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Ethylene Glycol intoxication with and without simultaneous diabetic ketoacidosis: A report of nine cases and review of the literature

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Abstract

Objective: To describe the clinical and biochemical observations made on nine patients with ethylene glycol intoxication (EGI) of whom five presented with simultaneous diabetic ketoacidosis (DKA). **Methods:** A retrospective chart search for discharge diagnosis including the term ethylene glycol intoxication was conducted at University Hospitals of Cleveland Information Services (Cleveland, OH) from 1986 through 1998. Nine (N=9) patients were identified and subsequently divided into two Groups (A & B). Group A included 5 patients with both DKA and EGI. Group B included 4 patients with EGI without DKA. Clinical manifestations and laboratory tests are summarized for both Groups. Serum specimens for all patients were analyzed for ethylene glycol, propylene glycol, methanol, serum ketones, glucose, pH, electrolytes, liver and kidney function tests, lipase, amylase, cholesterol, triglycerides, C-peptide and glycosylated Hb. **Results:** Group A patients presented with more severe hyperglycaemia accompanied by increased insulin requirements, glucose toxicity, more severe osmotic diuresis induced severe dehydration, pre-renal azotemia, transient rhabdomyolysis and hypertriglyceridaemia. Their acute renal failure was fully reversible upon discharge. Finally, the length of hospital stay of patients in Group A was significantly longer than that of Group B patients, although mortality rate was reduced. Permanent and irreversible kidney damage requiring haemodialysis was seen in all Group B patients. **Conclusions:** severe DKA presenting with simultaneous high anion and osmolal gap should prompt suspicion to the hypothetical concomitant EGI, particularly in those patients with a history of alcoholism, depression and past suicidal attempts.

Keywords: *Ethylene glycol intoxication, diabetic ketoacidosis, anion gap, osmolal gap, haemodialysis*

Introduction

Ethylene glycol is a colourless, odourless, water-soluble liquid with a sweet taste resembling some liqueurs, commonly found in radiator-antifreeze, detergent, paints, lacquers and solar collectors, among others. Intoxication is usually due to accidental ingestion, suicide attempt, or consumption as a substitute for ethanol.

Initial diagnosis is frequently delayed if history of ingestion is unavailable. Classical clinical presentation includes central nervous system symptoms (decreased mental status varying from lethargy to obtundation and coma), tachycardia, tachypnea, and acute renal failure.[1-8] The biochemical profile is that of a high anion ([Na]-([Cl] + [HCO3]) and osmolal gap (measured plasma osmolality – calculated plasma osmolality) metabolic acidosis, acute renal failure and the presence of oxalate as well as hyppurate crystals in the urine.[9-16] Haemodialysis, parenteral ethanol, 4-methylpyrazol and bicarbonate infusions have been shown to be useful in eliminating the toxin, blocking its hepatic metabolism and correcting the initial severe metabolic acidosis. Interestingly enough and to the best of our knowledge, the finding of simultaneous occurrence of true EGI and emerging diabetic ketoacidosis (DKA) has not been reported.

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Material and Methods

A retrospective chart search of admissions at University Hospitals of Cleveland Information Services (Cleveland, OH) was conducted in a twelve year period from January 1986 to December 1998. Nine consecutive adult patients were found with the discharge diagnosis of EGI during that period. Their demographic characteristics are depicted in Table 1.

EGI was defined as classical clinical manifestations presenting with a history of ethylene-glycol containing product ingestion and serum concentrations higher than 3 mg/dl.

DKA was defined as a triad including hyperglycaemia-acidosis-ketosis, the primary cause of which is relative or absolute insulin deficiency. According to their biochemical profile on admission, patients were classified as:

Group A (N=5): presenting with DKA and EGI. Gender distribution was M4/F1. Mean±SD age was 41.4 ± 14.6 years. Four out of five were previously known diabetics while two out of five had a previous psychiatric diagnosis. Group B (N=4): presenting with EGI without DKA. Gender

Table 1: Demographic characteristics of patients with ethylene glycol intoxication.

Group	Patient #	Sex	Age	DM	Previous psychiatric diagnosis
A	1	M	34	Yes	No
A	2	M	54	Yes	Schizophrenia
A	3	F	53	Yes	Bipolar disorder
A	4	M	50	No	No
A	5	M	16	Yes	No
B	6	M	32	No	No
B	7	F	52	Yes	Depressive disorder
B	8	M	49	Yes	No
B	9	F	52	No	Schizophrenia

M=male, F=female, DM=diabetes mellitus.

