Ethylene glycol poisoning

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Summary

Although an uncommon cause of death in Great Britain, ethylene glycol poisoning is potentially serious in that renal and cardiopulmonary failure and central nervous system dysfunction can occur when doses of the order of 100 ml or more are ingested. A case is described in which a child who swallowed approximately 100 ml of ethylene glycol was treated by prolonged peritoneal dialysis. In addition, measures were taken to correct a marked acidosis. Substantial amounts of ethylene glycol were removed by the dialysis fluid and the child made a complete physical and mental recovery.

ETHYLENE glycol, $(\text{CH}_2\text{OH})_2$, is a colourless, odourless, water-soluble liquid that has a variety of commercial applications. It is, however, most commonly used as an anti-freeze fluid to protect car radiators. It has been suggested that its sweet taste and its ready availability have contributed to its popularity as a suicide agent and as a poor man's substitute for alcohol (Parry and Wallach, 1974). Ethylene glycol came into widespread use in the 1920's and the first case of poisoning was described in 1930 (JAMA, 1930). The toxicity of the glycols was, however, not fully appreciated until 1937 when seventy-six people died following the use of elixir of sulphanilamide which contained 72% diethylene glycol (Geiling and Cannon, 1938). It is appalling that in 1969 seven children died in Cape Town as a result of the ingestion of an hypnotic also containing this substance (Bowie and McKenzie, 1972).

Deaths from ethylene glycol poisoning are uncommon in Great Britain: there have only been twelve reported in a period of 29 years (1945-73). In contrast forty to sixty deaths occur each year in the U.S.A. (Haggerty, 1959). It is thought that the minimum lethal dose of ethylene glycol is about 100 ml for an adult, although recovery has been reported after the ingestion of 240 ml (Kahn, 1950) and 400 ml (Seeff *et al.*, 1970). The pathogenesis of the clinical manifestations of this form of poisoning is now better understood. We therefore report a case of

ethylene glycol poisoning in a child who subsequently recovered, despite the development of renal insufficiency, and describe the clinical presentation and management of ethylene glycol poisoning.

Case report

A previously healthy child of $2\frac{1}{2}$ years ingested about 100 ml of ethylene glycol during the evening of 12 March 1975. The child vomited but seemed otherwise well when his parents put him to bed. The next morning, however, he was found unconscious in bed and taken to the local hospital. On arrival he was collapsed, semi-conscious, and hyperventilating. His pulse rate was 140/min, BP 30/0 mmHg and scattered crepitations were present in both lung fields. He was given calcium gluconate intravenously; an infusion of ethyl alcohol was commenced and a diuresis was induced with frusemide. Subsequently, the child had several haematemeses and his level of consciousness deteriorated. In addition he was oliguric (150 ml urine in 24 hr) and haematuria and albuminuria were noted. Further investigations revealed a haemoglobin of 10.8 g/100 ml, a leucocytosis of $14.4 \times 10^9/\mu\text{l}$ (72% neutrophils), a serum bicarbonate of 3.3 mmol/l (base excess -30), an arterial pH of 6.87 and a urea of 12.36 mmol/l. He was transferred to the Paediatric Renal Unit at Guy's Hospital for peritoneal dialysis which was commenced on 13 March 1975 and continued for 8 days. The next day the child had six convulsions; a further five occurred on 15 March 1975 but all were controlled by diazepam. The child was thereafter given phenobarbitone. He remained irritable, developed a squint and had athetoid movements. By 16 March 1975 the urine output had increased to 2 l/day and the level of consciousness had begun to improve. The child later developed a urinary tract infection but by 17 days after admission he had made a complete physical and mental recovery. During the 8 days of dialysis (71.5 l) 26.9 g ethylene glycol (equivalent to 30 ml approximately) and 73 mg oxalate (between 10 and 40 mg oxalate are normally excreted in the urine each day) were removed.

