.

The first symptoms of poisoning are usually a feeling of exhaustion, weakness, and possibly mental confusion. These effects may be experienced during exposure, or up to 12 hours later, and could well

be ignored by a person using organophosphorus compounds. Vomiting, cramp-like abdominal pain, excessive cold sweating and salivation may soon follow.

Constriction of one or both pupils and a sensation of tightness in the chest during inspiration may also occur at an early stage but these signs are not reliable indices of the severity of the systemic poisoning because they may be caused by local anti-cholinesterase effects of spray mist in the eye or bronchi.

As poisoning progresses muscular twitchings begin in the eyelids and tongue and then other muscles of the face and neck become involved. Severely affected persons develop generalised muscular twitchings with severe muscular weakness and convulsions may also occur. Miosis is prominent and progressive. Later effects may include diarrhoea, tenesmus, incontinence, ataxia and mental confusion. Bronchial hypersecretion with broncho-constriction and cyanosis lead to respiratory depression and mental confusion, gradually advancing to coma and death from respiratory failure. The clinical picture in very severe cases is one of muscular twitching, profuse sweating, incontinence, mental confusion and progressive cardiac and respiratory failure.

Symptomless depression of cholinesterase levels may render a person much more susceptible to the action of depolarising muscle relaxants, such as succinylcholine, given in conjunction with anaesthesia. In these cases a degree of exposure to organophosphorus compounds which would normally only cause mild clinical poisoning can precipitate a more severe level of poisoning.

Management and Treatment
All cases of organophosphate poisoning should be dealt with as an emergency and the patient admitted to hospital as quickly as possible. A clear airway should be ensured, oxygenation maintained, any necessary skin decontamination carried out and atropine sulphate given as soon as possible in a dose of 2 mg by subcutaneous or intramuscular injection, or in severe cases by the intravenous route. The patient must not be allowed or made to exert himself in any way as muscular exertion may hasten the course of

poisoning by inducing more acetylcholine accumulation.

Ventilation must be maintained. In severe cases, especially if treatment has been delayed, there may be excessive mucous secretion, combined with broncho-constriction. Care must therefore be taken to keep the airway clear and it may be necessary to pass an endotracheal tube. There is ample evidence that the immediate treatment of respiratory arrest by aspiration of bronchial secretions and assisted ventilation may permit full recovery.

As the skin is the commonest route of absorption thorough decontamination is essential. All clothing that is, or might be, contaminated should be removed at once, and all possibly contaminated skin washed thoroughly with soap and cold water including exposed areas (eg hands, arms, face, neck and hair).

Two specific antidotes exist for use in organophosphorus compound poisoning. Atropine antagonises the so-called muscarinic effects of accumulating acetylcholine and may therefore considerably improve the patient's condition. Certain oxime compounds, notably pralidoxime, are able rapidly to reverse the inhibition of cholinesterase enzymes by some (but not all — see product label) organophosphorus compounds and may thus reverse the course of poisoning provided that they are given promptly after exposure has occurred.

In mild cases one injection of atropine may be enough to relieve symptoms, but if not, further atropine sulphate in 2 mg doses should be given at frequent intervals (15-30 minutes), until the patient is fully atropinised, ie dilated pupils, dry mouth and rapid pulse. Persons suffering from organophosphate poisoning tolerate more atropine than do normal persons. Very large amounts, 100 mg or more, may be required to maintain atropinisation and control symptoms throughout the course of poisoning. The heart rate is a particularly useful criterion in the use of atropine and a target rate for the first 24 hours is 80 beats per minute. At 24 hours the need for atropine should be reviewed.

In addition, diazepam by separate intravenous injection in doses of 5-10 mg, appears to have a beneficial, non specific effect, apart

from controlling tremors or convulsions. If a cholinesterase reactivator, eg pralidoxime, is available within 12 hours of the onset of symptoms it should be given intramuscularly or intravenously as early as possible, in any severe or progressive case of intoxication. Treatment by both atropine and pralidoxime should be carried out at the same time as the two methods are complementary. (If the reactivator is effective, the symptoms will be promptly controlled, and further atropine will probably not be needed). For slowly metabolised indirect inhibitors of cholinesterase it may sometimes be necessary to repeat both pralidoxime and atropine even after 24 hours.

In Britain, the oxime reactivator available is pralidoxime which can be obtained on demand from certain strategic depots (see Appendix IV). The dose is 1g pralidoxime, dissolved in 2-3 ml of water for intramuscular, or 6-20 ml water for intravenous injection. A single dose may be sufficient to control the toxic effects, but in some cases a second or even third dose per 24 hours may be necessary to maintain control. Use of the anticonvulsant diazepam (10 mg by separate intravenous injection repeated as necessary) will often improve the clinical condition.

