Patients with retinitis pigmentosa and neurological abnormalities detected on screening

Case No	Age (years)	Clinical findings
		Group 1 (with deafness)
26*	65	Deaf, diminished vibration sense in feet, diminished ankle jerks
37	70	Deaf, old right cerebrovascular accident
42*	40	Deaf, anosmia, ataxia, diminished tendon jerks
45*	34	Deaf, mild ataxia
		Group 2 (without deafness)
1	60	Vertebrobasilar ischaemia
5*	39	Small pupils, absent ankle jerks
12	65	Myasthenia gravis
16	36	Right hemiparesis (mitral valve prolapse)
21	62	Dementia, epilepsy, spinocerebellar degeneration, red ragged myopathy
30	62	Disc prolapse L4-5, ulnar nerve palsy
40*	31	Ataxia, mild sensory neuropathy
44*	59	Diminished peripheral sensation, diminished ankle jerks
46	11	Laurence-Moon-Biedl syndrome
55	16	Congenital sensory neuropathy

*Clinical suspicion of heredopathia atactica polyneuritiformis.

deteriorating retinitis pigmentosa, and deafness. She had suffered an acute episode of ataxia after a viral illness. Examination showed pes cavus, anosmia, retinitis pigmentosa, small reacting pupils, nerve deafness, wasting of the small muscles of the hands, diminished tendon reflexes, and reduced sensation in the feet. She was ataxic on heel and toe walking and coordination was poor in all limbs. Nerve conduction studies disclosed a mild sensory and motor polyneuropathy. The plasma phytanic acid concentration (1·1 mmol/l; 34 mg/100 ml) declined to 0·2 mmol/l (7 mg/100 ml) with a low phytanic acid diet.[4]

Comment

This is the first time that heredopathia atactica polyneuritiformis has been diagnosed by a screening procedure. The signs and symptoms were mild and the patient was much less ill than is usual at first presentation. Retinitis pigmentosa is present in all cases of heredopathia atactica polyneuritiformis and is not affected by short term changes in plasma phytanic acid concentration. Long term control cannot improve an already damaged retina, but early diagnosis and treatment, by limiting phytanic acid in the diet, will prevent the onset of polyneuropathy and may prevent deterioration in vision.

We conclude that it is important and practicable to screen patients with retinitis pigmentosa for heredopathia atactica polyneuritiformis. Fifty two patients were surveyed, of whom 17 had neurological abnormalities, but only six of them had signs compatible with heredopathia atactica polyneuritiformis. By looking in particular for any symptom or sign of anosmia, deafness, neuropathy, or ataxia a population may be identified in whom phytanic acid concentrations should be measured. It is therefore practical for those without special neurological skills to perform a quick and simple screening programme on patients with retinitis pigmentosa to select those in whom heredopathia atactica polyneuritiformis should be actively excluded.

We acknowledge the special trustees of Westminster and Roehampton Hospitals for funding this project.

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(*Accepted 18 January 1985*)

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Aluminium phosphide ingestion

Tablets and pellets composed of aluminium phosphide and ammonium carbamate (Phostoxin; marketed in India as Celphos and Quickphos) are used world wide against rodents and other pests in stored grain. Aluminium phosphide exposed to moisture liberates phosphine gas (PH_3), which is highly toxic.[1 2] It dissipates rapidly into the air, leaving very little residue. Such grain is then fit for human consumption.[1] Isolated cases of fatal exposure to phosphine gas have been reported when aluminium phosphide was used as grain fumigant, particularly for the bulk shipment of wheat.[3 4]

We believe that the following is the first reported series of oral ingestion of aluminium phosphide in man.

Present series

From July 1982 to October 1983 15 patients (eight male and seven female) were admitted after ingesting Phostoxin pellets or tablets (58% aluminium phosphide). Phostoxin is freely available for protecting stored grain in Indian households.

The patients were aged 15 to 41 years (average 22·5) and the stated amount of aluminium phosphide ingested ranged from 1·5 to 9·0 g (average 4·7 g). The interval between ingestion and admission to hospital ranged from 30 minutes to 16 hours (average 5·3 hours), and the time interval between ingestion and death ranged from one to 106 hours (average 31 hours). In 13 cases (86%) it was a suicidal attempt.