Methods

Ethylene glycol was measured in the dialysis fluid by a gas chromatographic method. Aqueous standards were prepared containing from 200 to 1,000 mg of ethylene glycol/l. To 1 ml of each of these standards and the sample were added 1 ml aliquots of propane 1,2-diol (1,000 mg/l in water) internal standard. After mixing thoroughly, 3 μ l of the solution were injected on to a Poropak Q column operating isothermally at 180°C. The calibration curve derived by plotting concentration against the ratio peak area of ethylene glycol: peak area of propane 1,2-diol was linear over the chosen range and the concentration of ethylene glycol in the sample was calculated by direct reference to this curve. Oxalate concentration was measured by the fluorimetric procedure of Zarembski and Hodgkinson (1965).

Comment

This child illustrates many of the features of ethylene glycol poisoning (Tables 1 & 2) including vomiting, haematemesis, coma, convulsions, ophthalmoplegia, tachycardia, tachypnoea, pulmonary oedema and acute renal damage. Investigations demonstrated leucocytosis, acidosis, uraemia, haematuria and albuminuria. Large amounts of ethylene glycol were removed by dialysis.

TABLE 1. Clinical features of ethylene glycol poisoning

Usual time sequence after ingestion	Clinical features
30 min–12 hr	Patient appears intoxicated with alcohol (but no alcohol on the breath). Nausea, vomiting, haematemesis. Coma and convulsions (often focal). Nystagmus, ophthalmoplegias, papilloedema, optic atrophy, depressed reflexes, myoclonic jerks, tetanic contractions.
12–24 hr	Tachypnoea, tachycardia, mild hypertension, and cyanosis. Pulmonary oedema, congestive cardiac failure.
24–72 hr	Flank pain and costovertebral angle tenderness. Acute tubular necrosis.

TABLE 2. Typical laboratory investigations in ethylene glycol poisoning

Investigation	Abnormality
White cell count	Raised (10–40 $\times 10^3/\mu$ l)—predominantly neutrophils
Serum bicarbonate	Reduced (may be < 10 mEq/l)
Serum calcium	Reduced
Serum potassium	Raised
Urinalysis	Low specific gravity Proteinuria Crystalluria (Ca oxalate) Microscopic haematuria
Cerebrospinal fluid	Compatible with meningoencephalitis

Metabolism of ethylene glycol

Ethylene glycol itself appears to be non-toxic. It has no effect on respiration, the citric acid cycle or other biochemical pathways until metabolized (Bachmann and Golberg, 1971). Metabolism takes place in the liver and kidney and proceeds as shown in Fig. 1. The toxicity of ethylene glycol may be explained on the basis of the accumulation of three metabolic products:

(i) Aldehydes, which inhibit oxidative phosphorylation, respiration and glucose metabolism (Bachmann and Golberg, 1971; Kun, 1952; Lamothe, Thuret and Laborit, 1971), protein synthesis (Kun, 1952), DNA replication and ribosomal RNA synthesis (Klamerth, 1968), central nervous system respiration (Lamothe *et al.*, 1971), serotonin metabolism (De Breyer, Ortiz and Soehring, 1970) and alter central nervous system amine levels (Laborit *et al.*, 1971). The cerebral symptoms that occur 6–12 hr after the ingestion of ethylene glycol (Table 1) coincide with the maximum production of aldehydes.

(ii) Oxalate, which may produce renal damage and acidosis. It is thought, however, that only about 1% of ethylene glycol is converted to this compound (McChesney *et al.*, 1971). The production of oxalate is also important in that it may chelate with calcium ions forming relatively insoluble calcium oxalate crystals; hypocalcaemia may result. As well as renal intratubular obstruction, impairment of cerebral function follows deposition of calcium oxalate.

(iii) Lactic acid, which is produced as a result of large amounts of nicotinamide adenine dinucleotide being formed during the breakdown of ethylene glycol (Oliva, 1970). In addition some of the condensation products of glyoxylate metabolism inhibit the citric acid cycle thereby increasing lactic acid production (Fig. 1).

