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Prognostic factors and treatment of severe ethylene glycol intoxication

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Abstract *Objective:* Analysis of prognostic factors and treatment of a large epidemic of ethylene glycol intoxication.
Design: Retrospective case review comparing 16 survivors with 6 patients who died.
Setting: Cooperative study between county hospitals, a university hospital, and a poison information centre.
Patients and participants: Survival review of 36 serious cases and chart review of 17 cases.
Intervention: Time to initial treatment with intravenous fluids, sodium, bicarbonate, ethanol, and dialysis.
Measurements: Clinical data at admission and blood chemistry at 0, 24, 48, and 72 h.
Results: 6 of 36 patients (17%) died; 11 of 17 patients whose charts were reviewed survived and 3 had chronic renal failure. All but 2 patients had acute renal failure. Neither delay to admission, intravenous dialysis, HCO_3 or alcohol was related to outcome. At admission more patients who subsequently died had seizures, were comatose, were more acidotic, and had lower base excess and higher potassium levels than those who survived. Urine contained oxalate crystals in 10 of 14 cases. At 24 h the potassium level was higher and the base excess lower in those who died. Blood ethylene glycol levels for the patients who died and survived were no different. All survivors were dialyzed, but 2 patients who died had no dialysis. No survivor needed chronic dialysis and none had organic brain lesions.
Conclusion: In patients with severe ethylene glycol intoxication, severe acidosis, hyperkalemia, seizures, and coma at admission carry a dismal prognosis. We believe very large amounts of intravenous HCO_3 should be used immediately for rapid correction of the metabolic acidosis. Intravenous ethanol and hemodialysis should be started early and continued until acidosis is corrected.

Key words Ethylene glycol · Acute renal failure · Intoxication · Metabolic acidosis · Therapy · Prognosis · Hemodialysis

Introduction

Ethylene glycol has a warm, sweet, agreeable taste and causes intoxication with a very high mortality. It is present in antifreeze, coolants, and brake fluid and has been used as a sweetener in low concentrations [1]. Its toxicity in humans was described over 60 years ago [2] and many cases have since been published [3, 4]. Most articles describe only a few patients. In reviewing 59 articles published since 1937, we found that 36 were single case reports, 18 presented two to five patients, and only 5 reports listed more than five cases. (A literature list is available on

request.) The mortality reported in these articles was 49%.

The rationale for giving intravenous ethanol and the use of dialysis has been well documented [1], but because of the sporadic occurrence of ethylene glycol intoxication, no thorough analysis and quantification of early treatment have been done. The reports of large epidemics have included only patients who died [3, 4].

In early 1987 there was widespread coverage in the Swedish daily newspapers of two lethal cases of accidental ethylene glycol intoxication. Detailed information was given about the dangers of ethylene glycol intoxication and the amounts that were lethal. A large epidemic of ethylene glycol intoxication involving 63 cases then occurred and was reported to the Swedish Central Poison Information Centre. A description of the epidemic has been published elsewhere [5]. There were 27 trivial and 36 severe cases, of whom 6 died. The cluster of many cases with severe intoxication offered a unique opportunity to do a detailed study of the relation or the timing and intensity of treatment and clinical and chemical variables to outcome.

Materials and methods

Patients

We contacted physicians at the local hospitals who had reported a patient to the Poison Information Center and obtained copies of the charts for 17 of the 36 patients, including the 6 who died. In 19 cases no charts were obtained, and for these cases the only information we had was that they survived the acute episode.

Factors reviewed

The charts of the 17 cases were reviewed for the following factors: age, sex, amount of ethylene glycol ingested, delay between intake of ethylene glycol and admission to hospital, and delay from intake to the start of treatment with alkali, ethanol, and dialysis. The following factors at admission were reviewed: systolic and diastolic blood pressures, pulse rate, breathing frequency, presence or absence of arrythmia, nystagmus, or ataxia, state of consciousness (awake, somnolent, stuporous, or comatose), and the presence of seizures. Clinical signs of pulmonary edema, urinary output per hour, and the need for respirator treatment or dialysis were also included. The following laboratory studies were reviewed at admission (time 0) and at 24, 48, and 72 h: urinary sediment, ethylene glycol levels in blood, levels of sodium, potassium, chloride, pH, PO_2, PCO_2, bicarbonate, base excess, urea, creatinine, calcium, and osmolality in serum.