In summary the management of organophosphate poisoning should be as follows:

1. Maintain oxygenation;

2. Decontaminate the skin thoroughly but gently;

3. Administer atropine sulphate subcutaneously or intravenously and also take a venous blood sample, at the time, into a lithium heparin tube for cholinesterase estimation (see below) if not already taken;

4. Give a cholinesterase reactivator intramuscularly or intravenously and,

5. Repeat 3 and 4 as necessary.

6. Take further blood samples as necessary to monitor recovery.

Laboratory diagnosis
Diagnosis of poisoning by organophosphorus compounds can be confirmed by demonstrating a significantly reduced cholinesterase activity in whole blood, red blood cells, or plasma. A blood test should be made in every suspected case, but only after any emergency resuscitation has been instituted. Ten ml of venous blood should be taken into a lithium heparin tube, avoiding haemolysis and sent to the nearest laboratory equipped for cholinesterase determination (Appendix III).

A significantly reduced level of cholinesterase activity in the red cells indicates that an anti-cholinesterase chemical has been absorbed. A reduction in pseudocholinesterase (plasma) activity merely indicates exposure to such a chemical. If the depression is marked, the patient will be more susceptible to the effects of further exposure to an organophosphorus compound. Any person who has been detectably affected should not, therefore, be allowed to return to work or come into contact with any organophosphorus compound until the level of blood cholinesterase activity has been restored. The rate of recovery of cholinesterase activity in the blood varies with the chemical responsible. Complete recovery in certain circumstances may take two or three months. It is therefore advisable for an affected person to have further blood examinations every 7-14 days until recovery is complete.

Difficulty often arises regarding the interpretation of results of blood tests as individuals vary quite widely in their normal complement of cholinesterase and it may be necessary to seek expert advice. Ideally, those likely to be repeatedly engaged with handling organophosphorus compounds, eg pilots involved in aerial spraying, contract sprayers on the ground, should have a baseline estimation carried out before starting on this work.

5. Carbamates

This section refers only to insecticidal (anticholinesterase) carbamates and not to other types of carbamates, such as those used as herbicides.

Uses
There are a number of compounds in this group used in agriculture and horticulture as insecticidal and nematicidal preparations whilst insecticidal preparations are used in food storage, animal husbandry and public hygiene practice. Carbamates are also incorporated in preparations for use in both home and garden.

Routes of Absorption
Carbamates are generally and readily absorbed by inhalation and through the skin, as well as by ingestion. They can also have local effects on the eyes.

Pharmacology and Toxic Effects
The acute toxicity, speed and duration of effect, of which there is great variation between the separate carbamates, is influenced by the chemical structure. All of these compounds nevertheless have the same basic mode of toxic action, namely the depression of cholinesterase activity in blood, brain and most other tissues. The resulting accumulation of acetylcholine at synapses and nerve endings blocks the transmission of nerve impulses.

The toxic effects are therefore similar to those of the organophosphorus insecticides, but both onset and recovery are markedly more rapid. Prolonged or repeated unsafe use can result in progressive depletion of cholinesterase reserves until toxic effects occur. Their onset and severity depend mainly on both the speed and degree of cholinesterase depression.

The symptomatology of poisoning by anticholinesterase agents is described in detail in the section on organophosphorus compounds. Early signs are headache and nausea followed by a sensation of

tightness in the chest, coughing and constriction of the pupils. As poisoning progresses muscular twitching occurs and becomes generalised, and there may be marked central nervous or gastro-intestinal manifestations. Poisoning by carbamates may also cause circulatory failure, dyspnoea, hypopnoea and marked bradycardia. The clinical picture in a severe case is one of muscular twitching, profuse sweating, incontinence, mental confusion and progressive cardiac and respiratory failure.

Symptomless depression of cholinesterase levels increases susceptibility to the action of depolarising muscle relaxants such as succinylcholine given in conjunction with anaesthesia and can give rise to severe poisoning with other anticholinesterase agents at levels of exposure which would normally only produce mild clinical effects.

Management and Treatment

All cases of carbamate poisoning should be dealt with as an emergency. The patient must not be allowed or made to exert himself in any way as muscular exertion may hasten the course of poisoning by inducing more acetylcholine accumulation. A clear airway should be ensured, adequate oxygenation maintained, any necessary decontamination carried out and atropine sulphate given as soon as possible in a dose of 2 mg by subcutaneous or intramuscular injection, or in severe cases by the intravenous route, to reverse the signs of poisoning. The patient should be admitted to hospital as quickly as possible.

Respiratory failure is the usual cause of death. If respiratory depression occurs, ventilation must be maintained. There may be excessive mucous secretion combined with broncho-constriction and care must be taken to maintain a clear airway; it may sometimes be necessary to pass an endotracheal tube. Prompt treatment of respiratory arrest by aspiration of bronchial secretions and assisted ventilation is essential.

