

DIETHYLENE GLYCOL POISONING IN NIGERIAN CHILDREN

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Summary

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Clinical and pathological features in 23 children who developed acute renal failure from what was subsequently proven to be diethylene glycol poisoning are presented. Symptoms of cases included anuria, fever, diarrhoea and vomiting. Eighteen (78.3%) had hepatomegaly, 11 (47.8%) had evidence of respiratory distress and 7 (30.4%) had acidotic breathing. Seven (30.4%) of the children were dehydrated on physical examination. Alteration in the level of consciousness was observed in 13 (56.5%) children. The major biochemical abnormalities were acidosis and elevated blood urea nitrogen. Although serum bilirubin was normal in those in whom it was determined, the liver enzymes were elevated in the 2 patients in whom they were determined. Patients were treated as for acute renal failure of renal origin and four children had peritoneal dialysis. Twenty-two (95.6%) of the patients died and outcome was unknown in the remaining patient who was discharged against medical advice. Autopsies in 7 patients revealed a characteristic nephrotoxic acute tubular necrosis and centrilobular hepatic necrosis characterized by vacuolar and ballooning degeneration of the metabolically active renal tubular cells and hepatocytes.

Introduction

One of the earliest reports of diethylene glycol poisoning in the literature was that of the death of at least seventy-six people in various localities in

the United States of America in 1937 following poisoning by a drug named "Elixir of Sulfanilamide Massengill", which was shown by analysis to be a 10% solution of sulfanilamide in about 72% diethylene glycol¹⁻⁵.

Diethylene glycol is a common industrial solvent which may assume medical importance when used in error in pharmaceutical preparations or used illegally to sweeten wine^{1,6}.

In experimental animals given diethylene glycol, Von Oettingen and Jirouch⁷ noted hydropic degeneration of the kidney. Haag and Ambrose found that concentrations of diethylene glycol ranging from 3% to 10% proved rapidly fatal while

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lower concentrations (0.03% to 1%) did not significantly affect the growth of experimental animals². In humans, major clinical manifestations of diethylene glycol poisoning reported in the literature include symptoms and signs suggestive of renal, hepatic and lung toxicity with histopathological evidence of damage in these organs^{4,9}. To the best of our knowledge there has been no previous report of diethylene glycol poisoning in Nigeria until July through August 1990 when there was an outbreak of acute renal failure deaths in children due to diethylene glycol poisoning. This communication therefore presents the clinical and pathological features found in the children that died of diethylene glycol poisoning in the University College Hospital, Ibadan.

Materials And Methods

Between Friday, 24th of August, 1990 and Wednesday, 19th of September, 1990, a total number of 23 children were referred from a general hospital in Ibadan to the Children's Emergency Ward of the University College Hospital (UCH), Ibadan Nigeria with a history of anuria following treatment at the referring hospital for various febrile illnesses. Details of clinical features and drug therapy in the referring hospital were recorded for each case. The biochemical investigations done included estimation of serum electrolytes, blood urea, and in two cases liver enzyme studies were carried out. Haematological investigations included determination of packed cell volume and white blood counts. The clinical findings, treatment and outcome in these patients are presented. Autopsy findings are available for seven of the patients whose parents had given consent for postmortem examination. A left over sample of the paracetamol syrup retrieved from 2 of the mothers, along with the ingredients used for its preparation (raspberry syrup, amaranth syrup, paracetamol powder and a sample labelled "Propylene glycol") in the referring hospital were sent to the Centers for Disease Control (CDC) Atlanta, Georgia for analysis by one of us (RAS).

Results

Clinical Features

The 23 children in our study included 12 males and 11 females. Their ages ranged from 2 to 33 months with a mean of 12.2 months (Table 1).

TABLE 1

Age Distribution of the Patients

AGE(months)	NO	PERCENTAGE
0 - 5	6	26.1
6 - 11	4	17.4
12 - 23	11	47.8
24 and over	2	8.8
TOTAL	23	100.0

All the 23 children initially presented to the outpatient department of the referring institution with fever for which they had various types of medication including paracetamol syrup compounded in the referral hospital. Although it was not possible to ascertain the exact dose of the paracetamol syrup given to each child, in those for whom dosage ingested was reported, it ranged from 5ml three times daily for one day (15mls) to 5ml three times daily for four days (60ml). The presenting symptoms at the UCH are shown in Table 2.