Clinical features

Berman, Schreiner and Feys (1957) have suggested that the clinical syndrome of ethylene glycol poisoning may manifest itself in three stages (Table 1). If the patient survives the initial 24–72 hr after ingestion, when cerebral and cardiopulmonary symptoms are predominant, renal failure may become evident. The severity of each stage and the progression from one to the other depends very largely on the amount of ethylene glycol ingested. Death may occur in any of the three stages.

Diagnosis

Ethylene glycol poisoning should be strongly suspected in the presence of:

- An apparently inebriated patient with no alcohol on the breath.
- Coma associated with metabolic acidosis and a large anion gap.

Fig. 1. Pathways of metabolism of ethylene glycol showing mechanism of production of lactic acidosis.

(iii) Urinalysis demonstrating calcium oxalate crystalluria.

The suspicion may be confirmed by measuring the serum levels of ethylene glycol and oxalate acid. Other abnormalities which may be found on investigation are shown in Table 2.

Pathology

In patients who have died within 72 hr of ingestion of ethylene glycol there is considerable cerebral oedema, capillary engorgement and haemorrhage, evidence of chemical meningoencephalitis (Pons and Custer, 1946; Hagemann and Chiffelle, 1948), Betz's cell and Purkinje's cell chromatolysis, and perivascular and meningeal deposition of calcium oxalate crystals. It is of interest that rats given regular small doses of ethylene glycol have cerebral oxalate deposits in the brain but no symptoms (Lyon, Borden and Vermeulen, 1966); whereas rats given the aldehyde derivatives of ethylene glycol may have severe central nervous system symptoms in the absence of crystals (Bove, 1966). It would appear, therefore, that although the central nervous system symptoms are related to ethylene glycol and its aldehyde derivatives, the deposition of calcium oxalate further impairs cerebral function.

Pathologically the lungs show generalized oedema with early bronchopneumonic changes. Widespread petechial haemorrhages are found in the pleura, lungs, heart and pericardium. Cardiac dilatation may occur together with degenerative myocardial changes. Occasionally, oxalate crystals have been found in the lung parenchyma.

The proximal tubules may become dilated and degeneration of tubular epithelium is seen in those

patients with renal involvement. Calcium oxalate crystals and fat droplets are found in tubular epithelial cells. Distal tubular degeneration may also be present, although less pronounced. Glomerular damage is not a prominent feature but increased cellularity, thickened basement membranes and granular deposits in Bowman's membrane are found. Animal experiments suggest that the tubular damage is due to the aldehyde derivatives of ethylene glycol (Bove, 1966) rather than, or as well as, calcium oxalate. Yet it seems that ethylene glycol is most toxic to those animal species which oxidize it most readily to oxalate, despite the small percentage metabolized along this pathway.

Treatment

Early diagnosis and appropriate therapy can significantly reduce the mortality from ethylene glycol poisoning. Treatment may include:

(i) Supportive measures to combat shock and respiratory distress.

(ii) Correction of the metabolic acidosis. Animal work has shown that the LD₅₀ for rats poisoned with ethylene glycol and then treated with sodium bicarbonate is over four times that for untreated rats. Parry and Wallach (1974) have suggested that while the correction of the acidosis does not seem to alter the depth of coma in humans, it enhances survival.

(iii) Correction of hypocalcaemia.

(iv) Use of ethyl alcohol as a competitive inhibitor of ethylene glycol metabolism. Ethyl alcohol, the normal substrate of alcohol dehydrogenase, inhibits the oxidation of ethylene glycol by liver alcohol dehydrogenase (Von Wartburg, Bethune and Vallee,

1964). The value of this treatment has been demonstrated (Wacker *et al.*, 1965). As the half-life of ethylene glycol is about 3 hr in humans (McChesney *et al.*, 1971), an ethanol infusion should be commenced as soon as possible after ingestion if it is to be effective. Sufficient alcohol (5–10 g ethyl alcohol hourly may be required) is given to maintain the blood alcohol level between 100 and 200 mg/100 ml.

