EUROPEAN JOURNAL OF EMERGENCY MEDICINE, 2000, 7, 237–240

CASE REPORT

Survival with extremely high blood methanol concentration

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Fatalities are still reported following methanol poisoning. Methanol is extensively metabolized by alcohol dehydrogenase to formaldehyde and by aldehyde dehydrogenase to formic acid which is the main toxic metabolite. Survival with extremely high blood methanol concentration is possible provided that aggressive symptomatic and specific therapy is applied. This is illustrated by the clinical observation of a 27-year-old man who was admitted 22 hours after poisoning and presented a peak blood methanol concentration of 12.9 g/l. Treatment included correction of metabolic acidosis, ethanol infusion, haemodialysis and peritoneal dialysis. The patient survived with moderate visual sequelae and oesophageal stenosis. The range of toxicity of methanol according to blood levels determination is discussed.

Keywords: poisoning; methanol; blood concentration; extracorporeal epuration

CASE REPORT

A 27-year-old man (60 kg weight) was admitted in a first regional hospital with a suspicion of drug ingestion. He had been found comatose with poorly reactive pupils. Soon after orotracheal intubation, the patient presented cardiocirculatory arrest but was successfully resuscitated after the administration of adrenaline, isoprenaline and sodium bicarbonate (100 mmol). He was referred to our emergency department 2 hours later, that is 22 hours after the presumed time of poisoning. On arrival, he was deeply comatose with poorly reactive dilated pupils. His vital signs were: arterial blood pressure 92/52 mmHg, heart rate 109/minute, temperature 37°C. The first arterial blood gas analysis revealed: pH 7.21, pO_2 71 mmHg, pCO_2 21 mmHg, total bicarbonate 8 mmol/l, base deficit 17 mmol/l, lactate 1.8 mmol/l ($n < 2$). The relatives suggested that the patient could have ingested about 1000 ml of a concentrated (> 60%) methanol solution.

The blood methanol concentration was 10.3 g/l on admission but rose to 12.9 g/l 2 hours later (Fig. 1). Serum osmolality was 730 mOsm/kg H_2O. The methanol concentration in gastric fluid was 100 g/l. No other substance was found at comprehensive toxicological screen. The peak blood formic acid concentration was 901 mg/l.

A gastric lavage was performed and allowed the epuration of 300 g methanol. Supportive and specific therapy of methanol poisoning included sodium bicarbonate, ethanol and folinic acid administration (1 mg/kg every 4 hours) together with extracorporeal epuration. Inotropic support (dopamine and dobutamine up to 10 μg/kg/min) was required for 36 hours. After a loading dose of 0.6 g/kg, 2112 g of ethanol (administered via a central venous line as ethanol 94° diluted in dextrose 5%) were infused over 120 hours and the patient received 740 mmol sodium bicarbonate for the correction of metabolic acidosis which was achieved after 11 hours. Haemodialysis was performed over a total period of 14 hours. Unfortunately, haemodialysis had to be withdrawn because of poor haemodynamic tolerance (systolic blood pressure less than 65 mmHg for more than 0.5 hour despite optimal inotropic support). At the end of haemodialysis, blood methanol concentration had decreased to 1.26 g/l (Fig. 1). We calculated from the dialysate tank ([methanol concentration] × [tank capacity]) that more than 350 g of methanol had been eliminated by haemodialysis (in comparison, 300 g were recovered by gastric lavage, and about 15 and 22 g respec-

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tively were eliminated by spontaneous diuresis and peritoneal dialysis) (Fig. 2). The methanol extracorporeal clearance ranged between 85.7 and 210.3 ml/min, and the formic acid corporeal clearance between 42.9 and 189 ml/min.

The patient developed an acute oedematous pancreatitis (blood amylase 1625 IU/l, lipase 832 IU/l) with ascites documented by abdominal computed tomography.

As haemodialysis had been poorly tolerated (systolic blood pressure < 65 mmHg for more than 0.5 hour despite catecholamines infusion) and after evidence of pancreatic injury, we decided to continue with peritoneal dialysis for 72 hours. The methanol concentration in the fluid recovered from peritoneal lavage was initially 1.34 g/l and fell gradually to 0.36 g/l after 48 hours (1 litre was exchanged every 2 hours). Methanol disappeared totally from blood 98 hours following admission.

The blood methanol half-life for the whole period was 17.8 hours (4.7 hours during haemodialysis and 21.3 hours during peritoneal dialysis).