TABLE II

Presenting Symptoms

SYMPTOMS	NO. OF PATIENTS	% OF TOTAL
Anuria	23	100
Fever	23	100
Diarrhoea	9	39.1
Vomiting	7	30.4
Cough	4	17.4

All the 23 patients had anuria, the duration of which ranged from 1 to 6 days with a mean of 3 days. The interval between the ingestion of drugs and

anuria ranged from 2 to 8 days with a mean of 5.2 days. Nine of the patients had diarrhoea and 7 had vomiting. Clinically, 12 of the children were well nourished, 7 were undernourished while 4 were malnourished according to the Wellcome classification¹⁰

TABLE III
Presenting Signs

SYMPTOMS	NO. OF PATIENTS	% OF TOTAL
Hepatomegaly	18	78.3
Tachypnoea	11	47.8
Acidotic breathing	7	30.4
Dehydration	7	30.4
Depression of consciousness	13	56.5
Irritability	2	8.7

Table 3 shows the presenting signs detected in our patients. Eighteen of them had hepatomegaly with the liver size ranging from 2 to 10cm below the costal margin. All the livers felt firm in consistency. Tachypnoea occurred in 11 patients including 7 patients with acidotic breathing. Six of the patients were dehydrated. In 13 patients there was alteration of the level of consciousness, while only 2 patients were noted to be irritable.

Laboratory Results

Of the patients who had serum electrolytes and urea done, 12 had metabolic acidosis with serum bicarbonate of 16mmol/L or less. Potassium level was normal in 11 patients. Two patients had very low potassium level of 1.3 and 1.4mmol/L respectively, and a third patient had hyperkalemia (6mmol/L). Urea levels in the 14 patients ranged from 60-260mg/100ml with a mean of 141mg/100ml. Two patients had liver function tests done and both had elevated liver enzymes, but normal serum bilirubin. Of the 22 patients who had packed cell volume (PCV) determination, 6 were anaemic with a PCV of 20% or less. There was leukocytosis in 4 of the 7 patients who had white cell count determination with a total count ranging

from 12,800 to 21,900. Differential white cell counts were not done.

Treatment

Treatment consisted of rehydration and the correction of metabolic acidosis. All patients were treated as for acute renal failure of renal origin. This treatment included peritoneal dialysis in 4 patients.

Outcome Of Treatment

There was no significant improvement in response to dialysis or any other therapy in all the patients, 22 out of the 23 patients were known to have died. The outcome in the remaining one patient was not known because the parents took the child away without the consent of the attending clinician. The mean number of days between admission and death was 3 days. Seven patients died within 24 hours of admission and only 6 died after 3 days (Table 4). Four of the 6 patients who died after 3 days had dialysis. Two survived for 5 days, while 2 survived for 7 days after admission.

TABLE IV

Interval Between Admission and Death		
INTERNAL	NO. OF PATIENTS	% OF TOTAL
Over 24 hours	7	30.4
1 - 3 days	10	43.5
Over 3 days	6	26.1

Result Of C Analysis Of Medications Ingested

Diethylene glycol was identified in the paracetamol syrup retrieved from some mothers and in one of the ingredients used in compounding the paracetamol syrup using proton nuclear magnetic resonance and fast atom bombardment/mass spectrometry at the Centers for Disease Control (CDC), Atlanta, Georgia, USA. The diethylene glycol found to be the toxic ingredient had been wrongly labelled "propylene glycol".

Autopsy Findings

Out of the 22 patients who died, autopsies were performed on 7 of them. Pathologically, the two organs selectively poisoned by diethylene glycol in our cases were the kidneys and the liver.

Kidney

In all the 7 autopsies, both kidneys macroscopically appeared pale and swollen. Their cut surfaces showed a striking corticomedullary differentiation with a pale edematous bulging cortex contrasting with a congested dark red medulla. Microscopically, there was a characteristic acute tubular necrosis resulting in vacuolation and ballooning of the lining epithelial cells of the cortical proximal and distal convoluted tubules along with the epithelial cells lining the loops of Henle at the corticomedullary junction, (Figure 1). The nuclei visible in some of the ballooned cells appeared pyknotic. The tubular basement membrane appeared intact in most areas as demonstrated by periodic acid Schiff (PAS) stain, but disrupted in some areas with associated interstitial oedema.

In patients who had dialysis we observed that some abortive efforts at regeneration of surviving tubular epithelial cells had resulted in the formation of bizarre epithelial giant cells seen in Figure 2.

Liver

The liver microscopically was soft and pale, appearing yellow or dark-brown in some cases. Microscopically, diethylene glycol strikingly affected the metabolically active hepatocytes causing necrosis characterized by vacuolation and ballooning of the hepatocytes. The nuclei of these latter cells were pyknotic and eccentrically placed. Their cytoplasm was PAS negative (Figures 3 and 4). The effect of diethylene glycol poisoning in the liver appears to start in the cells of the adjoining centrilobular zones, thus forming a peculiar mosaic pattern interspersed by trabeculae or bands of normal hepatocytes. However, in 2 of our cases we observed panlobular ballooning of the hepatocytes possibly due to ingestion of massive doses of diethylene glycol. One of these latter patients had a very severe hypokalemia of 1.4mmol/L (Figure 7).

