Review

Uncoventional Views on Certain Aspects of Toxin-Induced Metabolic Acidosis

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This discussion will highlight the following 9 specific points that related to metabolic acidosis caused by various toxins. The current recommendation suggests that alcohol dehydrogenase inhibitor fomepizole is preferred to ethanol in treatment of methanol and ethylene glycol poisoning, but analysis of the enzyme kinetics indicates that ethanol is a better alternative. In the presence of a modest increase in serum osmolal gap (<30 mOsm/L), the starting dose of ethanol should be far less than the usual recommended dose. One can take advantage of the high vapor pressure of methanol in the treatment of methanol poisoning when hemodialysis is not readily available. Profuse sweating with increased water ingestion can be highly effective in reducing methanol levels. Impaired production of ammonia by the proximal tubule of the kidney plays a major role in the development of metabolic acidosis in pyroglutamic acidosis. Glycine, not oxalate, is the main final end product of ethylene glycol metabolism. Metabolism of ethylene glycol to oxalate, albeit important clinically, represents less than 1% of ethylene glycol disposal. Urine osmolal gap would be useful in the diagnosis of ethylene glycol poisoning, but not in methanol poisoning. Hemodialysis is important in the treatment of methanol poisoning and ethylene glycol poisoning with renal impairment, with or without fomepizole or ethanol treatment. Severe leucocytosis is a highly sensitive indicator of ethylene glycol poisoning. Uncoupling of oxidative phosphorylation by salicylate can explain most of the manifestations of salicylate poisoning.

Key Words: metabolic acidosis; toxin; ethylene glycol; methanol; poisoning; urine osmolal gap

The following contains short discussions on certain aspects of toxin-induced metabolic acidosis, which represent this author's unconventional views on them or highlight some underemphasized or misunderstood aspects of these disorders.

Which is better: ethanol or fomepizole?

The current consensus is that fomepizole is better than ethanol for treatment of methanol and ethylene glycol poisoning, mainly on the basis that it has fewer side effects and is easier to use[1, 2], although that the cost of fomepizole, at $1,000 for a 1.5 g ampule or an average cost of about $4,000 per patient, is much greater than that of ethanol. The comparison of side effects is based on the usual recommended dose of ethanol, which is set to maintain plasma levels at 100 mg/dL or higher until plasma methanol or ethylene glycol levels decrease below 20 mg/

dL. At the recommended dose of ethanol, many patients, especially those not accustomed to ethanol drinking, would indeed be severely intoxicated, and develop side effects.

The recommended maintenance level of plasma ethanol for treatment of methanol and ethylene glycol poisoning has not been determined either by careful theoretical analysis or by empirical evidence[3]. Ethanol is used to treat intoxication of methanol and ethylene glycol because hepatic ethanol dehydrogenase is the main enzyme for their metabolism, but the enzyme has much greater affinity to ethanol than to either chemical. Since toxic effects of these alcohols result from production of their metabolites, administration of ethanol, being the preferred substrate of the enzyme, prevents metabolism of toxic alcohols. In fact, Km values of ethylene glycol and methanol are about 40–50 fold greater than that of ethanol[4, 5]. Km for ethanol is 5.2 mg/dL, while those for methanol and ethylene glycol are 171.7 and 275.2 mg/dL respectively[4, 5].

Patients with ethylene glycol and methanol poisoning have varying plasma levels of the toxic alcohols at the time of admission to the hospital. For example, in case reports by Ekins et al., the initial plasma levels ranged between 46 mg/dL and 377 mg/dL[6]. Similarly, patients of Pappas and Silverman had plasma methanol levels between 42 and 464 mg/dL[7]. Yet, everyone was treated with ethanol at the same plasma level, 100 mg/dL. Furthermore, during hemodialysis, plasma levels of toxic alcohols decrease rapidly, but it is recommended to maintain the same plasma levels of ethanol. Davis et al. treated a patient with a plasma ethylene glycol level of 888 mg/dL (143 mmol/L)[8], with the same ethanol dose. Schwerk et al. treated a patient with a even higher level of ethylene glycol, 3,900 mg/dL (629 mmol/L), with the standard dose of ethanol[9]. The highest concentration of plasma methanol intoxication was the case reported by Martens et al.[10], and the patient had a plasma methanol of 921.2 mg/dL, and was again treated with the standard dose of ethanol.

