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Formic and Lactic Acidosis in a Fatal Case of Methanol Intoxication

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A 33-year-old white man was admitted to the University of Utah Hospital after about 30 h of various symptoms, including blurred vision and (eventually) severe left flank and back pain. Upon admission, his serum pH was 6.80 and serum bicarbonate concentration (calculated from p_{CO_2} and pH) was 3.9 mmol/L. The etiology for the acidosis became apparent 10 h after admission, when assay of the serum prepared from a blood specimen obtained at admission revealed a methanol concentration of 74 mmol/L (2.4 g/L). At this time the patient was placed on hemodialysis and intravenously infused with sodium bicarbonate. The methanol concentration in serum had decreased to 21 mmol/L 2 h later. Formate and lactate concentrations were, respectively, 10 and 23 mmol/L in serum sampled 4.5 h after hospitalization, at which time serum pH was 6.91 and bicarbonate concentration 7 mmol/L. The patient eventually died with extensive neuropathy.

Additional Keyphrases: toxicology · electrolytes · "anion gap"

Methanol intoxication in primates has been associated with various degrees of metabolic acidosis and neuropathy (1-5). Formate, a product of methanol metabolism, has been regarded as a major contributor to the acidosis of methanol poisoning (2, 3, 6). It remains uncertain, however, whether lactate is also a component of the acidosis of methanol intoxication in humans (3, 7).

Here we report a case of severe methanol poisoning in which the concentrations of methanol in serum were as great as 74 mmol/L (2.4 g/L). To our knowledge, only one other case of methanol poisoning has been reported in which both formate and lactate were actually measured in the serum (7). In agreement with that report (7), lactate was the major component of the acidosis in this patient. However, formate and lactate together accounted for approximately double the observed decrease of bicarbonate concentration or increase of anion gap, with the concentrations of other major serum electrolytes being within reference limits.

Materials and Methods

Bicarbonate concentrations (calculated from p_{CO_2} and pH) and pH were determined by an ABL 300 blood gas analyzer

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(Radiometer America, Inc., Westlake, OH). Lactate concentrations were measured in an *aca* III discrete analyzer (Clinical Systems Division, Du Pont Co., Wilmington, DE). Anion gap was calculated from the formula $(Na^+) + (K^+) - (Cl^-) - (HCO_3^-)$. Sodium, potassium, and chloride ion concentrations were determined by use of ion-selective electrodes, in an Astra-8 analyzer (Beckman Instruments, Inc., Brea, CA).

Methanol and ethanol concentrations were measured in a Model 2700 "Moduline" gas chromatograph (Varian Associates, Inc., Walnut Creek, CA) as previously described (8). Formate concentrations were determined by an enzymatic fluorescence method (9), with use of a modified blanking procedure (10).

The normal reference values (mean \pm 2SD) for the various analytes are as follows: bicarbonate, 24 ± 4 mmol/L (3, 6); anion gap, 16 ± 2 mmol/L (11); lactate, 0.4 ± 0.4 mmol/L (7); formate, 0.2 ± 0.2 mmol/L (10, 12); methanol, 0; pH, 7.4 ± 0.05 .

Case History and Results

The patient was a 33-year-old white man who had been complaining over a 30-h period of various symptoms of methanol poisoning, including abdominal pain, nausea, weakness, dizziness, blurred vision, and eventually severe pain in his left flank and back. Enroute to the University of Utah Hospital, he became unresponsive and was in seizure upon arrival. By arrival he was flaccid with no tonic-clonic movements and no incontinence, having been intubated by the paramedics. Respiratory arrest also occurred enroute to the hospital, but he was adequately compensated for oxygen by immediate use of a respirator. Blood pressure was normal, and the patient maintained adequate peripheral perfusion and urinary output throughout his hospitalization until shortly before his irreversible cardiorespiratory arrest.

At admission, the patient was severely acidotic—serum pH 6.80, calculated bicarbonate concentration 3.9 mmol/L—the etiology of which was not known until 10 h after admission, when a methanol concentration of 74 mmol/L (2.4 g/L; toxic concentration, >0.2 g/L) was measured in serum from a specimen collected 0.5 h after admission. The patient was then immediately placed on hemodialysis and at the same time intravenously infused with sodium bicarbonate. In 2 h the concentration of methanol in his serum had decreased to 21 mmol/L (from 64 mmol/L measured just before dialysis). The formate concentration, which had been 10 mmol/L 4.5 h after admission, was now decreased to 1 mmol/L.

Table 1 lists serum pH, anion gap, and some pertinent analyte concentrations in serum with time. Approximately 5 h after admission, formate alone accounted for roughly half of the decrease in bicarbonate concentration (from the

Table 1. Serum pH, Anion Gap, and Concentrations of Pertinent Analytes in a Case of Methanol Intoxication

Time after admission, h	pH	Concentration, mmol/L				
		Bicarbonate	Anion gap	Methanol	Formate	Lactate
0.5	6.80	4	—	—	—	—
1	7.02	6	34	74	—	8
4.5	6.91	7	35	—	10	23
11 ^a	—	—	—	64	—	—
13	7.61	16	—	21	1	4

^aHemodialysis begun in conjunction with infusion of sodium bicarbonate.

normal reference value of 24 mmol/L) and half of the increase in anion gap (from the normal reference value of 16 mmol/L). Formate and lactate together, however, accounted for approximately double the decrease in bicarbonate concentration and the increase in anion gap. All other major electrolyte concentrations in the serum were within reference limits, hence the molar equivalence between the decrease in serum bicarbonate concentration and the increase in anion gap (Table 1).