Repeated vomiting and hypotension occurred in all patients, and 13 were in shock on admission (systolic blood pressure < 90 mm Hg). Other common features were impaired sensorium, restlessness, tachypnoea, pulmonary crepitations, oliguria, anuria, and jaundice. Half the patients had raised blood urea, serum creatinine, serum bilirubin, and transaminase values. Electrocardiographic abnormalities were observed in six of 11 patients tested —supraventricular premature contractions (one patient); widened QRS complex (two); right bundle branch block (one); left anterior hemiblock with atrial fibrillation (one); ventricular premature contractions (one). Severe metabolic acidosis with blood pH values of 6·97-7·31 and bicarbonate values of 4·6-14·5 mmol(mEq)/l were present in all six patients tested.

All the patients were given supportive treatment, gastric lavage, and continuous dopamine infusion to combat shock. Eleven of the 13 patients in shock did not respond to dopamine and subsequently died. Haemodialysis was given to one patient who developed acute renal failure, and the patient survived.

Gross examination in the four cases that came to necropsy showed congestion of most organs. The mucous membrane of the upper gastrointestinal tract was congested in all, and in two cases haemorrhagic fluid was present in the stomach. Lungs were congested and heavy.

Histological examination of liver in six cases (four necropsy, two biopsy samples) showed mild fatty infiltration (three), areas of centrizonal necrosis (two) with haemorrhages in one, and small granulomas consisting of lymphocytes, a few macrophages, and occasional polymorphonuclear cells (one). The kidneys showed medullary congestion in one necropsy sample and hydropic degeneration of tubular epithelium in another. Lungs showed non-fibrinous pulmonary oedema in two cases. Brain and myocardium appeared to be normal.

Comment

These cases show that aluminium phosphide when ingested is highly toxic. The clinical and pathological features, mainly confined to the gastrointestinal tract and respiratory, cardiovascular, and central nervous systems, were thought to be due to metabolic changes. The most striking clinical feature was the severe hypotension in all cases. This has not been reported after exposure to phosphine gas,[3 4] though other clinical features have been noted.

The mortality in our series was very high. Eleven (73%) of the 15 patients died, but death was not related to the amount of Phostoxin ingested. We cannot explain this, unless the stated amounts ingested were incorrect. Death did not relate to the time interval between ingestion of the poison and admission to hospital. The only clinical feature which differentiated non-survivors from survivors was persistent shock not responding to dopamine infusion. Routine biochemical investigations did not help in differentiating survivors and non-survivors, except that metabolic acidosis was more severe in those who died.

The necropsy finding of congestion of most organs in this series has also been observed after phosphine inhalation.[3 4] Changes in the liver, however, have not been reported. Areas of centrizonal necrosis in two cases with haemorrhages in one may have been due to shock.

The mechanism of poisoning after ingestion of aluminium phosphide is presumably the liberation of phosphine gas in the body. Phosphine has been detected in the expired air of rats fed on zinc phosphide in excess of LD_{50} (40·5 (±2·9) mg/kg).[2] The exact mechanism of

action of phosphine in man is not known. It has, however, been found to cause non-competitive inhibition of cytochrome oxidase of mitochondria in mouse liver, housefly, and granary weevil.[5]

Since the mortality is so high and there is no specific antidote, we suggest that a less toxic but equally effective agent should be sought to replace this lethal substance.

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(*Accepted 8 January 1985*)

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Severe cutaneous reactions to captopril

Captopril is an angiotensin converting enzyme inhibitor used to treat hypertension and cardiac failure. Cutaneous reactions to captopril are common, occuring in about 12% of patients treated for hypertension,[1] and generally thought to be mild and self limiting; they include angio-oedema, a pruritic maculopapular eruption, a rash resembling pityriasis rosea,[1] mild toxic erythema,[2] and exfoliative dermatitis.[3] None of these reactions was confirmed by challenge. We recently saw a more serious and extensive pattern of eruption develop during treatment of cardiac failure with small doses of captopril.

Case reports

The table gives details of the four patients reported on.

Case 1—A 59 year old woman was given captopril, up to 75 mg daily, for cardiac failure. After two weeks she developed a pruritic macular eruption, which settled without change in treatment. Four weeks later a scaling erythema that began on her hands and face led to erythroderma. Captopril was withdrawn, and after six weeks the eruption had settled. A challenge dose of captopril 12·5 mg reproduced the eruption in four days, which resolved in two weeks. Her heart failure was subsequently controlled by enalapril.