The various therapies for ethylene glycol were reviewed for days 1, 2, and 3 after admission. The following factors were recorded: amount of fluids, bicarbonate, and ethanol given per 24 h. We also reviewed the stated time from intake of ethylene glycol to the start of intravenous bicarbonate, ethanol, and dialysis, the amount of alcohol, bicarbonate, and fluids given on days 1, 2, and 3 after admission, and the number of dialysis treatments and type of dialysis.

For follow-up, a blood sample for serum creatinine was taken at discharge and if it was abnormal, the patient was followed up with blood tests for serum creatinine for at least 6 months.

Laboratory investigations were performed in clinical laboratories by the usual methods. Ethylene glycol blood determinations were performed at various clinical laboratories using a chromatographic method by either Wells [6] or by Johnsson et al. [7].

Statistical analysis

The data were analyzed using Student's *t*-test for unpaired values, Fisher's exact probability test and analysis of variance and by binary logistic and linear regression. Values reported are mean ± SD.

Results

General

Of the 36 serious cases of intoxication, 6 (17%) patients, all males, died. Sixteen of the 17 patients with detailed records were male. The mean age of those who survived was 38 ± 15 years and of those who died 37 ± 10 years ($p = 0.86$). In the patients who died, death occurred within 3 days in all except 1 patient who died after 11 days. Five surviving patients were discharged within 2 weeks five within a month, and 1 patient who had chronic renal failure spent 58 days in the hospital before discharge. This was the only patient who was over 70 years of age. No serum creatinine concentration could be found before admission in that patient, who had a history of chronic prostatic hypertrophy.

Renal failure

Among the 17 patients, all but 2 developed acute renal failure with creatinine levels over 125 μmol/l. One of these 2 survived and 1 died within 48 h. During the first day 2 patients were anuric (< 50 ml/24 h), 11 were oliguric (50 – 300 ml/24 h), and 4 had a normal urine output. At discharge the patients' mean serum creatinine level was 244 ± 227 μmol/l (normal range < 120 μmol/l) and only 2 of 11 surviving patients of the patients had a creatinine level below 120 μmol/l. All but two patients who died received dialysis. One died within 24 h, the other within 48 h in the therapy-resistant hypotension.

Intake of ethylene glycol and time to admission

Records of the estimated intake of ethylene glycol in eight patients (all survivors) were available. The mean intake was 481 ± 217 ml and all patients had ingested > 250 ml ethylene glycol. The amount of intake was not known for either the six patients who died or for the three surviving

patients. The patients who developed chronic renal failure included both the patients who had drunk the least amount of ethylene glycol, 250 ml, and the one who had taken the most, 800 ml.

Of the six patients who died, four were admitted between 7 and 12 h after intake and two between 13 and 24 h after intake. We had records of the time between intake and admission for seven of the survivors. Two were admitted within 6 h; both regained complete renal function. One was admitted within 12 h and had chronic renal failure. The remaining four patients were admitted approximately 24 h after intake. Of these patients, two recovered normal renal function and two developed chronic renal failure. There was no relation between blood levels of ethylene glycol at admission and delay to admission ($r = 0.17$, $p = 0.717$) or amount of ethylene glycol ingested ($r = 0.39$, $p = 0.514$) (linear regression analysis).

Clinical findings at admission

The results of clinical findings at admission are summarized in Table 1. The presence of seizures and coma was significantly more common in the patients who died. There was no difference in cardiovascular stability between survivors and the patients who died. The latter were treated more often with a respirator ($p = 0.054$). The urinary sediment at admission was evaluated in 14 patients. In 10 of those many oxalate crystals were seen. There was no relation between crystalluria and the dose of ethylene glycol. There was also no difference in crystalluria between the patients who died and survived.