Indeed, it has been shown in dog experiment that plasma level of ethanol of 35 mg/dL is as effective in preventing metabolism of ethylene glycol as 140 mg/dL of ethanol[11]. At the plasma level of ethanol at 35 mg/dL, most people would not be too symptomatic. It is not even known whether 35 mg/dL of ethanol is the minimum necessary level for most patients with toxic alcohol poisoning. If a patient with a methanol level of 961.3 mg/dL can be effectively treated with 100 mg/dL of ethanol, it would seem reasonable to assume that a patient with methanol intoxication at 1/5 of the plasma level should be effectively treated at 1/5 the usual dose of ethanol, 20 mg/dL (6.3 mmol/L). The concentration of 20 mg/dL is still more than 5 times the Km value of ethanol for alcohol dehydrogenase, and at this concentration ethanol metabolism would occur at about 83% of the maximal capacity. In the management of ethanol and ethylene glycol poisoning, one can quickly assess the approximate plasma level of the toxic alcohols by the measurement of osmolal gap. If the gap is less than 50 mOsm/L, one can safely initiate the ethanol treatment with maintenance of plasma level at about 20 mg/dL. This level that can be easily achieved by drinking a half glass of wine or a can of beer. At higher level of toxins, one can start ethanol therapy at a proportionately higher rate, but the rate can be safely reduced once hemodialysis is initiated. I might add that complete inhibition of metabolism of methanol and ethylene glycol is not necessary; but the aim should be to reduce its metabolism sharply, e.g. to less than 20 mg/dL. The body can handle the small load of these metabolites, which are normally produced in the human body in small quantities.

On the basis of the same principle, it would not be necessary to maintain the same plasma concentration of fomepizole (8.6–24.6 mg/L; 100–300 µmol/L) for all patients with methanol or ethylene glycol poisoning regardless of the plasma levels of the toxins[12-15]. Velez et al. treated a patient with an ethylene glycol level of 706 mg/dL with fomepizole at the standard dose, while others have treated patients with plasma ethylene glycol levels of under 50 mg/dL with the same dose. Since both the drug and toxins are competitive inhibitors of the toxic alcohol on alcohol dehydrogenase, lower blood levels of

toxic alcohols would demand commensurate reductions in fomepizole. The current recommendation calls for increasing the fomepizole dose during hemodialysis on the rationale that the drug is rapidly removed by dialysis. However, as the drug is removed, the toxic alcohols are also removed, and hence competition is lessened also. Thus, increases in fomepizole dosage would be necessary during hemodialysis.

There is evidence that H-2 blockers inhibit alcohol dehydrogenase and would inhibit the metabolism of methanol[16]. Indeed, ranitidine has been used to treat methanol toxicity in rats[17]. Perhaps, this class of drugs could turn out to be a much cheaper alternative to fomepizole in treating methanol poisoning. On the other hand, inhibition of ethylene glycol by H-2 blockers is not as effective.

Sauna bath and exercise for methanol intoxication

Near complete inhibition of alcohol dehydrogenase to prevent metabolism of methanol either with ethanol or fomepizole results in a very long half life of methanol, 43 hours[18]. The concentration of methanol in urine is equal to that in plasma, but there is some extra-renal loss through insensible perspiration. Hemodialysis is the best way to remove methanol, but the procedure is not always available. Forced diuresis can increase the excretion of methanol somewhat; excreting 10 L of urine per day by a person with 40 L of total body water could remove about 25% of the methanol in the body in 24 hours. Another approach is to increase insensible loss by sauna bath or exercise. This is based on the principle that methanol has much higher vapor pressure than water. At 37°C, vapor pressure of water is 47 mm Hg, and that for methanol is 230.5 mm Hg, about 5 times that of water. Loss of 1 L of water by evaporation would have an equivalent methanol clearance of 5 L, or 83 mL/min. This is not as efficient as hemodialysis clearance of methanol, about 200 mL/min, but is still quite substantial.