Case 2—A 57 year old man with insulin dependent diabetes was given captopril 75 mg daily for cardiac failure. After six weeks he developed an urticated scaling erythema of the hands and face that extended to other areas. This lasted for six weeks despite withdrawal of captopril. A challenge dose (12·5 mg) exacerbated the eruption, which resolved in two weeks.

Case 3—An 80 year old man with cardiac failure received captopril, up to 75 mg daily. Three weeks later he developed an eczematous eruption of the hands and arms that led to erythroderma and persisted for four weeks despite withdrawal of captopril. His other treatment was not changed. He died of uncontrollable cardiac failure shortly afterwards.

Case 4—A 63 year old man with cardiac failure was given captopril 75 mg daily. He developed an urticated erythema four weeks later. Allopurinol, which he had taken for two years, and captopril were stopped. The eruption persisted for two weeks, and he died soon afterwards. The pattern and time course of his skin eruption strongly implicated captopril.

Comment

These cases show stages of the same eruption, characterised by an urticated erythema with eczematous features leading to erythroderma. The delayed onset, relentless progression, and intractability of the eruption after withdrawal of captopril were consistent features. A single challenge dose of 12·5 mg reproduced the reaction. Biopsy showed acute or acute on chronic dermatitis with perivascular inflammation. Immunofluorescence studies yielded negative results.

This pattern of eruption was different from those previously described, which were thought to be pharmacological in nature, probably due to inhibition of inflammatory mediator metabolism by angiotensin converting enzyme, and were dose related.[1]

This new eruption seems to be a truly allergic response to captopril reproducible with one dose and not dose related. The patients had impaired renal function, but even so captopril 75 mg daily is not a high dose, although delayed clearance may have contributed to the intractability of the eruption. The delayed pattern of onset suggests a photosensitive element, and as the patients were receiving several drugs an interaction with captopril was also possible. All these factors may have affected the final pattern of eruption, and the sulphydryl group of the captopril molecule, not present in enalapril, may have been the allergenic focus, as has been previously suggested.[4]

We believe that these four cases show a new, severe pattern of eruption due to captopril as used to treat cardiac failure. If the potential of angiotensin converting enzyme inhibitors is to be exploited in the next five years[5] we must be sure that each new therapeutic indication is not accompanied by a new, more serious side effect.

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(*Accepted 7 January 1985*)

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Details of four patients with skin eruption after treatment with captopril up to 75 mg daily

Age (years) and sex	Eruption	Time course of eruption	Duration of captopril treatment	Other drugs (daily doses)	Abnormal biochemical results (mmol/l)	Result of challenge	Result of biopsy
59 F	Erythroderma	Onset six weeks after captopril started. Lasted six weeks after withdrawal	4 months	Frusemide 120 mg Warfarin	Urea 11·3 Creatinine 183	Positive (but no recurrence with enalapril)	Acute on chronic dermatitis with infiltrate of polymorphs and eosinophils. No immunofluorescence
57 M	Urticated erythema	Onset six weeks after captopril started. Lasted six weeks after withdrawal	2 months	Frusemide 120 mg Digoxin 0·25 mg Isosorbide 60 mg Insulin	Urea 13·8 Creatinine 190	Positive	Acute on chronic dermatitis with polymorphic and lymphocytic infiltrate. No immunofluorescence
80 M	Erythroderma	Onset three weeks after captopril started. Lasted four weeks after withdrawal	4 weeks	Frusemide 120 mg	Urea 23·1 Creatinine 428	Patient died before challenge	Acute dermatitis with perivascular eosinophilic infiltrate. No immunofluorescence
63 M	Urticated erythema	Onset four weeks after captopril started. Lasted two weeks after withdrawal	5 weeks	Frusemide 250 mg Hydralazine 75 mg Digoxin 0·125 mg Warfarin Allopurinol 200 mg	Urea 19·3 Creatinine 211	Patient died before challenge	Acute dermatitis with perivascular polymorphic and eosinophilic infiltrate. No immunofluorescence

Conversion: SI to traditional units—Urea: 1 mmol/l ≈ 6 mg/100 ml. Creatinine: 1 mmol/l ≈ 11·3 mg/100 ml.