Blood chemistry findings

The blood chemistry findings at time 0, 24, 48, and 72 h are summarized in Table 2. Blood ethylene glycol levels were no different between the survivors and the patients who died. Sodium, chloride, PO_2, urea, creatinine, calcium, and osmolality were also similar. There were important differences in blood pH, bicarbonate, base excess, and serum potassium levels (Table 2). The patients who died had a higher potassium and a lower pH, base excess, and bicarbonate than those who survived. The base excess was significantly lower in those who died, even at 24 h, suggesting a slower correction of the acidosis than in those who survived. The acid-base findings are summarized in Fig. 1. The blood ethylene glycol levels are summarized in Fig. 2. In binary logistic regression analysis, potassium and PCO_2 values at admission were independent factors predicting death, but pH, base excess, and bicarbonate levels were not. At 24 h only base excess was an independent variable predicting death.

Table 1 Result of physical examination at admission

	Survived ($n = 11$)	p	Died ($n = 6$)
Lucid	3	0.272	0
Somnolent	5	0.334	1
Comatose	3	0.049	5
Systolic BP[a]	150 ± 38	0.156	179 ± 39
Diastolic BP[a]	90 ± 18	0.126	109 ± 27
Pulse rate[a]	97 ± 18	0.490	106 ± 31
Resp. rate[a]	29 ± 8	0.195	40 ± 13
Arrhythmia	0	1.0	0
Nystagmus	1	0.833	0
Ataxia	0	1.0	0
Pulmonary edema	0	1.0	0
Seizures	1	0.027	4
Needed respirator.	6	0.054	6

[a] Student's t test for unpaired values, all others Fisher's exact probability test

Amount of electrolyte fluid therapy

The time from admission to hospital and the start of dialysis, i.v. ethanol, and i.v. bicarbonate was compared between survivors and patients who died. None of the differences were statistically significant; both patients admitted within 6 h of ethylene glycol intake survived, but

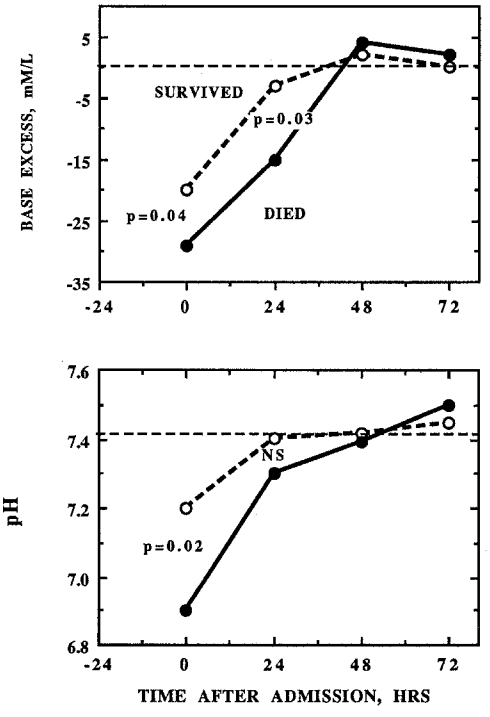

Fig. 1 Progress of base excess and blood pH over the first 3 days in patients who survived and patients who died. The surviving patients have a higher pH at admission. In those who died, base excess is lower, both at admission and 24 h later.

Table 2 Review of Laboratory date. All comparisons by Student's *t*-test for unpaired values

