Methanol intoxication: a case report and review of the literature

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Methanol intoxication in human is a potentially lethal poisoning characterized by a latent period with subsequent development of visual impairment, conscious disturbance, abdomen pain. A 36-year-old male patient was admitted because of nausea, vomiting, epigastralgia , general weakness 24 hours after ingestion of one bottle of unknown quality of alcoholic beverage. Physical examination showed a conscious male with mild tenderness over epigastric area with normal blood pressure and respiratory rate. Laboratory data including were all in normal range initially. But 4 hours later, he experienced dyspnea, blurred vision, bilateral leg soreness, with Kussmaul's respiration. The arterial blood pH was 7.065, pCO_2 8.2 mmHg, bicarbonate 2.3 meq/l. Sudden onset of coma and cardiopulmonary arrest with bilateral fixed dilated pupils 20 minutes later. Methanol level 96.5 mg/dL was noted on the second day.

Introduction

Methanol is easily available as a solvent. Lethal poisoning may due to inadvertent exposure, such as spilling concentrated solvents onto the skin, or consciously abused, such as inhaling fumes or drinking solutions[1].

Symptoms of methanol poisoning may be delayed for 1 to 72 hours due to methanol is nontoxoic itself. A latent period is needed for being metabolized to formaldehyde and formic acid which is responsible for metabolic acidosis and toxication of methanol. The treatment of methanol toxicity focuses on three major issues: 1. prevention of methanol conversion to its toxic metabolites 2. correction of metabolic acidosis 3. elimination of methanol and its toxic metabolites[2,3,4,5]. In Taiwan, methanol intoxication has been reported in inadvertent ingestion of methanol substituted for ethanol. We present a fatal case of methanol intoxication and review the literature.

Case report

A 36 year-old male with a history of alcohol abuse was admitted to ER with complaints

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of nausea, vomiting with some blood clot, epigastric pain, dizziness and headache 24 hours after ingestion of a bottle of unknown quality of alcoholic beverage. Physical examination revealed a clear conscious, grossly normal appearance with mild tenderness over epigastric area, blood pressure 120/80 mmHg, respiratory rate 16/min and, pulse rate 85/min. Laboratory data including BUN, creatinine, electrolyte, hemoglobin, amylase, white blood cell count were all in normal range initially except abnormal transaminase (AST 136, ALT 66). 4 hours later, however, he experienced dyspnea, blurred vision, bilateral leg soreness and Kussmaul's respiration. The blood sample was taken again by that time and arterial blood showed pH 7.065, pCO_2 8.2 mmHg, bicarbonate 2.3 meq/L; sugar 120 mg/dL, sodium 142 mmol/L, potassium 4.3 mmol/L, chloride 95 mmol/L, BUN 12 mg/dl, creatinine 1.6 mg/dl, AST 119 IU/dL, ALT 55 IU/dL, anion gap 48 was calculated. Sudden onset of unconscious and cardiopulmonary arrest with bilateral dilated, fixed pupil happened 20 minutes later, but he was successfully resuscitated with fluid, bicarbonate, epinephrine, external cardiac massage, intubation with mechanical ventilation. Then he was transferred to medical intensive care unit. At medical ICU, DM, lactic acidosis, sepsis, alcoholic ketonacidosis, uremia, ethanol, methanol intoxication was taken into consideration for different diagnosis of high anion gap of metabolic acidosis. No ketone was found in urine. Lactic acid 25.4 mg/dl, ethanol level <10 mg/dl were noted. Blood methanol level was sent to other laboratory due to inadequate equipment at our hospital. Hemodalysis was considered for persistant severe metabolic acisosis which was difficult to correct. However, severe hypotension (BP around 80/40 mmHg) although with adequate fluid and high dose of dopamine make hemodialysis impossible.

Serum methanol level up to 96.7 mg/dL was noted on the second hospitial day more than 48 hours after withdraw his ingestion. Patient expired on the 4th hospital day.