The clinical course was complicated by gastrointestinal haemorrhage and a nosocomial pneumonia. The patient remained in the intensive care unit (ICU) for 25 days. Late complications included oesophageal stenosis and permanent visual deficits. Acuity was only 1/200 in the left eye (4/10 in the right eye), and electrophysiological recordings at 3 months were consistent with optic neuropathy.

DISCUSSION

The range of toxicity of methanol is extremely variable. Death has occurred after ingestion of as little as 15 ml of 40% methanol, yet survival has been reported after ingestion of 500 ml.[1] In the literature, fatal levels of methanol in blood have been reported over a wide range from 0.2 to 6.3 g/l.[2]

Methanol is rapidly absorbed through the gastrointestinal tract and peak plasma levels are usually reached within 30–60 minutes following ingestion. If we assume that the patient had really ingested 1000 ml of 60% methanol, a rough estimate of the early potential blood methanol concentration should be 13.2 g/l ([Amount ingested × % solution × specific gravity]/[Volume of distribution × weight]). In severe methanol in-

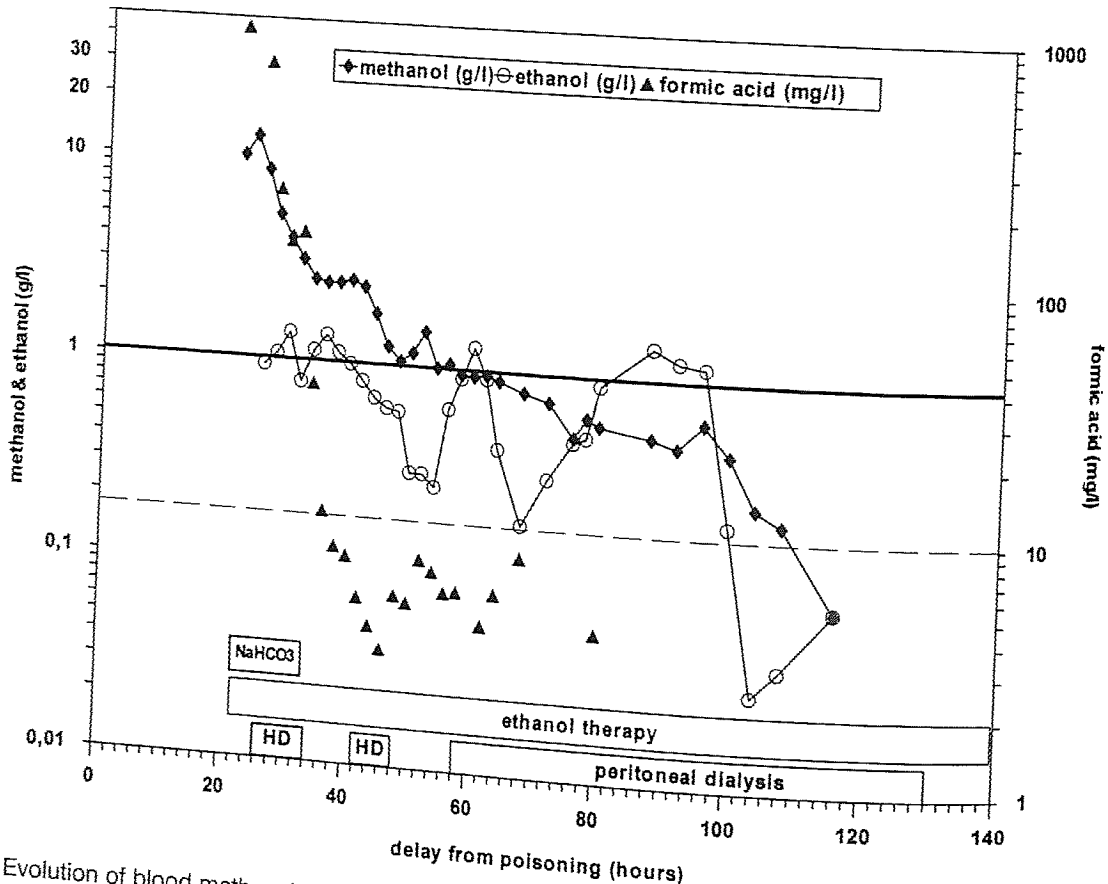

Fig. 1. Evolution of blood methanol, ethanol and formic acid levels and timing of specific therapies.

