PHOSPHAMIDON POISONING

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A fatal case of poisoning with phosphamidon, a recently developed organophosphate insecticide, is described. A second, probable case of mild phosphamidon poisoning is also reported. The clinical picture in both cases resembled that seen in poisoning with other organophosphate compounds.

The first patient was an 18-year-old girl who had swallowed about 50 ml. of a 50% solution of phosphamidon and developed jaundice, bronchopneumonia, and pulmonary oedema. She died on the sixth day in hospital despite prolonged respiratory support and treatment with massive doses of atropine, PAM, and antibiotics. Post-mortem examination revealed a fatty liver, congestion of the internal organs, and brain damage of the type seen in anoxia. The second patient was a 50-year-old agricultural worker, who was engaged in uprooting and cutting shrubs which had been sprayed two weeks earlier with phosphamidon. He was admitted to hospital in a state of confusion and recovered within several hours.

The importance of securing a free airway and of artificial ventilation as first-aid measures in organophosphate poisoning is stressed, and the value of early massive dosage of PAM is emphasized.

Phosphamidon (2-chloro-2-diethylcarbamoyl-1-methylvinyl dimethyl phosphate) (Fig. 1) is a potent, recently introduced insecticide which is widely used in agriculture.

It is a colourless, odourless fluid with a boiling point of 120°C. and is miscible in all proportions with water, alcohols, ethers, esters, and aromatic hydrocarbons (Jaques and Bein, 1960). In Israel a

50% solution of phosphamidon in isopropanol is marketed for use as a spray-insecticide under the trade name Dimecron 50. It is coloured a dark violet as a precautionary measure and to aid identification.

After being sprayed on, phosphamidon rapidly penetrates into the tissues of the plant, where it is distributed by the sap stream throughout the plant and its fruit. It undergoes breakdown within the

FIG. 1.—Structural formulae of phosphamidon and of its degradation products in the plant (Jaques and Bein, 1960).

plant and on its surface, and both phosphamidon itself and one of its degradation products (compound II, Fig. 1) are toxic. Insects are destroyed not only by the direct spray but also by sucking and chewing the poisoned plant. The manufacturers claim that after a period of one to three weeks from the date of spraying all toxicity disappears, and the plant and crops do not constitute a danger to man (CIBA, summary report DIM, IVWe, 1011). The instructions on the label of Dimecron 50 state that four weeks should elapse after spraying. In a recent study, the phosphamidon residue in various crops was found to disappear within four to 16 days of spraying (Menzer and Ditman, 1963).

The lethal intravenous or subcutaneous dose (LD_{100}) for mice, rats, and rabbits varies between 7 and 30 mg./kg., and the oral LD_{100} is between 20 and 70 mg./kg. (Jaques and Bein, 1960). If the toxicity in man is similar, a lethal dose (LD_{100}) for a 70 kg. man would lie between 1.5 and 5 grams.

Phosphamidon penetrates through the skin, especially if the latter has been damaged by disease or injury (Jaques and Bein, 1960). Absorption also readily occurs through mucous membranes and via the lungs.

The insecticidal properties of phosphamidon are related to its phosphate component and it acts similarly to other organic phosphates by inactivating cholinesterase by phosphorylation of the enzyme's active centre (Jaques and Bein, 1960; Nachmansohn and Feld, 1947; Wilson and Bergmann, 1950; Hobbiger, 1961).

Many cases of organophosphorus poisoning have been recorded with a variety of compounds, especially parathion, TEPP and HETP, but also with malathion and DFP (Büch and Florange, 1954; Seifert, 1954; Maresch, 1957; Davies and Green, 1959; Erdmann and Latki, 1960; Hayes, 1961, 1963; Pinhas, 1961; Durham and Hayes, 1962; Quinby, Loomis, and Brown, 1963; Vercruysse and Deslypere, 1964). However, we are unaware of any published reports on phosphamidon poisoning in man.

Two cases are presented here. The first, a massive intoxication, ended fatally. The second, a probable case of phosphamidon poisoning, was mild, and recovery was complete.

Case Reports

Case 1.—An 18-year-old student was brought to the hospital with no manifest signs of life. She was described by her friends as a quiet, withdrawn girl, who had appeared to be depressed of late. Her room-mate had left their room to fetch some food and on returning 20 minutes later found the patient on the floor unconscious but still breathing.

A 100 ml. bottle labelled 'Phosphamidon-poison' and

one-quarter filled with a dark violet fluid was found beside her. Spots of the fluid were found on her clothes, the floor, and the sink.

An ambulance was summoned immediately but a further 15 to 20 minutes elapsed before the patient's arrival at hospital.

Physical examination revealed a well-developed girl in deep coma, apnoeic and cyanosed, with abundant secretions at the mouth and nose. The pulse rate was 80 per minute and the blood pressure 90/55 mm. mercury. The pupils were pin-point. Both superficial and deep reflexes were absent. The muscles were entirely flaccid and there were no fasciculations. Artificial respiration was started immediately and 2 mg. of atropine was injected intravenously. An intravenous infusion of 1 g. pyridine-2-aldoxime methiodide (PAM) in 5% glucose was started. A tracheostomy was performed and a silver cannula fitted with a cuff was introduced. Copious secretions were aspirated from the tracheobronchial tree. Gastric suction yielded 300 ml. of a violet-blue-coloured fluid, later identified as phosphamidon.