	Hours							
	0		24		48		72	
	Surv.	Died	Surv.	Died	Surv.	Died	Surv.	Died
Glycol[a]	33.0±36.8	8.7±6.1	11.5±7.2	4.7±4.0	7.2±9.5	0±0	0.9±1.6	0±0
p	0.302		0.163		0.231		0.395	
Sodium[a]	140±5	144±5	142±3	140±4	140±5	145±3	139 ±4	138±4
p	0.191		0.250		0.098		0.845	
Potassium[a]	4.4±0.9	6.1±1.2	3.7±0.5	4.8±1.1	3.7±0.5	3.8±0.3	4.0 ±0.8	4.0±1.2
p	0.011		0.012		0.788		0.979	
Chloride[a]	104±7	99	101±7	96±11	105±3	99±6	108 ±20	98±4
p	0.596		0.511		0.165		0.514	
Bicarbonate[a]	10.7±5.5	7.8±1.1	20.7±5.5	13.6±5.0	22.8±3.6	21.7±10.1	25.1±4.2	25.3±3.5
p	0.262		0.030		0.740		0.924	
Base excess[a]	−19.6±8.7	−28.6±2.1	−3.1±7.8	−14.8±8.9	−1.6±3.9	4.4±2.3	0.1 ±4.9	1.6±4.6
p	0.044		0.018		0.070		0.659	
pH	7.2±0.1	6.9±0.2	7.4±0.1	7.3±0.1	7.4±0.1	7.4±0.3	7.5 ±0.1	7.5±0.0
p	0.024		0.150		0.665		0.867	
PO_2[b]	15.9±3.4	17.3±3.0	16.2±5.8	14.8±6.1	14.3±5.5	9.6±3.3	14.9±5.7	8.9±2.8
p	0.466		0.674		0.193		0.119	
PCO_2[b]	2.4±1.0	1.6±0.8	4.3±0.9	2.9±1.9	4.6±0.9	4.3±0.7	4.3 ±1.1	4.4±1.0
p	0.167		0.089		0.624		0.816	
Urea[a]	5.5±2,2	6.3±1.8	7.8±4.0	12	10.3±5.3	11.8±6.6	14.4±4.6	14.8±7.9
p	0.667		0.383		0.692		0.899	
Creatinine[c]	154±40	195±59	283±136	325±119	442±224	555±128	631 ±282	646±187
p	0.159		0.552		0.369		0.931	
Calcium[a]	2.3±0.2	2.2±0.4	2.2±0.4	1.9±0.3	2.2±0.1	1.9±0.7	2.3 ±0.3	1.9±0.7
p	0.682		0.298		0.286		0.278	
Osmolality	359±53	325	321±27	343±32	331±16	330	–	–
p	0.585		0.349		0.964			

[a] mmol/l
[b] kPa
[c] µmol/l

so did all four patients for whom the delay was more than 24 h.

The volume of i.v. ethanol and bicarbonate was compared between survivors and patients who died (Table 3). There were no statistically significant differences but there was a more rapid correction of potassium, base excess, and pH in the survivors (Fig. 1, Table 2).

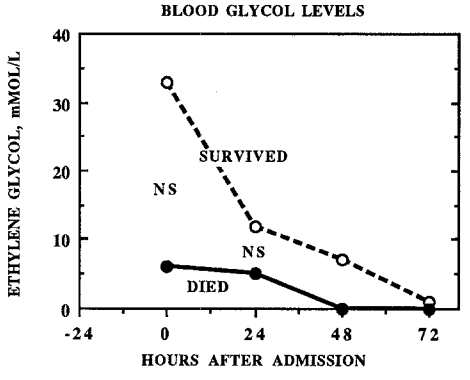

Fig. 2 Blood glycol levels over the first 3 days in survivors and in patients who died. At all times the blood ethylene glycol level is higher in the patients who survived than in those who died, although there is no statistical difference

Dialysis treatment

All 11 survivors underwent dialysis, in 2 cases with both peritoneal dialysis and hemodialysis, in 1 case with peritoneal dialysis only, and in the other 8 cases with hemodialysis only. Patients received a mean of five dialyses (range 1–10). No one needed dialysis for more than 14 days. Of the 11 survivors, 2 were dialyzed within 6 h after intake of ethylene glycol, 1 within 12 h, and 2 within 24 h. In 6 patients there was a delay in treatment of over 24 h. Of the 6 patients who died, 2 did not receive dialysis, 1 was treated with peritoneal dialysis, and 3 were treated with hemodialysis. Dialysis was started within 7–12 h in 2 patients, in 13–24 h in 1, and after 24 h in 1 of the patients who subsequently died.