Table 2: Acid-base and biochemical profiles of two groups of patients, one (Group A) with ethylene glycol intoxication and diabetic ketoacidosis, and the other (Group B) with ethylene glycol intoxication only.

	Group A	**Group B**
Glucose (mg/dl)	1305 ± 425	216 ± 154**
C-peptide (ng/ml)	1.31 ± 0.76	NA
HbA1c (%)	19.5 ± 1.2	7.2 ± 2.4**
Lactate (mmol/L)	2.28 ± 0.68	17.3 ± 17.2
B-OH-Butyrate (mmol/L)	6.19 ± 2.24	NA
pH	7.11 ± 0.07	7.22 ± 0.1
HCO3 (mEq/L)	6.60 ± 2.70	7.95 ± 3.0
AG (mEq/L^3)	35.6 ± 6.1	32.4 ± 6.5
OsmG (mOsm/Kg $H2O^3$)	36.24 ± 8.83	49.3 ± 49.4
Ethylene Glycol (mg/dl)	11.7 ± 8.4	172 ± 235
BUN (mg/dl)	62.2 ± 23.6	24.5 ± 15.6*
Creatinine (mg/dl)	3.7 ± 1.1	4.3 ± 1.2
BUN/Creat	16.6 ± 2.5	6.8 ± 1.4**
Uric acid (mg/dl)	15.0 ± 3.8	10.8 ± 5.7
Creatine Kinase (U/L)	6972 ± 610	279 ± 313**
Triglycerides(mg/dl)	1244 ± 940	213 ± 201*
Haematocrit (%)	51.3 ± 6.1	36.1 ± 9.6*
Albumin (mg/dl)	4.0 ± 0.7	3.7 ± 0.4

HCO3:bicarbonate, AG=anion gap, OsmG= osmolal gap, NA= not assessed, B-OH-Butyrate=beta-hydroxy-butyrate. **P<0.003, *P<0.01.

Table 3: Daily insulin requirements/need for parenteral ethanol.

Patient #	Group	IU/Kg/day	IU/24h@D/C	HD	Ethanol drip	Methyl-pirazol	Permanent HD
1	A	4.07	90	-	-	-	no
2	A	2.6	26	+	+	+	no
3	A	0.55	55	-	-	+	no
4	A	2.19	100	+	+	-	no
5	A	1.51	215	-	-	-	no
6	B	0	0	+	+	+	+
7	B	0	0	+	+	+	+
8	B	0	0	+	+	+	+/deceased
9	B	0	0	+	+	+	+

IU= insulin units, Kg=kilogram, IU/24h@D/C= insulin units per day at discharge, HD=haemodialysis

distribution was M2/F2. Mean±SD age was 46.3 ± 8.3 years. Two out of four were previously known diabetics while 2 out of four had previous psychiatric diagnosis.

Serum electrolytes, complete blood count, amylase, lipase and other biochemical results were performed using a routine hospital serum multiple analyzer. Ethylene glycol determination was performed using a sensitive enzymatic assay GCMS from COBAS-BIO/*Roche (Nurtely, NJ, USA, City/State*) (17*).* The lower detection limit is 3 mg/dl and linearity is assured in the 3-200 mg/dl range (value of high standard). Interfering substances include: Glycerol, 1.2-Propane-diol, 2.3-Butane-diol, 1.4-Butane-diol, inositol, isopropanol, propylene glycol and sorbitol. The latter can produce falsely elevated results if present in the serum sample. Formulas for anion and osmolal gap calculation are the following: Anion gap= [Na] – ([Cl] + [HCO3]); NV=12 ± 2 mEq/L. Osmolal gap= measured plasma osmolality – calculated plasma osmolality; NV= 10 ± 2 mOsm/Kg. Calculated plasma osmolality=2 X [Na] + [Glucose]/18 + [BUN]/2.8 + [ethanol]/4.6.

Extracellular fluid markers of dehydration and plasma volume contraction and haemoconcentration in both Groups were defined as BUN, creatinine, albumin, uric acid and haematocrit.

Statistical methods: Data is expressed as mean ± standard deviation. Unpaired Student's t-test and Chi square test were employed. Results displaying a $P<0.05$ were considered to be significant.

Results

Table 1 depicts the demographic characteristics of the study population. As shown, three patients (N=3) in Group A and two patients (N=2) in Group B had diabetes mellitus prior to admission. All of them were treated with oral hypoglycaemic agents and none was on insulin.