Other Organs

We observed no direct effect of diethylene glycol poisoning on other organs. However we found bronchopneumonia in 4 of our patients, which probably was the primary cause for presentation to the initial health centre. Interstitial pneumonia and hyaline membrane disease, all secondary to uremia were noted in each of patients, while cerebral oedema was present in 7 patients.

Discussion

There have been reports of diethylene glycol poisoning in human beings from various parts of the world including North America², South Africa⁴, Australia^{11,12}, Spain¹³ and India¹⁴. To the best of our knowledge, death due to diethylene glycol poisoning has not been reported from West Africa. Diethylene glycol can cause death in any age group or sex^{2,4,13,14}. Although most of our patients are children under 3 years of age. Geiling and Cannon² reported cases whose ages ranged from 11 months to 70 years. The compound can cause death when taken orally, as in our cases, when applied topically¹³, or given intravenously¹⁴.

The finding of anuria in all our cases is similar to previous reports^{4,9}. Gastrointestinal symptoms i.e. diarrhoea and vomiting found in our patients were also reported previously, however, the fever and cough found in 100% and 17% of the patients respectively were probably not due to diethylene glycol poisoning but symptoms of the primary illnesses for which the children were taken to hospital outpatient department and given paracetamol syrup. Acidosis, dehydration, hepatomegaly and depression of consciousness found in our patients have been previously reported^{4,9}. Raised blood urea and metabolic acidosis were the most significant biochemical abnormalities, the urea and bicarbonate values in our patients are similar to those in previous reports^{4,9}. Vale and Buckley¹⁵ suggest that metabolic acidosis in diethylene glycol may result from oxidation of the intact molecule by alcohol and aldehyde dehydrogenase. Diethylene glycol poisoning is usually fatal and the clinical course is rapid. It is not clear whether ingestion of sublethal doses of DEG causes residual organ damage. Bowie⁴ reported 100% fatality in hospi-



Figure 1: Section of kidney showing acute tubular necrosis characterised by vacuolation and ballooning degeneration of the tubularepithelial cell (H & E, x 200).

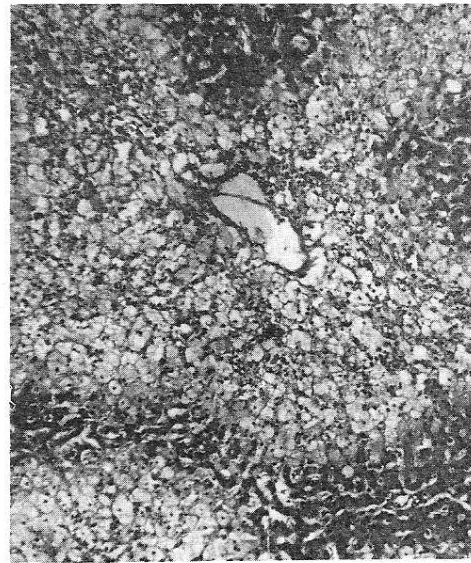


Figure 3: Section of liver showing centrilobular vacuolation and ballooning degeneration of the hepatocytes (H & E, x100)

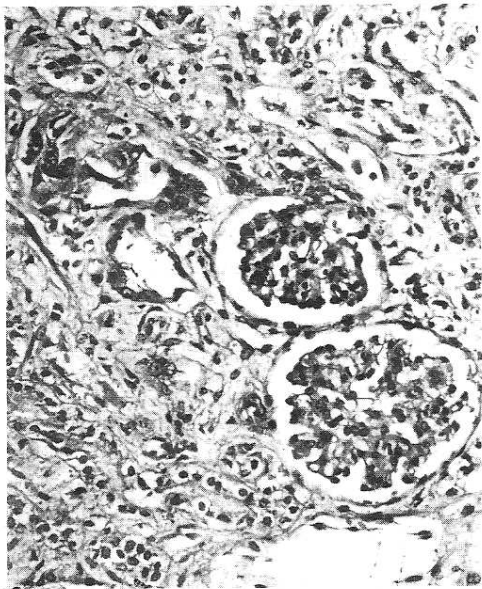


Figure 2: Section of kidney showing acute tubular necrosis with abortive efforts at tubular regeneration. H&E x 200