All clothing that is, or might be, contaminated should be removed at once and all possibly contaminated skin washed thoroughly with soap and cold water especially the exposed areas of hands, arms, face, neck and hair. If there have been splashes in the eyes these

should be irrigated with water or physiological saline.

Atropine is the specific antidote for carbamate-induced inhibition of cholinesterase. In mild cases one dose may be sufficient, but if the patient does not respond or continues to develop toxic manifestations further 2 mg doses should be given at frequent intervals (15-30 minutes), using the intravenous route in severe cases until the patient is fully atropinised ie dilated pupils, dry mouth and rapid pulse. Pralidoxime has little, if any, value in the treatment of carbamate over-exposure and should not be used for this purpose.

Laboratory Diagnosis

Diagnosis of poisoning by carbamates can be confirmed by demonstrating a significantly reduced cholinesterase activity in whole blood, red blood cells or plasma. A blood test should be made in every suspected case. 10 ml of venous blood should be placed in a lithium heparin tube, avoiding haemolysis, and sent to the nearest laboratory equipped for cholinesterase determination (Appendix III), as quickly as possible (within 1-4 hours). Because of the rapid reactivation of cholinesterases inhibited by carbamate compounds it is not recommended to send such samples by post.

Appendix III

Cholinesterase Estimations

The following laboratories are able to carry out estimations relevant to pesticide poisoning of cholinesterase activity in heparinised whole blood. Red cell acetyl-cholinesterase activity can be measured as well as plasma cholinesterase activity.

Despatch Instructions

To comply with the Inland Postal regulations pathological specimens (blood, gastric contents, excreta, urine, etc) must be sent by letter post **not** parcel post or sample post — packed in the manner described below, and conspicuously marked FRAGILE WITH CARE and bearing the words PATHOLOGICAL SPECIMEN (AGRICULTURAL POISON). A note should accompany each specimen giving (a) the name and age of the patient; (b) an indication of the degree of exposure to the poison, naming it if possible; and (c) details of any symptoms which may be referable to such exposure.

Specimens must be enclosed in a receptacle, hermetically sealed or otherwise securely closed, and this receptacle must itself be placed in a strong wooden or metal case, or an alternative container approved by the Post Office in such a way that it cannot shift about, and with a sufficient quantity of some absorbent material (such as sawdust or cotton wool) packed about the receptacle to prevent absolutely any possible leakage from the package in the event of damage to the receptacle. Such specimens — which are otherwise prohibited for transmission by post may be sent for medical examination or analysis only to a recognised medical laboratory or institute (whether or not belonging to a public health authority) or to a qualified medical practitioner. Any packet containing specimens, found in the parcel post or sample post, or found in the letter post not packed and marked as directed, will be at once stopped and destroyed with all the wrappings and enclosures. Anyone sending by post such a specimen (described in the regulations as "deleterious liquid or substance") other than as provided for by the regulations is liable to prosecution.

Receptacles used by a laboratory or institute which are not cleared for transmission by post must be submitted to Postal Headquarters (PMk 1) St Martin's-le-Grand, London EC1A 1HQ to ensure that they comply with the regulations.

Regional Health Authority Laboratories

England

Northern Region

Department of Pathology,
Newcastle General Hospital,
Westgate Road,
Newcastle upon Tyne, NE4 6BE
Tel: 0632 738811
(during normal working hours)

Department of Pathology,
Middlesbrough General Hospital,
Ayresome Green,
Middlesbrough,
Cleveland TS5 5AZ
Tel: 0642 81333
(during normal working hours)

Yorkshire Region

Department of Pathology,
Hull Royal Infirmary,
Anlaby Road,
Hull HU3 2JZ
Tel: 0482 28541

Trent Region

Department of Chemical Pathology,
University Hospital,
Queen's Medical Centre,
Nottingham NG7 2UH.
Tel: 0602 700111

East Anglian Region

Department of Clinical Chemistry,
Peterborough District Hospital,
Thorpe Road,
Peterborough PE3 6DA.
Tel: 0733 67451

North East Thames Region

Department of Pathology,
Essex County Hospital,
Lexden Road,
Colchester,
Essex CO3 3NB.
Tel: 0206 69244

Department of Pathology,
Chase Farm Hospital,
The Ridgeway,
Enfield,
Middlesex EN2 8JL.
Tel: 366 6600

North West Thames Region

Department of Clinical Chemistry,
Watford General Hospital,
Peace Memorial Wing,
Rickmansworth Road,
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Department of Clinical Chemistry,
Barnet General Hospital,
Wellhouse Lane,
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Herts. EN5 3DJ.
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Edgware General Hospital,
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Middx. HA8 0AD.
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Chemical Pathology Department,
Central Middlesex Hospital,
Acton Lane,
NW10 7NS.
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Chemical Pathology Department,
St Albans City Hospital,
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St Albans,
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Department of Clinical Enzymology,
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