Discussion

A alcoholic patient, may conceal the ingestion of an ethanol substitute or may be unable to provide a history of his ingestion. The symptoms of methanol intoxication, such as nausea, vomiting, abdominal pain, dyspnea, hyperventilation and conscious disturbance may not be easily to differential from the symptoms of drunk. In Taiwan, many cases of methanol intoxication have reported, as methanol is easily available and inexpensive.

Methanol in its pure form is a colorless, volatile, nontoxic, odorless liquid. Methanol has been used as an ethanol substitute for over a century. It can be absorbed from the gastrointestinal tract mucosa, the skin or by inhalation. Intoxication has been reported in those three form of absorption[6,7]. Peak level occur from 30 minutes to 4 hours after ingestion[1][2].

Small quantity of methanol are eliminated by the lung and kidneys. Diuretics can not enhance the elimination. Bulk of methanol is eliminated by oxidation to its toxic compounds. Formaldehyde and formic acid (especially the later) are the toxic metabolites.

Pathophysiology

Methanol intoxication occurs reproducibly only in humans, primates, and certain folate-deficient nonprimates. Methanol and ethanol share the common metabolic pathway. The hepatic enzyme alcohol dehydrogenase converted methanol to formaldehyde and aldehyde dehydrogenase oxidizes formaldehyde into formic acid. Formaldehyde administered intravenously to a monkey, had a half life of 1.5 minutes[8]. The

metabolism of formic acid is the folate-dependent rate-limiting step in the detoxication of methanol.

Formate accumulation was primarily responsible for the metabolic acidosis. This has been demonstrated in many studies in monkeys [8], unless hypotension with lactate formation prevails[3].

Sign and symptoms

Methanol intoxication has a characteristic latent period before onset of clinical symptoms and signs. The symptoms occur between 12 and 24 hours after ingestion but may appear as early as 1 hours or delay as late as 72 hours, depending on the level of alcohol dehydrogense and the coingsetion of ethanol. Initial symptoms (epigastric pain, nausea, vomiting) was noted about 18-24 hours after methanol ingestion of methanol in our patient. The clinical symptoms are almost limited in the CNS, gastrointestinal tract, and eyes. Blurred vision, decreased visual acuity, photophobia, are the most common complaints, "like being in a snowstorm" was a frequently quoted description in the patients[1,9]. The CNS symptoms includ inebriation, lethargy, headache, vertigo, delirium, Kussmaul's respiration, inspiratory apnea, coma, terminal opisthotonus and seizure. About 50% of victims had nausea, vomiting. Excruciating upper abdominal pain was complained in about 60% of the patients in two large epidemics[1]. In the present case, gastointestinal tract symptoms including nause, vomiting, epigastraglia was the initial complaints, then follow with headache, blurred vision, dizzness. When Kussmaul's respiration present, the patient's condition shock down very quickly.

Ocular signs include fixed and dilated pupil, optic disk hyperemia, retinal edema. Demyelination of the optic nerve secondary to inhibition of axoplasmic flow is the postulated mechanism of ocular toxicity[10].The imaging of bilateral putaminal hemorrhage necrosis, cerebral and intraventricular hemorrhage, cerebellar necrosis and diffused cerebral edema have been described as sequelae of severe methanol intoxication[11,12,13]. Cerebral edema, putamen necrosis, brain hemorrhage demonstrated by CT scan in a review study of methanol intoxication showed the incidence of at least 15/45, 7/45, 6/45, respectively[12]. Systemic heparinization during hemodyialysis may contribute to the hemorrhage [12]. An elevated serum amylase level was frequently reported and pancreatic necrosis was confirmed in 13 of 17 autopsies in the Altanta epidemic. It was also noted (serum amylase: 321 U/L on hospital 2nd day) in our patient.

Laboratory data reveals high anion gap metabolic acidosis and a significant increase in the osmolar gap. Coingestion of ethanol also increase the osmolar gap. However, one should quantitate the contribution by ethanol to the osmole gap. One way of accomplishing this is to include a term by ethanol (EtOH) in the equation for calculated osmolality.