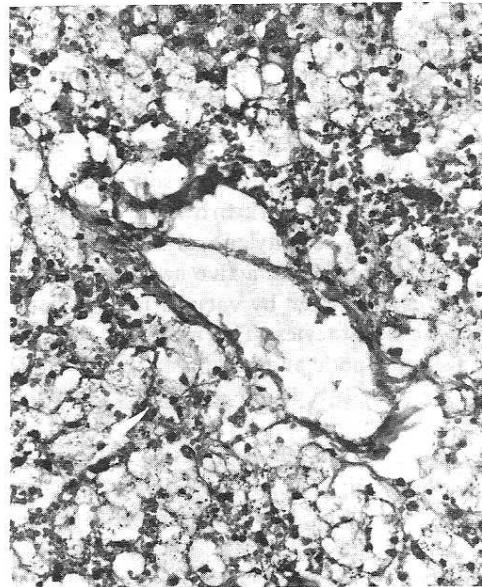


Figure 4: High power view of Fig.3 showing nuclear pyknosis in the ballooned hepatocytes (H & E, x200)

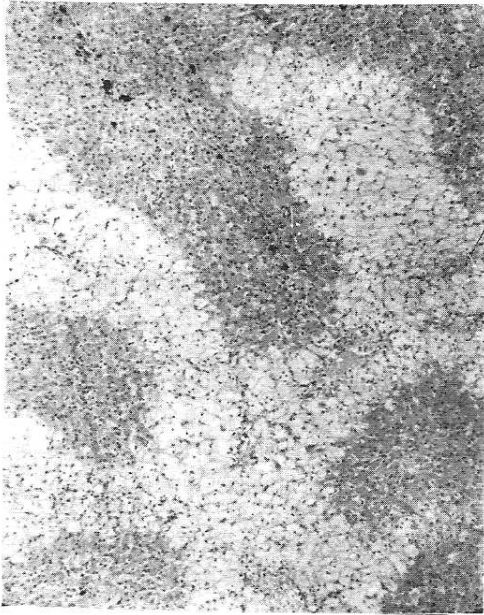


Figure 5: Section of liver showing bridging necrosis between adjoining centrilobular zones to form a characteristic mosaic pattern (H & E, 100)

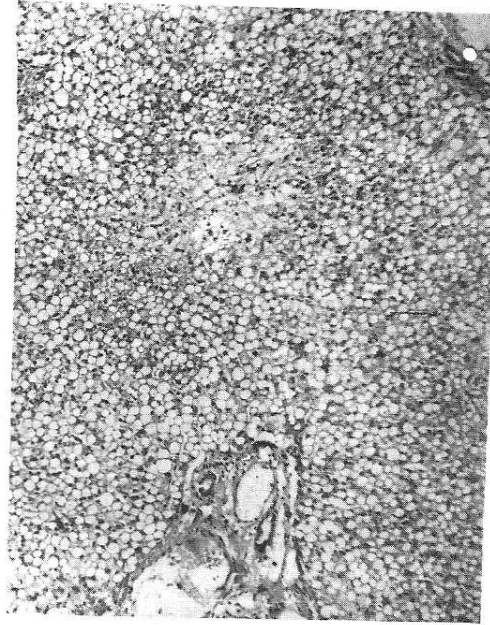


Figure 7: Section of the liver showing panlobular ballooning degeneration of the hepatocytes with centrilobular necrosis (H & E, x 100)

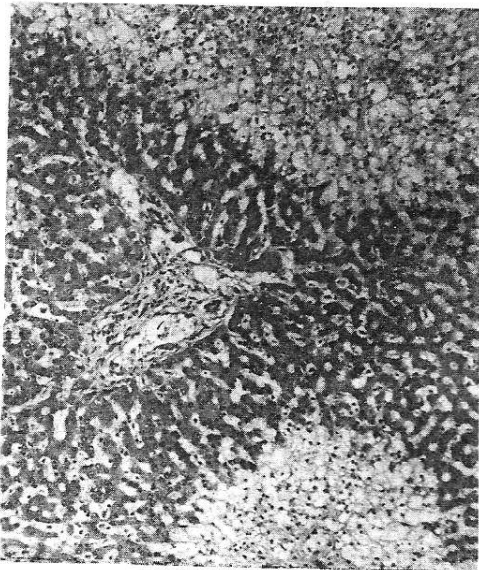


Figure 6: Section of liver showing normal portal tract and surrounding trabeculas of normal periportal hepatocytes (H & E, 100)

talised patients and the average time from admission to death of 4 days. This is confirmed by our finding in which 22 of 23 patients were known to have died with 73.9% of the deaths occurring within three days of admission. A detailed clinicopathological study of 4 cases by Lynch⁹ revealed that diethylene glycol poisoning affected mostly the kidney and the liver. Our current finding have confirmed this observation. In addition to this however, secondary effects of uraemia were found in other organs.

The major problem posed by this disaster is how to prevent recurrence of a similar event in future. A similar event reported from America in 1937² was a major contributory factor to modification of legislation in that country regarding introduction of new drugs. It is hoped that this tragic incident will lead to more stringent control of importation and marketing of pharmaceutical chemicals in Nigeria.

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