Leucocytosis in ethylene glycol poisoning: possible diagnostic value

Leucocytosis is a consistent finding in ethylene glycol poisoning, and usually it is quite severe[19-22]. Mydlik et al. noted, in his review of the record of 17 patients with ethylene glycol poisoning, leucocytosis in all of them[23]. It is possible that the leucocytosis is in response to the stress of severe metabolic acidosis, but leucocytosis is not always found or as severe in metabolic acidosis caused by other toxins. The mechanism is unknown, but is tempting to speculate that it could be a response to tissue deposits of calcium oxalate crystals. Leucocytosis is a common clinical manifestation, and is not a specific finding for ethylene glycol poisoning, but its universal finding makes it a useful diagnostic tool in that one can rule ethylene glycol poisoning in the absence of leucocytosis.

Oxalate is not the major endproduct of ethylene glycol metabolism

In the discussion of ethylene glycol metabolism, most authorities emphasize metabolism of ethylene glycol to oxalic acid as the major metabolic pathway[14]. It is clear that production of oxalic acid is a clinically relevant and diagnostically useful pathway of ethylene glycol metabolism. Appearance of calcium oxalate crystals in urine is almost universal, and deposits of calcium oxalate in the tissues including the kidney is well recognized, and is implicated as the cause of some of the toxic effects of ethylene glycol[24, 25]. Oxalate over-production also explains hypocalcemia, which is very common in ethylene glycol poisoning. However, quantitatively, oxalate is a minor byproduct of ethylene glycol poisoning. The immediate precursor of oxalate is glyoxylate, which is converted to oxalate by the action of lactate dehydrogenase (LDH). The most important pathway is conversion to glycine by the action of alanine-glyoxylate aminotransferase with vitamin B6 as a co-factor[26]. The quantitative unimportance of oxalate pathway can be easily appreciated when one

calculates the total extracellular calcium content. At plasma calcium of 10 mg/dL (2.5 mmol/L), the amount of total calcium in the extracellular fluid (ECF) is about 1,600 mg for a person with extracellular volume of 16 L. The lethal dose of ethylene glycol is considered to be about 100 mL. Since specific gravity is 1.246, the amount is equal to about 124 g or about 12,414 mg/dL. Conversion of mere 2% of these 12,414 mg/dL would chelate the entire calcium pool of the ECF compartment. Clearly, the amount of oxalate production is much less than 1,800 mg (40 mmol).

Ethanol and fomepizole are not useful in toluene and benzyl alcohol poisoning

Ethanol dehydrogenase is a non-specific enzyme with many substrates including benzyl alcohol. However, either ethanol or fomepizole has been tried or advisable to treat benzyl alcohol poisoning. One of the reasons for not using ethanol to treat benzyl alcohol poisoning is that the main enzyme responsible for metabolism of benzyl alcohol in humans is nicotinamide adenine dinucleotide phosphate (NADPH)-dependent cytochrome-450 oxidase [27], not alcohol dehydrogenase. In certain species, alcohol dehydrogenase metabolizes benzyl alcohol, but the affinity of benzyl alcohol to alcohol dehydrogenase is actually greater than ethanol. Furthermore, metabolic endproducts of benzyl alcohol, benzoic acid and hippuric acid, do not have much harmful effects, but actually may possess some beneficial effects. Both acids are the main organic acids present in cranberry juice, and are thought to be responsible for its antibacterial effects in the prevention of urinary tract infection (UTI).