Atropine injections, in 1 to 4 mg. doses, were repeated every five to 10 minutes, and after one hour atropine administration was continued by intravenous drip. During the first six hours a total of 70 mg. atropine and 1 g. of PAM were administered.

Fifteen minutes after the start of the therapy irregular, spontaneous respirations returned. The respiratory pattern consisted of three or four breaths followed by 10 to 20 seconds of apnoea. A transient stimulation of respiration was noted after the injection of atropine. A tachycardia developed (140 beats/minute) and the excessive respiratory secretions disappeared. There was, however, no dilatation of the pupils, flushing of the skin or other signs of atropine toxicity. Because of a transient drop in blood pressure, angiotensin amide (Hypertensin) and prednisolone-sodium-tetrahydrophthalate (Ultracorten H) were added to the infusion fluid. After six hours of treatment hypoventilation became obvious and the tracheal cannula was connected to an intermittent positive pressure breathing apparatus* which was patient-triggered.

Routine haematological findings and blood chemistry were within normal limits. Cholinesterase activity of the blood 12 hours after admission was found to be absent.

For two days the patient remained unresponsive to external stimuli. Treatment was continued with atropine, 100 mg./day, and PAM, 2 to 3 g./day. On the third day a marked improvement was noted. The patient's sensorium cleared to a certain degree and she was able to whisper single words in answer to questions and to respond to simple commands. However, she still required respiratory support. The blood cholinesterase activity was reported as 4% of normal. Liver function tests on the fourth day were as follows: prothrombin, 37%; bilirubin, 2.5 mg./100 ml., mostly direct; cholesterol, 92 mg./100 ml.; alkaline phosphatase, 4.2 B.-L. units; thymol turbidity, 1; cephalin flocculation, ++; serum albumin, 2.7 g./100 ml.; globulin, 3 g./100 ml.

On the fifth day there was a rapid deterioration in the

* Bennet, Los Angeles.

patient's condition. Severe bilateral bronchopneumonia developed, despite the massive antibiotic treatment which had been given from the day of admission. The patient died on the sixth day in hospital.

The main findings at necropsy were as follows (Drs. M. Sacks and E. Theodor): The lungs were heavy, dark red, and showed numerous small yellowish spots on the cut surface. Microscopically, areas of severe bronchopneumonia with early abscess formation were seen. Elsewhere the lung sections showed pulmonary oedema with pink-stained amorphous material within the alveolar lumina. The liver was of yellow colour and showed marked fatty change on histological examination. The fatty change was diffuse and showed no special predilection for either the central or peripheral portions of the lobules. The kidneys showed marked generalized congestion and nuclear pyknosis of the cells lining the loops of Henle. The brain showed congestion, oedema, and neuronal degenerative changes of the type found in anoxia. The other internal organs showed congestion of the blood vessels.

Case 2.—A 50-year-old agricultural worker was brought to the hospital confused and very restless. He had been engaged all day in uprooting and cutting shrubs which two weeks previously had been sprayed with phosphamidon. He worked without gloves. In the afternoon he suffered from dizziness and repeated severe vomiting, and collapsed. He was sweating and showed excessive lacrimation. On examination, pulse, blood pressure, respiration, and temperature were normal. Physical findings, including neurological examination, were essentially negative except for the presence of mental confusion.

He received an intravenous injection of 1 mg. atropine. Within a few hours his general condition improved and full consciousness returned. He complained of generalized muscular weakness for two days, but his subsequent recovery was complete. Serum cholinesterase activity 12 hours after admission was 80%.

Discussion

The clinical picture in the two cases of phosphamidon poisoning reported above resembles that seen in severe and mild poisoning, respectively, with other organophosphates, notably parathion (Maresch, 1957; Durham and Hayes, 1962; Hayes, 1963; Vercruysse and Deslypere, 1964). However, some aspects of the clinical course and therapy deserve further consideration.

The possible role of the solvent isopropanol in producing the coma and in accounting for the lack of response to atropine and PAM in the first patient should be borne in mind. Isopropanol is known to be more narcotic and toxic than ethanol, and the fatal dose for man has been estimated at about 170 ml. (McCord, Switzer, and Brill, 1948; Lehman and Chase, 1944). The amount necessary to produce narcosis, however, is unknown. The administration

of 10 to 15 ml. of isopropanol resulted in drowsiness in three of seven volunteers (Fuller and Hunter, 1927), and doses of 25 ml. given to six other volunteers caused slight dizziness after half an hour and mental depression after two to three hours (Grant, 1923). Coma did not develop with these doses. In the fatal case reported above the patient retained several lethal doses of phosphamidon, but probably no more than 30 ml. of pure isopropanol. The deep and rapidly developing coma can therefore hardly be attributed to the alcohol and should rather be considered due to the phosphamidon. A mild or moderate effect of isopropanol cannot, however, be excluded.