(v) Dialysis. Schreiner *et al.*, (1959) have suggested that dialysis is indicated both to remove ethylene glycol and to treat uraemia which often ensues. It is known that oxalate is also dialysable, although poorly (Walls, Morley and Kerr, 1969) and it is believed that the aldehyde derivatives of ethylene glycol may also be removed in this way. Dialysis was first employed in the treatment of ethylene glycol poisoning in 1959, although the patient so treated by Schreiner and his colleagues was not dialysed until the eleventh day after admission. Since then a number of patients have had the uraemic complications treated with dialysis (Levy, 1960; Hagstam *et al.*, 1965; Collins *et al.*, 1970; Gutman, Hamon and Striker, 1970; Seeff *et al.*, 1970; Gallyas, Járay and Csata, 1971; Aquino and Leonard, 1972); few, however, have been dialysed early to remove ethylene glycol and its metabolites (Wacker *et al.*, 1965; Joly *et al.*, 1968; Underwood and Bennett 1973; Parry and Wallach, 1974). Our own patient demonstrates the advantages of early intervention in that significant amounts of ethylene glycol were removed.

Acknowledgments

We are grateful to Dr C. Chantler and Dr A. Piesowicz for allowing us to publish details of this patient, and to Dr R. Goulding of the Poisons Unit for considerable advice and encouragement.

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Postgraduate Medical Journal (September 1976) **52**, 602-604

Stricture of the descending colon due to schistosomiasis

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Summary

An example of a localized non-fibrous stricture of the colon due to *Schistosoma mansoni* infection is reported. The radiological and colonoscopic features are described. After treatment of the infection with niridazole, the stricture resolved completely. The pathogenesis of bowel lesions in schistosomiasis is briefly discussed.

Introduction

The pathological changes in schistosomiasis *mansoni* result from immune responses to ova retained in host tissues (Warren, 1972). The granulomata formed around ova resolve slowly with varying amounts of residual fibrosis. Gross colonic lesions are, however, remarkably rare (Manson-Bahr, 1958; Cheever and Andrade, 1967). A case is reported of *Schistosoma mansoni* infection which resulted in a localized stenosis in the descending colon. This stenosis regressed following anthelmintic treatment.

Case report

A 32-year-old Negro male from St Lucia, came to Britain in 1968. He presented at the Hospital for Tropical Diseases in 1970 with a history of blood in the stools. Physical examination was unremarkable, apart from schistosomal tubercles seen in the rectum on sigmoidoscopy. Viable ova of *S. mansoni* were found in the stool. He was treated with niridazole 500 mg, thrice daily for 10 days, but was lost to

follow-up. The patient presented with the same history in April 1974. He had returned to St Lucia in October 1973, for 4 weeks, but had not been exposed to fresh-water pools or streams. Physical examination, including sigmoidoscopy, was normal. Viable ova of *S. mansoni* were found in the stool. Treatment with niridazole was repeated. Immediately after finishing the course of anthelmintic, a barium enema was performed. This showed marked angulation in the mid-descending colon at the mid-point of a smooth, narrowed segment with tapering extremities, suggesting a benign lesion (Fig. 1).

Four weeks after treatment, colonoscopy was performed. This confirmed the stricture in the mid-descending colon, but the instrument was passed on to the caecum. The mucosa was friable distal to the splenic flexure with friability most marked at the level of the stricture. Biopsies from this area showed remnants of schistosome ova.

A repeat barium enema 3 months after treatment showed only slight indrawing of the lateral wall of the descending colon at the site of the initial stricture with normal distensibility and alignment of bowel (Fig. 2). Further examinations of the stool for schistosome ova have been negative.

Discussion

The appearance of the colonic mucosa in schistosomiasis *mansoni* is usually normal (Manson-Bahr, 1958; Gelfand, 1963). Most ova pass into the lumen