Computerized axial tomographic (CAT) scans of the head on the fourth and 12th day of hospitalization revealed diffuse low-density areas in the white matter and the basal ganglion, consistent with extensive necrosis. Electroencephalograms recorded on the first and 10th day of hospitalization were consistent with sequelae of severe, diffuse cerebral insults. On the 18th day of hospitalization, the patient had no brainstem response, his pupils being fixed and dilated. His blood pressure declined over the next 4 h, and electrocardiographic activity ceased, with no spontaneous respirations.

Discussion

Experimental methanol poisoning in certain monkeys (1, 2, 4), in folate-deficient dogs (13) and rats (14), and clinical observations (3, 6, 8, 15) indicate that formic acidosis is a major contributor of the metabolic acidosis of methanol intoxication. Formic acid seems to be the cause of the visual impairment characteristic of methanol poisoning in humans (4, 5).

McMartin et al. (1) stated that formate concentrations could account for only 50% of the increase in anion gap in their studies of methanol-poisoned monkeys. Values for all the major blood electrolytes except bicarbonate were within reference limits; thus other organic anions may accumulate in monkeys intoxicated by methanol. The authors did not report lactate measurements. Clay et al. (2), however, found that the increased concentrations of formate in plasma from their methanol-poisoned monkeys almost completely accounted for the decrease in plasma bicarbonate concentrations; concentrations of plasma lactate were only slightly increased (2). In two cases of methanol poisoning involving humans, formate accounted for approximately half of the bicarbonate deficit and anion gap excess in one case, but was equivalent to 120% of the decrease in bicarbonate concentration in the other case (6). In 10 cases of methanol poisoning recently reported (16), formate accounted for 45 to 120% (mean, 90%) of the decrease in bicarbonate concentration and made up for 80 to 200% (mean, 120%) of the increase in anion gap (3). In a case involving combined methanol and formaldehyde poisoning (17), formate accounted for approximately a third of the decrease in serum bicarbonate concentration and a third of the increase in the anion gap. However, in none of these cases was lactate measured.

Increased blood concentrations of lactate in methanol poisoning have been reported by several investigators (7, 18).

In one case, a considerable amount of lactate was measured in the absence of circulatory failure (7, 19), such that lactate (11.5 mmol/L) and formate (7 mmol/L) together accounted for approximately 90% of the decrease in serum bicarbonate concentration and the resulting increase in anion gap.

In the present case, the concentration of lactate in serum was considerably increased (as much as 30-fold the upper reference limit). Although the patient underwent respiratory arrest enroute to the hospital, there was an immediate and adequate respiratory compensation throughout the patient's hospitalization. Considering the patient's normal cardiac and urinary output, lactate probably did not result from ischemia related to hypotensive shock. As Smith et al. (7) observed in a case of advanced methanol intoxication, lactic acid contributed significantly (in fact, approximately double that of formic acid) to the acidosis in the case we report. Smith et al. proposed that the oxidation of methanol would increase the intracellular NADH/NAD⁺ ratio, thus stimulating anaerobic glycolysis and lactate production. Formate inhibits mitochondrial respiration at the cytochrome *aa₃* stage of the electron-transport chain (20). In severe cases of metabolic acidosis, aerobic metabolism is compromised, organic acids leak from cellular compartments, and lactic acid accumulates. Consequently, we conclude that the increase in serum lactate from 8 mmol/L 0.5 h after admission to 23 mmol/L 4 h later despite adequate circulation is, at least in part, the result of the metabolic effects of formate.

Because of equimolar relationships between formic acid concentration and bicarbonate deficit, some investigators have concluded that formic acid is the major, if not the sole, contributor to methanolic acidosis (3, 6). The formate concentration alone surpassed the decrease in bicarbonate concentration in half of the cases of methanol poisoning (3, 6). In the case reported here, although formic acid accounted for half of the decrease in bicarbonate concentration, combined with lactic acid it was responsible for approximately double the decrease in bicarbonate concentration. These observations may be explained by considering other proton acceptors such as proteins and inorganic phosphate, both of which have good buffering capacities at physiological pH. In general, the concentrations of all the acids contributing to an acidotic state is expected to exceed the decrease in bicarbonate concentration because some of the protons would be accepted by anions other than bicarbonate. The contribution of phosphate as a proton acceptor may become even more important, phosphate having been reported to be increased in lactic acidosis (21). Therefore, an equimolar relationship between the increase in formate (or in the anion of any other strong acid) and the decrease in bicarbonate concentration cannot preclude other acids (e.g., lactic acid in methanol poisoning) from being considered as a contributor to the acidosis.

In this patient the concentration of formate in serum was 25-fold the upper reference limit of normal (0.4 mmol/L) about 6 h before methanol intoxication was diagnosed. This could have reached 16 mmol/L (40-fold the upper reference limit) just before hemodialysis, considering that formate oxidation to carbon dioxide is probably the rate-limiting step in the overall metabolism of methanol in humans (6, 17) and that methanol was metabolized and cleared in this case at the rate of 1 mmol/L per hour (Table 1). Assuming a uniform distribution of methanol to total body water (22),

we can conclude that the patient probably ingested at least 1.5 g of methanol per kilogram of body mass.

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