$Osm_{est} = 2\ Na^{+} + BUN/2.8 + glucose/18 + EtOH/4.6$[14]

High anion gap metabolic acidosis (serum pH 7.065, bicarbontae 2.3 meq/L, anion gap 48) was measured in our patient.

Treatment

The treatment of methanol include three major issues: prevent methanol conversion to its toxic metabolities, correct the metabolic acidosis, eliminate the methanol and its toxic metabolities [2,4,5,6]. Ethanol has approximately 10 times greater affinity for alcohol dehydrogenase than methanol. Thus, the administration of ethanol to prevent methanol conversion is a well-known measure of treatment of methanol intoxication.

Methanol level greater than 20 mg/dL, methanol intake greater than 30 ml or 0.4 ml/kg, or evidence of metabolic acidosis or abnormalities in vision, are the absolute indications for treatment with ethanol administration[2,6]. Serum ethanol concentration should be maintained over 100 mg /dL, then alcohol dehydogenase could be maximally occupied by ethanol and very little methanol is metabolized.

The administration of ethanol can be by intravenous or by oral route. The loading dose is 0.6 g/kg. Maintenance infusions of ethanol depend on the drinking history of the patient. Ethanol is also be easily dialyzed, so closely monitoring of levels are needed to adjust the maintenance infusion rate to maintain level around 100 mg/dL. Intravenous ethanol solutions are not commercially available in Taiwan. If oral ethanol therapy is difficult (e.g. ileus after shock in the present case), absolute (95%) alcohol, may be diluted to a 10% solution by the way of IV-tubing with micropore filters[1].

Folate is an important cofactor in the detoxication of methanol. Primates have decreased hepatic store of folate and less dihydrofolate reductase activity than rodents[15]. Some investigators suggest that folate supplements be included in treatment of patient. Fifty mg of folic acid or folinic acid IV every 4 hours for several days has was recommended.

4-methyl pyrazole (4-MP) is a competitive inhibitor of alcohol dehydrogenase. In animal experiment, 4-MP slow the metabolism of methanol to their toxic metabolites. Controlled clinical studies are under way[1,2]. It is still unavailable in Taiwan now.

Severe metabolic acidosis may leading to myocardio-depression and decrease systemic vascular resistance[16]. But many investigations demonstrated no significant effect of severe acidosis on myocardial contractility and sodium bicarbonate seem to have no significant effect on intramyocardial pH in animal model[17]. Although some authors suggest the administration of sodium bicarbonate for correction of metabolic acidosis, there are no definitive role and indications on treatment of methanol intoxication. Sodium biacarbonate was administrated for correcting the metabolic acidosis in our patient, no obivous improvement was got.

Methanol and its toxic metabolities are low molecular weight and are easily dialyizd. Hemodialysis or peritoneal dialysis is useful in removal of them, but the former is superior. The indications for hemodialysis include evidence of metabolic acidosis which is difficult to correct with bicarbonate, ingestion of more than 30 ml of methanol (the minimal lethal dose), serum methanol level greater then 50 mg/dl, evidence of visual impairment or abnormalities on fundoscpoic examination and alteration in mental status. Dialysis should be continued until the serum methanol fall below 25 mg/dl[2,6]. As mentioned above, heparinization during hemodialysis may contribute brain hemorrhage, the use of systemic heparinization during hemodialysis in treatment of methanol intoxication should minimized[12]. Ethanol is also easily dialyized, ethanol level during hemodialysis should be closely monitored and be kept greater than 100 mg/dl. Hemodialysis was certainly considered in the present case, but uncorrectable hypotension (systolic blood pressure <80 mmHg) even with high dose of inotropic agent making it impossible.

Lacking of accurate history of methanol ingestion, rapid disorientation of patient's condition, and unable to performed hemodialysis due to severe hypotersion contribute the death of this patient. The outocome in patients with methanol intoxication does not depend on initial serum methanol level only, the interval between ingestion of methanol and institution of treatment and the level of metabolic acidosis are also important

determining factors. The treatment should not be delayed when methanol intoxication is suspected.