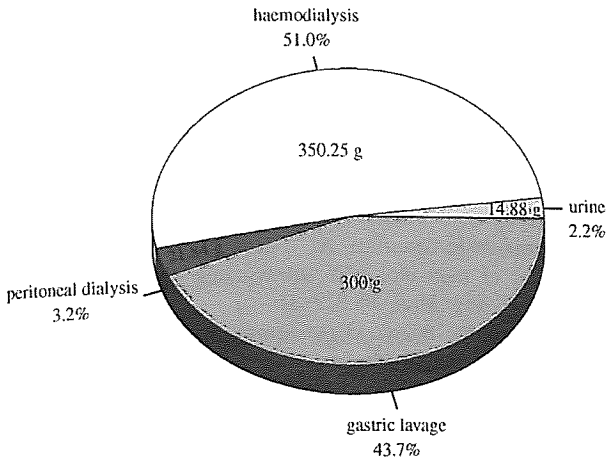

Fig. 2. Comparison between methanol epuration by gastric lavage, spontaneous diuresis, haemodialysis and peritoneal dialysis.

toxication, profound coma and respiratory arrest may develop as a consequence of the depressant properties of alcohols on the central nervous system. According to the literature data, however, toxicity is mainly related to the metabolic effects of the metabolites rather than to methanol *per se*. Methanol is converted relatively slowly in the liver to formaldehyde and then formic acid by the action of alcohol dehydrogenase (ADH) and acetaldehyde dehydrogenase. It is likely that in our case the extremely high blood methanol concentration greatly exceeded saturating concentrations for hepatic ADH. Jacobsen *et al.* reported zero-order elimination of methanol with a rate of 8.5 mg/dl/h prior to institution of ethanol therapy or haemodialysis.[3]

To our knowledge, this is the highest blood methanol concentration reported in the literature to be associated with survival.

In a previous report, Martens *et al.* described a patient who survived to a peak blood methanol concentration of 9.2 g/l following the ingestion of 500 ml of 40% methanol.[4] More recently, Wu *et al.* identified criminal methanol intoxication in an extremely young victim; in this 5-week-old infant, the admission serum methanol concentration was 11.48 g/l.[5] The infant recovered after folic acid and i.v. ethanol therapy, and did not develop any visual impairment.

As illustrated by other observations, the prognosis of methanol poisoning is more closely related to the degree of metabolic acidosis caused by formic acid accumulation rather than to methanol level.[6-8] Blood formic acid concentration above 0.5 g/l is usually associated with poor visual prognosis or death.[6]

Haemodialysis has been shown to remove effectively not only methanol but also its metabolites. According to Jacobsen *et al.*, haemodialysis should be considered on the basis of the following criteria: (1) any degree of visual impairment, provided methanol or formate is still present; (2) severe metabolic acidosis (base deficit > 15–20 mmol/l); (3) blood methanol levels above 0.6 g/l; (4) consumption of more than 40 ml of 100% methanol (adults).[9] Haemodialysis should be continued until the blood methanol level is at least below 0.3 g/l. In the present case, haemodialysis was performed for 14 hours, but, due to haemodynamic complications, it was withdrawn before blood methanol concentration reached this value. Continuous venovenous haemofiltration and peritoneal dialysis are less effective than haemodialysis and cannot be recommended.[10]

Ethanol is the main specific antidotal treatment for methanol poisoning.[11] The present case illustrates the difficulty of achieving constant ethanol blood levels despite continuous infusion. As ethanol has a much greater affinity than methanol for hepatic ADH, ethanol blood level of 100 mg/dl has been shown to completely block methanol metabolism in humans. Theoretically (based on the relative activity of methanol versus ethanol as ADH substrate), lower levels of ethanol (30–60 mg/dl) should still be effective.[9] In the present observation, although ethanol blood levels fell below 100 mg/dl for several hours, toxic metabolites did not accumulate after the end of haemodialysis and metabolic acidosis did not reappear.

Alternative antidotal therapy with 4-methylpyrazole (4-MP), a potent competitive inhibitor of alcohol dehydrogenase, is currently under investigation; preliminary data suggest that 4-MP can be safely used not only in ethylene glycol but also in methanol poisoning.[12-14] Ideally, treatment with 4-MP should be started sufficiently early to prevent toxic metabolite accumulation. In such cases, haemodialysis would not be needed. In case of massive overdose, the prolonged methanol half-life would limit the potential efficacy of 4-MP. In addition, when the patient has developed ocular effects or acidosis, haemodialysis is indicated.

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