There was no statistical difference in the time between intake of ethylene glycol and the time dialysis was begun between the patients who died and those, who survived ($p = 0.624$). Patients who died had received fewer dialyses

Table 3 Electrolyte fluid therapy. All comparisons by Student's *t*-test for unpaired values

	Day 1		Day 2		Day 3	
	Surv.	Died	Surv.	Died	Surv.	Died
Volume (ml)	4568 ± 2252	5328 ± 1577	4281 ± 1482	3583 ± 3049	2785 ± 1618	2875 ± 671
p	0.553		0.564		0.942	
Bicarbonate (mmol)	407 ± 337	293 ± 115	168 ± 263	50 ± 70	70 ± 80	165 ± 21
p	0.528		0.578		0.164	
Alcohol (mmol)	1276 ± 814	1638 ± 170	1789 ± 1080	562 ± 675	491 ± 647	0 ± 0
p	0.409		0.063		0.498	

(one versus four) because of their short survival ($p = 0.034$).

Follow-up

We had complete follow-up information on 9 of the 11 survivors. None of these patients had an organic brain syndrome at follow-up but functioned at premorbid levels. Of the 9 patients from whom we obtained a creatinine value more than 6 months after the intoxication episode, 6 had a normal creatinine level, 2 had a level just above the upper limit of normal (132 and 134 μmol/l), and only 1 patient had moderate chronic renal failure with a creatinine of 213 μmol/l (Fig. 3). This patient, however, was known to have had prostatic problems before ethylene glycol intake and had mild dilatation of both ureters.

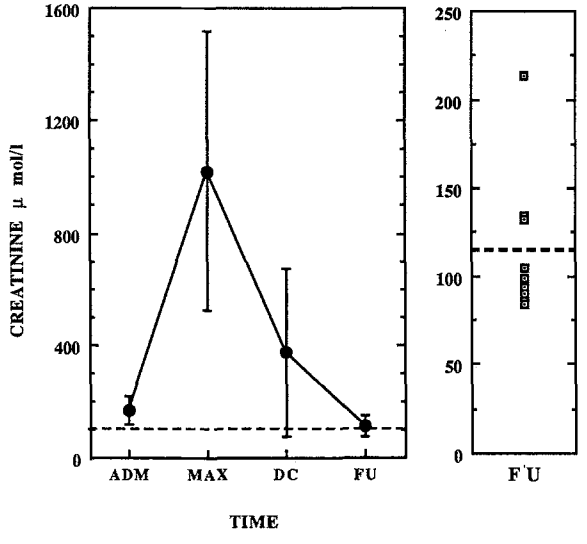

Fig. 3 Progress of serum creatinine levels in the patients at admission *ADM* and maximal *MAX*, discharge *DC*, and follow-up *FU* creatinine blood levels in nine patients who survived. Only one patient had moderate renal failure more than 6 months after discharge and two patients had borderline elevations of their creatinine levels more than 6 months after discharge

Discussion

The largest epidemic of ethylene glycol poisoning occurred in the USA in 1937 when 76 patients died after using a sulfa drug dissolved in ethylene glycol [3]. The second largest epidemic occurred in Nigeria 53 years later, in 1990, when over 47 children died when given paracetamol syrup sweetened with ethylene glycol [4]. In neither of these epidemics were any detailed analyses presented.

Our analysis of outcome and treatment of patients with serious ethylene glycol intoxication is the largest yet performed. Several findings at presentation and treatment factors appear important. The first is the very high mortality for ethylene glycol intoxication. Seventeen percent of the patients died, although most of the patients we studied were admitted very quickly and treated with dialysis, i.v., ethanol, and i.v. bicarbonate. We expected that late treatment would be associated with a poor prognosis, but our findings did not support this. Our sample was small and numerous other variables (i.e., concomitant ethanol ingestion, amount of ethylene glycol ingestion) could have accounted for this observation. Regardless, insofar as some patients in our series survived despite late treatment, our data suggest that all patients with significant ingestion (high osmolalities and anion gap acidosis) should be treated aggressively, regardless of the time from ingestion.