Reference

1. Burkhart KK. and Kulig KW. The other alcohols. Emerg Med Clin of Nor Am 1990; 8:913-928.
2. Pamies RJ, Surgar D, Rives LA, et al. Methanol intoxication. Postgraduate Medicine 1993; 8:183-194.
3. Jacobsen H, Wiik-Larsen E, et al. Studies on methanol poisoning. Acta Med Scand 1982; 212:5-10.
4. Palmisano J, Gruver C, Adams ND. Abence of anion gap metabolic acidosis in severe methanol poisoning: a case report and review of the literature. Am J of Kid Dis 1987; 9:441-444.
5. Gonda A, Gault H, Churchill D, et al. Hemodialysis for methanol intoxication. The Am J of Med 1978; 64: 749-58.
6. McCormick MJ, Mogabgab E, Adams SL. Methanol poisoning as a result of inhalational solvent abuse. Ann Emerg Med 1990; 19:639-42.
7. Kahn A, Blum D. Methyl alcohol poisoning in an 8-month-old boy: an unusual route of intoxication. J Pediatr 1979; 94:841-3.
8. McMartin Ke, Martin-Amat G, Makar AB, et al. Methanol poisioning. V. Role of formate metabolism in the monkey. J Pharmacol Exp Ther 1977; 201:564-72.
9. Ellenhorn MJ, Barceloux DG. Medical toxicology: diagonsis and treatment of human poisoning. New York: Elsevier, 1988:801-5.
10. Sharpe JA, Hostovsky M, Bilbao JM, et al. Methanol optic neuropathy: a histological study. Neurology 1982; 32:1093-100.
11. Gaul HP, Wallace CJ, Auer RN, et al. MR finding in methanol intoxication. Am J of Neuroradiology 1995; 16:1783-86.
12. P. T. Phang, et al. Brain hemorrhage associated with methanol poisoning. Crit Car Med 1988; 16:137-40.
13. Rubinstein D, Escott E, and Kelly JP. Methanol intoxication with putamen and white matter necrosis: MR and CT findings. Am J of Neuroradiology 1995; 16:1492-94.
14. Kruse JA and Cadnapaphornchai P. The serum osmale gap. J of Crit Car 1994; 9:185-97.
15. Black KA, Eells JT, Noeker PE, et al. Role of hepatic tetrahydrofolate in the species difference in methanol toxicity. Pro Natl Acad Sci USA 1985; 82:3854-8.
16. Kette F, Weil MH, vonPlanta M, et al. Buffer agents do not reverse intramyocardial acidosis during cardiac resucitation. Circulation 1990; 81:1660-6.
17. Prabodh M. and Robert A. Kloner. Effects of acid base disturbance on cardiovascular fuction. Crit Car Clin 1987; 5:747-58.

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甲醇中毒病例報告及回顧

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甲醇中毒對人類而言是一種致命的中毒，其毒性具經潛伏期後，逐漸發生視力缺陷、意識混亂及腹痛等症狀的特性。我們報告一36歲男性，在喝完一瓶酒24小時後，因噁心、嘔吐、上腹痛、全身無力到院求診。身體檢查除輕微上腹壓痛外，其它生理現象尙屬正常。實驗室檢查也都在正常範圍。但4小時後，病人感到呼吸困難、視力模糊、兩腳酸痛、併急促呼吸。動脈血氣體分析酸鹼值爲7.065、二氧化碳濃度8.2mmHg，重碳酸濃度爲2.3mg/L。20分鐘後，病人昏迷、心肺衰竭、腫孔放大。雖經積極治療，病人於住院後四日死亡。住院第二日測得血液中甲醇濃度爲96.5mg/L。甲醇中毒起初症狀不明顯，但如果病人有食用酒精的病史、併發腹痛、視力模糊、意識混亂、血液氣體分析呈現代謝性酸中毒，甲醇中毒因列入重要鑑別診斷。文中並討論甲醇中毒治療的時機及方法。