Impaired hepatic function with jaundice was manifest, and the liver showed severe fatty change at necropsy. The latter is not a rare finding in organophosphate poisoning (Büch and Florange, 1954; Seifert, 1954; Maresch, 1957; Vercruysse and Deslypere, 1964). As fatty livers have been found in patients dying only half an hour to eight hours after poisoning with parathion (Seifert, 1954; Maresch, 1957; Vercruysse and Deslypere, 1964), the liver damage seems to be a specific toxic effect of the insecticide. However, prolonged anoxia *per se* has been found to produce similar changes (Rosin, 1937). Anoxia with severe, resultant brain damage has been recorded in organophosphate poisoning due to depression of respiration in cases in which artificial respiration has been delayed or inadequate (Hayes, 1963).

Some degree of anoxia was probably present in our patient, especially in the early stage before admission, and also later, with the development of pneumonia. The brain damage found at necropsy supports this view. One may therefore infer that anoxia may also have been a factor in causing or aggravating the liver damage.

The isopropanol solvent is another possible factor which may have played a role in the causation of the liver damage. Fatty changes have been found in the livers of mice killed after being subjected to intermittent isopropanol narcosis for 24 hours (Weese, 1928).

Case 2 presented several points of interest. The initial impression obtained by the resident doctor in the emergency room was that of a mild cerebrovascular accident. Only thorough questioning of the patient's relatives, prompted by the nature of the patient's employment, revealed the fact that he had been exposed to phosphamidon, and this gave a clue to the probable diagnosis. The confusion, a valuable sign of organophosphate poisoning (Edson, 1957), the rapid recovery, and lack of residual signs supported the diagnosis of phosphamidon poisoning. The lack of a significant depression of acetylcholine-

esterase activity in this patient does not exclude phosphamidon poisoning. In mild poisoning with parathion the level of cholinesterase has frequently been found to be normal (Durham and Hayes, 1962).

The dosage schedule of PAM in phosphamidon poisoning warrants further consideration. Injected PAM rapidly leaves the blood stream (Jager, Stagg, Green, and Jager, 1958), and within one hour 41% of injected ^{14}C -labelled PAM appears in the urine (Quinby *et al.*, 1963). It is obvious therefore that repeated doses of PAM are required in cases in which absorption of the insecticide is slow and continuous.

One gram of PAM, repeated when necessary, has been suggested by Durham and Hayes (1962). However, as much as 3.5 g./ $\frac{1}{2}$ hour, 12 g./24 hours, and 21 g./48 hours were given successfully by Clemmesen and his group in cases of parathion poisoning (Milthers, Clemmesen, and Nimb, 1963). In addition the patients received atropine. A case of severe parathion poisoning successfully treated with 40.5 g. of PAM administered over a six-day period has recently been reported (Namba, 1961).

Kewitz and Wilson (1956) and Wislicki (1960) demonstrated the low toxicity of intravenously or intraperitoneally injected PAM in mice, rabbits, and cats. Only very large amounts of the oxime (corresponding to a human dose of 14 to 28 g.) given as a single dose or in divided doses over a period of about half an hour resulted in respiratory depression and death. These results and the dosage used by Clemmesen and his group (Milthers *et al.*, 1963) suggest that doses larger than those used by the earlier workers (Namba and Hiraki, 1958; Durham and Hayes, 1962) may be given with impunity. However, renal function must be taken into account as PAM is eliminated mainly through the kidney (Jager *et al.*, 1958). Further studies on the optimal dosage of PAM are required.

In our first patient an immediate stimulation of respiration and lightening of the coma followed the PAM injections during the first two days. This response was not, however, evident later. This phenomenon may be explained by the fact that the dialkyl - phosphorylated acetylcholine - esterase, formed initially by the interaction of the phosphate with cholinesterase, is converted on ageing to a monoalkyl derivative highly resistant to PAM (Hobbiger, 1961). With the dimethylphosphorylated

enzyme this process is complete after six hours (Hobbiger, 1961). It may be concluded that in severe organophosphate poisoning, large doses of PAM should be used from the outset in order to obtain the maximum effectiveness of the oxime.

Diacetyl monoxime (DAM), unlike PAM, has been shown to appear in the cerebrospinal fluid within one hour after intravenous administration (Jager *et al.*, 1958). As phosphamidon and compound II depress the activity of brain cholinesterase more than that of serum cholinesterase (Jaques and Bein, 1960), a therapeutic trial with DAM seems to be worth while in cases of phosphamidon poisoning. There is, however, no unanimity as to the effectiveness of DAM in organophosphate poisoning (Milthers *et al.*, 1963; Namba, 1961).

With the increasing use of organophosphate insecticides, the possibility of poisoning should be kept in mind in cases of suicide and when confusion or coma of uncertain origin develop, especially in agricultural workers. In organic phosphate poisoning, steps should be taken to secure a free airway and assure a proper ventilation as first-aid measures.

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