There are some clinical markers at admission that predict death. Convulsions and coma appeared to be ominous signs. There are also predictive biochemical data that can be quickly obtained. The most important finding perhaps is that ethylene glycol blood levels at admission are not predictive of outcome, but the levels of the toxic acid metabolites, as evidenced by a low pH and low base excess, do predict death. The lower blood levels of ethylene glycol and the extremely low base excess in the patients who died were probably due to the fact that these patients had converted much of their ethylene glycol to its acid, toxic metabolites. The survivors appeared to be metabolizing ethylene glycol to its toxic acid radicals more slowly. Perhaps they had a high intake of ethanol, which is a competitive inhibitor of ethylene glycol metabolism or, alternatively, perhaps some patients are slower

metabolizers of ethylene glycol because of lower amounts of alcohol dehydrogenase. As we had no data on blood levels of ethanol at admission for our patients, this remains conjectural. The toxic effect of ethylene glycol is caused by the conversion by alcohol dehydrogenase to glycolic acid, formic acid, and then to oxalate. These and other acid metabolites contribute to the severe acidosis that one sees in these patients, and oxalate is also believed to cause the renal damage [1, 8, 9–11]. Whatever the reason for the fast metabolism, i.e., the absence of competing ethanol or the presence of large amounts of alcohol dehydrogenase, it is important to realize that it is not the ethylene glycol blood level at admission that is important, but the rapidly and more easily available indirect measures of the toxic acid radicals as expressed by a low blood pH and base excess. These appear to be the determinants of the severity of the intoxication.

There are three more important clues to the diagnosis that were available almost immediately: (a) the finding of oxalate crystals in many of the urine samples from these patients; (b) a high anion gap; and (c) a high osmolal gap. Although measured in only four of our patients, the anion gap was over 24 mmol/l and the osmolal gap 20 mmol/l or higher in all patients. Those three findings, however, are not always present [12], and ethanol in particular can contribute to an osmolal gap, while a high anion gap is also seen in other types of intoxication, i.e., salicylate, methanol, and paraldehyde. In the case of mixed intoxications, in particular, it is necessary to know the blood levels of poisons to make a definitive diagnosis. In spite of this, it is possible to make an early diagnosis based on the combination of severe metabolic high anion gap acidosis, a high osmolal gap, and oxalate crystals in the urine. These laboratory methods are available at most hospitals, unlike those for the determination of blood ethylene glycol levels. The lessons for treatment are clear: the finding of severe acidosis in a patient after glycol ingestion, independent of the blood concentration of ethylene glycol, is a medical emergency.

The pathophysiology of ethylene glycol intoxication is well known. Ethylene glycol itself appears to be non-toxic but it is metabolized by alcohol dehydrogenase to its intensely acid and toxic metabolites, which include glycolic acid, formic acid, and oxalic acid [1, 8]. General management of the condition includes the use of ethanol or 4-methylpyrazole to block the metabolism of ethylene glycol by alcohol dehydrogenase, treating the acidosis with bicarbonate infusion, and removal of the ethylene glycol and acid metabolites by hemodialysis, gastric lavage, and charcoal. This protocol is well known and well described [1, 8, 13].

The second finding that we think is important rests on this knowledge and on the combined observations of treatment intensity in our patients with i.v. bicarbonate and ethanol and the changes in base excess. Although there was no statistical difference between the amount and timing of i.v. bicarbonate and ethanol in those who survived and died, a low base excess was the only independent factor at 24 h that predicted death.

From these results, we believe that we can make the following observations. Given the non-significance of our finding regarding delays, the first, paradoxically, is that we believe that time is of importance. Those patients who are metabolizing ethylene glycol faster, either because of an abundance of alcohol dehydrogenase or because there is no concomitant ethanol intake, are changing the ethylene glycol to its toxic acid endproducts. Such patients should be treated very quickly with high-dose i.v. ethanol to stop the metabolism and simultaneously should be given large amounts of bicarbonate. The survivors in our series received a mean of over 400 mEq, or 3 l, isotonic (1.2%) bicarbonate solution intravenously in the first 24 h. Two of the surviving patients received almost 1000 mEq bicarbonate the first 24 h. This resulted in normalization of their acidosis within 24 h. On the contrary, the patients who died received only 293 mEq, or 2 l, isotonic bicarbonate, and at the end of the first day their base excess was still −14 mmol/l. It appears that the acidosis was much more aggressively managed in the cases who survived and the acid metabolites were neutralized earlier by the bicarbonate.