Depression had been diagnosed prior to admission in two patients in Group A and in all (4/4) in Group B. Altogether 4/9 of the patients had psychiatric diagnoses prior to admission while 3/9 had concomitant diabetes and psychiatric conditions. The initial presenting symptoms in both Groups were polyuria, polydipsia, weakness, tachypnea and altered mental status. Kussmaul respirations were equally noted in both Groups (data not shown). Table 2 illustrates the acid-base and biochemical profiles of both Groups upon admission. Table 3 shows their daily insulin requirements as well as their need for parenteral ethanol and methyl-pirazol. Finally, the transient or permanent need for haemodialysis is outlined.

Group A presented with significantly higher blood sugar, BUN, BUN/creatinine ratio, haematocrit and triglyceride levels. Interestingly both groups presented similar arterial pH, anion-gap, osmolal-gap and bicarbonate and lactate levels. Beta-OH-butyrate levels were elevated in Group A patients and were not available for Group B patients. Ethylene-glycol and uric acid levels were higher in Group B but the difference did not reach statistical significance.

Both groups presented with similar creatinine values upon admission (Table 2). As depicted in Table 3 two out of five patients in Group A required urgent haemodialysis (HD) while upon discharge, their values had returned to normal (0.98 ± 0.64 mg/dl) and none of them remained on HD. On the contrary, every single patient (4/4) in Group B required urgent HD. One patient died of sepsis and the remaining three required permanent treatment of renal failure by HD.

Every single patient in the Group A required intravenous insulin administration for a period ranging between 4 to 10 days with insulin doses ranging between 0.55 to 4.07 units/Kg/day (mean insulin dose= 264 ± 169 IU/day) (Table 3). These same patients were discharged on subcutaneous insulin doses ranging between 26 to 215 units/day (mean insulin dose=97 ± 34 IU/day).

Patients in Group B did not require intravenous insulin administration to correct acidosis and/or hyperglycaemia and were not discharged on subcutaneous insulin despite the fact that two of them (2/4) were previously known type 2 diabetics. On the contrary, they were discharged on oral hypoglycaemic agents. In four out of five patients in Group A, C-peptide levels determined on admission averaged 1.3 ± 0.76 ng/ml in the presence of simultaneous blood glucose values averaging 1305 ± 425 mg/dl (Table 2). Unfortunately, C-peptide levels were not available for Group B patients.

Oxalate and hyppurate urine crystals could not be detected in any (0/5) of Group A patients while one out of four (1/4) in Group B presented with calcium oxalate micro-crystalluria.

Transient chemical pancreatitis was present in two out of five patients in Group A and in one out of four patients in Group B. Both amylase and lipase values were corrected before discharge in both groups (data not shown).

Mean hospital stay in Group A patients was 10.2 ± 4.8 days versus 4.6 ± 4.4 days in Group B ($P<0.031$). Mortality was similar in both groups (none out of five in Group A and one out of four in Group B; $P=0.2635$). Permanent HD was more frequent in Group B (4/4 vs. 0/5; $P=0.0392$)

Discussion

According to our database, nine patients were discharged from University Hospitals of Cleveland (Cleveland/OH) with the diagnosis of EGI in the twelve year period from 01/86 to 01/98. Among them five (Group A) presented with simultaneous diabetic ketoacidosis (DKA) and admission HbA1c values in the 19.5-20.1% range. Several unique and particular features in this patient group deserve comment: extreme hyperglycaemia, acidosis, previously uncontrolled diabetes mellitus (as reflected by the markedly elevated HbA1c values), increased anion-gap, increased osmolal-gap, dehydration and pre-renal azotemia, transient chemical pancreatitis, hypertriglyceridaemia and rhabdomyolysis.

Both DKA and EGI appear in the differential diagnosis of high anion gap metabolic acidosis.[8,12,13,18,19] The finding of simultaneously elevated anion and osmolal gap in a patient presenting with DKA raises the suspicion towards

intoxication with the latter since DKA does not usually present with elevated osmolal gap.[18-21]

Ethylene glycol false positive results have been reported using HPLC methodology in two patients with diabetic ketoacidosis.[22] It is presently unknown whether ethylene glycol ingestion can precipitate DKA in a previously poorly controlled diabetic patient and whether there is a direct beta islet-cell cytotoxicity from ethylene glycol and its metabolites.