Uncoupling of oxidative phosphorylation is the main mechanism of salicylate poisoning

Salicylate poisoning, a major cause of poisoning because of its widespread use, has many different clinical manifestations, and one unifying mechanism that could explain most of the manifestations of salicylate poisoning

is uncoupling of oxidative phosphorylation. Salicylate is an uncoupler [28, 29], and has a chemical structure that is quite similar to a better known uncoupler, 2, 4-dinitrophenol. Glarborg et al. have shown that uncoupling of oxidative phosphorylation occurred at a salicylate concentration between 483.4 and 773.5 mg/L [30]. Extensive uncoupling increases glucose and oxygen consumption, and results in adenosine triphosphate (ATP) deficiency. Evidence indicates that much of excess glucose utilization occurs in the brain. In one case report of salicylate poisoning, 125 g of glucose had to be infused over 5 hours to treat hypoglycemia, indicating that glucose consumption by the brain had increased more than five fold [31]. There is some evidence that salicylate inhibits Krebs cycle [32], but this would cause lactic acidosis, not excessive consumption of glucose. The following are some of the manifestations of salicylate poisoning that can be explained by uncoupling.

1. Fever

Aspirin is an antipyretic, but fever is common in salicylate poisoning, and this is explained by excessive glucose utilization creating heat.

2. Tinnitus and deafness

ATP deficiency of inner ear due to uncoupling could be the cause.

3. Ketoacidosis

This is more common in children and women, and is likely to be due to increased production of lipolytic hormones in response to central hypoglycemia. Hypoglycemia is common in salicylate poisoning [33], and sometimes brain glucose is low while plasma glucose is normal because of increased utilization of glucose due to uncoupling that is most pronounced in the brain [34].

4. Lactic acidosis

Extensive uncoupling causes deficiency of ATP, which increases production of nicotinamide adenine dinucleotide (NADH) and lactic acidosis.

5. Respiratory alkalosis

Respiratory alkalosis is the commonest acid-base disorder of salicylate poisoning, and the current explanation is that the drug stimulates the respiratory center directly. However, one plausible explanation is that increased glucose utilization in the brain would increase production of CO_2 in the brain including the central respiratory center. Thus, what appears to be systemic respiratory alkalosis could be a normal physiological response to the central nervous system (CNS) respiratory acidosis.

Urine osmolal gap for diagnosis of ethylene glycol poisoning

Unlike methanol, ethylene glycol is substantially concentrated in the urine. Mean renal clearance has been measured at 27.5 mL/min with fractional excretion of 19.8%[35]. Similar clearance values were obtained by Harry et al.[36]. This would mean that for a person who has 2 L of urine output, the urinary concentration of ethylene glycol would be about 10 times the concentration in the blood. A common recommendation for the diagnostic screening of methanol and ethylene glycol poisoning is to measure serum osmolal gap. However, when concentrations of the toxic alcohol levels are not very high, the change in serum osmolal gap would be too small to be useful for a diagnostic purpose. For example, a concentration of ethylene glycol of 50 mg/dL, the generally considered to be a clinically significant level, would give a plasma osmolal gap of mere 8 mOsm/L. A 10 fold concentration in the urine would result in urine osmolal gap of about 80 mOsm/L, and this would be much easier to detect. One concern is that measurement of urine osmolal gap is more difficult. Ideally, it should include all major cations in the urine, namely Na^+, K^+, NH_4^+, Ca^{2+}, and Mg^{2+}, and then include urea, glucose, and creatinine. The predicted urine osmolality would be then: $(Na^+ + K^+ + Ca^{2+} + Mg^{2+} + NH_4^+) \times 2 + urea/2.8 + creatinine/11.3 + glucose/18$. All of these tests are readily available in most hospital laboratories with the exception of NH_4^+ If the NH_4^+ measurement is not available, one can assume an amount of about 30 mEq/g of urine creatinine.

Urine osmolal gap = Measured Osmolality - Predicted Osmolality

This is my theoretical suggestion that has not been tested. Perhaps, experiments can be carried out in an animal model.

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