One could argue that the patients with lower pH and base excess were already doomed to die, and that any therapy was futile. There are two arguments against this: (a) the survivors received the right amount of bicarbonate for complete correction of their acute acidosis (based on a body weight of 70 kg with a calculated bicarbonate space of 30%) and (b) the patients who died received only one-half of necessary amount of bicarbonate. The bicarbonate space, which is 0.3, in these patients is similar to that found by acute infusion experiments in humans [14]. A recent report of successful treatment of profound metabolic acidosis (pH 6.46 and an HCO_3 of only 1.3 mmol/l) in a patient with ethylene glycol intoxication with very large amounts of i.v. bicarbonate (264 mmol in 80 min) also suggests that early, aggressive bicarbonate treatment is life saving [15]. The use of bicarbonate in acidosis is a matter of intense debate, particularly in lactic acidosis [16, 17], but we agree with those who advise high-dose alkali in this organic acid acidosis [16] in which there is no concurrent lactic acidosis [18]. Although a retrospective review makes therapeutic conclusions tenuous, we believe our data indicate that early, very aggressive bicarbonate therapy will make the difference and save some of these patients. We advocate raising the base excess to normal within 12–24 h however much bicarbonate that requires. The dose should be calculated on base excess × 0.3 × body weight.

The final piece of advice is to start i.v. ethanol and aggressive hemodialysis early. This is based on physiological considerations of the nature of ethylene glycol intoxication. Both the toxin, ethylene glycol, and its acid metabolites, glycolic acid and oxalate, are small, water-soluble

molecules. The fastest way of removing such molecules is through high-efficiency hemodialysis. The biomolecular permeability of the dialysis membrane makes no difference for molecules of this size [19, 20]; therefore hemodialysis should by started quickly with large bore blood access catheters and with the biggest dialysis filters available to allow the highest possible blood flow and thus a high, small molecular clearance. This will remove both the unmetabolized toxin and the acid metabolites. Furthermore, it will prevent sodium accumulation, which may be a danger of aggressive i.v. bicarbonate therapy. During dialysis the ethanol infusion needs to be increased or ethanol can be added to the concentrate to maintain the blood concentration at the desired level [1]. Peritoneal dialysis clears small molecules at a rate of approximately only one-tenth that of hemodialysis and should be used only if hemodialysis is not available.

Recently, 4-methylpyrazole has been used as a blocker of alcohol dehydrogenase [13]. It appears to be a promising drug to treat ethylene glycol intoxication and can perhaps replace i.v. ethanol. While it effectively blocks the metabolism of ethylene glycol to its toxic acid metabolites, in the severely acidotic patient there is a need for high-dose bicarbonate and rapid, high efficiency hemodialysis to remove the radicals that have already formed.

Finally, our study indicates that few of the patients who survive will have clinical evidence of lasting damage. None of the nine patients who were followed up over 6 months had any evidence of organic brain damage. Two patients had mild elevations of creatinine and only one, an older man, had a high serum creatinine, but this patient may have had some pre-existing renal disease. Renal damage from ethylene glycol is thus more like that of acute tubular necrosis, where chronic renal failure is rare, than like oxalate nephropathy, which leads to chronic renal failure.

The theoretical and practical use of intravenous alcohol and dialysis is already proven in ethylene glycol intoxication. We believe our analysis adds information that ethylene glycol intoxication can be quickly diagnosed by commonly available laboratory methods (severe, high anion and gap acidosis, high osmolal gap, and oxalate crystals in the urine) and that the early, aggressive use of very large amounts – often hundreds of millimoles – of intravenous sodium bicarbonate may improve survival.

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