Previous case reports have reported hyperglycaemia in non diabetic[6,8,23] as well as in diabetic patients[7] who had EGI (unpublished personal observations); nevertheless, none of the reported cases had glycaemias in the range of the cases described in the present report. This extreme hyperglycaemia is most likely to be multifactorial. As depicted in Table 3 insulin resistance (indirectly reflected by the markedly high daily insulin requirements in Group A patients during hospitalization) as well as glucose toxicity was clearly evidenced in all cases (indirectly reflected by the simultaneous C-peptide/blood glucose measurement). Additionally, marked dehydration and pre-renal azotemia secondary to osmotic diuresis and acidosis can all be accounted for by the degree of hyperglycaemia. Interestingly, Group B patients did not display insulin resistance. Unfortunately, their C-peptide levels upon admission were not available.

The practically indistinguishable acid-base status between both groups in spite of the marked hyperglycaemia of Group A (Table 2) raises at least two fundamental and unanswered questions: (i) does hyperglycaemia-induced osmotic diuresis explain the better kidney outcome in Group A? and (ii) do false positives in Group A -already reported in DKA settings-[22] explain the outcome while the true positive ethylene glycol intoxication causes irreversible kidney damage?

Interestingly and for both groups both anion-gap and arterial pH [6,8,24] were well within the literature reported ranges. On the contrary, Group B patients presented with an osmolal gap higher than those reported elsewhere.[3,11-15] The higher ethylene glycol levels in this group can probably account for the increased osmolal gap.

Group A patients presented with significantly higher dehydration and plasma volume contraction parameters (BUN, BUN/Creatinine ratio, uric acid, haematocrit) on admission when compared with Group B. Hyperglycaemia induced osmotic diuresis may probably be the cause of these differences.

Upon discharge, acute renal failure of the acute cortical necrosis type had resolved in all Group A patients (normal creatinine discharge values in all and none on permanent hemodialysis) while renal failure persisted in Group B (one died and 3 out of 3 were on permanent haemodialysis). This worsened renal outcome is mainly explained on the basis of the previously reported nephrotoxicity of ethylene glycol and its metabolites.[9,23-25]

The creatine phospho-kinase elevation may have resulted from both rhabdomyolysis –secondary to osmotic diuresis induced dehydration- and direct damage of vascular smooth muscle cell from ethylene glycol deposition in the media of small arterioles.[9,25] Moreover, rhabdomyolysis is frequently reported in alcoholic liver disease with metabolic acidosis, particularly in cases of concomitant EGI.[26,27]

None of Group A patients showed evidence for oxalate and/or hyppurate micro-crystalluria while two out of four in Group B showed calcium oxalate micro-crystals. The pathophysiology underlying this finding is unclear and bears no relationship with either admission or discharge glomerular filtration rate. Moreover there are reports of massive ethylene glycol poisoning without crystalluria.[28]

Mild to moderate exocrine pancreatic enzyme elevations are often encountered in the setting of diabetic ketoacidosis.[29-31] Additionally, we have witnessed similar amylase and lipase elevations in several (none reported) personal observations of EGI without hyperglycaemia. Interestingly, none of the Group B patients presented alterations in either amylase or lipase values upon admission. There is no experimental evidence substantiating a direct toxic effect of ethylene glycol or its metabolites on the exocrine pancreas; nevertheless, human studies addressing this issue are not available.

Finally, the transient elevation of triglycerides is frequently encountered in scenarios of acute insulin resistance such as diabetic ketoacidosis. Insulin resistance leads to an inhibition of hepatic lipoprotein lipase enzymatic activity. Upon treatment with insulin and normalization of glycaemic control and glucose homeostasis, these alterations tend to revert rapidly.[18, 31-36]

Summary

Five out of nine patients presenting with EGI had simultaneous DKA. Their salient biochemical features included extreme hyperglycaemia, marked insulin resistance and evidence for glucose toxicity as well as previously uncontrolled diabetes mellitus. They also presented with extreme metabolic acidosis with simultaneous elevated anion and osmolal gap, osmotic-diuresis induced severe dehydration and pre-renal azotemia, transient and reversible chemical pancreatitis and hypertriglyceridaemia.

Severe diabetic ketoacidosis presenting with simultaneous high anion and osmolal gap should prompt suspicion to the concomitant ethylene and/or propylene glycol intoxication, particularly in those patients with past suicidal attempts and/or a history of depression.

Patients with EGI but without DKA display a similar acid-base profile but they present with neither marked hyperglycaemia nor significant insulin resistance. On the contrary and it is noteworthy, it does cause irreversible kidney damage.

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