Folic acid in methanol toxicity: a retrospective cohort study

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ABSTRACT
Folic acid is a proposed adjunct to alcohol dehydrogenase inhibitors and hemodialysis (HD) in the treatment of methanol toxicity. Although animal models have shown increased formate clearance, human data regarding its efficacy are lacking. We performed a 7-year retrospective chart review of patients with methanol concentrations >10 mg/dL. We compared patients receiving scheduled dosing of 50 mg of folic acid (folate group) to those receiving no folic/folinic acid or <50 mg folic or folinic acid (low/no folate). We excluded patients who did not require hospitalization, those with alternative causes of acidosis, and those who died prior to therapy. The primary outcome measures were worsening metabolic acidosis, length of stay (LOS), and half-life of methanol. Of 27 patient visits with methanol concentration >10 mg/dL, 14 visits (11 patients) met inclusion criteria. Initial pH and methanol concentrations were similar between the two groups. There was no difference in LOS. No patients had worsening metabolic acidosis during therapy. In patients treated with and without HD, median half-lives of methanol were similar in both groups. Folic acid treatment provided no additional benefit to standard therapy for methanol toxicity. We cannot exclude potential benefit of folic acid on formate clearance.

Background
Methanol is the simplest of the alkyl alcohols and is highly toxic when ingested. Though methanol exposures in the United States have declined over the past century following the establishment of industrial regulations and pharmaceutical standards, clinically significant intoxication still occurs. Improper use of methanol-containing solvents or “outbreaks” of contaminated products continue to pose a risk to the population [1, 2].

Methanol is metabolized by alcohol dehydrogenase (ADH) then by aldehyde dehydrogenase (ALDH) to formaldehyde and formic acid, respectively. Formic acid causes metabolic acidosis by its own accumulation and through inhibition of mitochondrial cytochrome c. Vision loss results from formate accumulation in the eye because the retina lacks mechanisms to detoxify formic acid [1].

Alcohol dehydrogenase inhibitors (fomepizole or ethanol) and renal replacement therapy remain the standard treatments of methanol intoxication. ADH inhibitors prevent end organ damage by blocking metabolism to formaldehyde and formic acid. Indications for renal replacement therapy depend on the methanol concentration, presence of acidosis, or presence of end organ damage [3]. However, the benefit of folate supplementation with either folic acid or folinic acid (leucovorin) in treating methanol poisoning remains unclear. Tetrahydrofolate, the activated form of folic acid, plays a minor role in the elimination of formic acid via its incorporation into 10-formyltetrahydrofolate and subsequent hydrolysis into carbon dioxide and water (Figure 1). Though animal models suggest reduced morbidity and mortality from methanol following folic acid supplementation, human data are mixed [4–7]. We attempted to assess the benefit of therapeutic folic (or folinic acid) supplementation in methanol toxicity.
Methods

We performed a retrospective chart review from 2012 to 2018 at a tertiary care referral center with a Toxicology service. We used our clinical laboratory’s database of patients who had “toxic alcohol” testing performed (a bundled test that included ethylene glycol, isopropyl alcohol, acetone, and methanol concentrations) to screen for patients with an elevated methanol concentration (>10 mg/dL, the cutoff for a positive value in our laboratory). We used this cutoff to identify all cases of methanol intoxication that providers potentially treated. Because guidelines recommend enhanced elimination and adjunctive therapies for indications (pH < 7.15, seizures, coma, new vision deficits, etc.) other than absolute methanol concentration we wanted to initial screen all potential cases [3, 5]. We excluded patients with inadequate medical records, those with no documentation of folate dosing, and those treated at other hospitals who had specimens sent to our laboratory for quantification of methanol concentration. Additional exclusion criteria included patients discharged from the emergency department, those with toxicity from ethylene glycol or isopropyl alcohol, those with an alternate cause of acidosis, and those who died prior to initiation of therapy. We compared patients who received initial dosing with folic acid at the recommended treatment dose of either 1 mg/kg or 50 mg (therapeutic folate group) to those who either did not receive folate supplementation or received doses below recommend dosing (low/no folate group) [5]. For comparison, we further divided patients into two subgroups: those receiving hemodialysis or continuous renal replacement therapy (CRRT) and those who did not.

A single abstractor, aware of the study’s purpose, collected data into a standardized data sheet. Data collected included initial and serial methanol concentrations, pH, bicarbonate, and creatinine. We collected the dose of folic acid, frequency of dosing, and number of doses administered into a standardized data sheet. Primary outcome measures included the frequency of worsening metabolic acidosis defined as a decreasing bicarbonate during admission, length of stay (LOS), and any serious adverse outcome (including death, cardiac arrest, or development of shock). We also calculated the half-life of methanol for each patient encounter. A second abstractor separately reviewed the data blinded to folic acid dosing and ensured accuracy of half-life and outcome measures.

We performed descriptive analyses for the data. We calculated median values and interquartile ranges for the laboratory data and outcome measures.

Results

We identified 27 patient encounters with detectable methanol concentrations. Of these, 14 patient encounters met inclusion criteria, totaling eleven patients (Figure 2). Ten patients did not require treatment given low presenting methanol concentration and absence of end-organ dysfunction, one died prior to treatment, one had co-ingested ethylene glycol concomitantly, and one patient’s metabolic derangements was attributed to non-toxicologic causes. Nine patient encounters included adjunctive treatment with folic acid 1 mg/kg or 50 mg (treatment group). All received 50 mg regardless of weight. The no/low folate group comprised five patients who received no folic acid (three patients) or 1 mg daily (two patients). In the treatment group, providers ordered folic acid to be given every six hours, although administration ranged from every four to every eight hours. No patients received folinic acid. One patient was hospitalized three times with methanol intoxication, receiving therapeutic folate on two occasions and low-dose (1 mg daily) supplementation once. Another patient had one encounter in the treatment group and another in the low/no dose group.

Initial pH and serum methanol concentration were similar between groups (Table 1). There was no difference in length of stay between groups (Table 2). None of the patients included in the study developed worsening metabolic acidosis following initiation of therapy. Use of hemodialysis led to an expected reduction in the half-life of methanol. However, after stratifying patients into groups based on folate administration and HD, there was no difference in half-life with folic acid (Table 2). None of the patients included in the case series died.
Discussion

The American Academy of Clinical Toxicology recommends the use of folates in the treatment of methanol intoxication to “enhance...formic acid metabolism” [5]. These recommendations are based on our current understanding of the biochemical pathways responsible for the detoxification of methanol and limited animal data [4–6, 8]. To date, no robust human data on the efficacy of folate supplementation have been published. Zakharov analyzed patients given folate supplementation during an outbreak of methanol intoxication and found no difference in visual sequelae between groups [7]. We found that though presentation characteristics including serum methanol concentration were similar between the two groups, folic acid supplementation had no discernible effect on the patient’s length of stay in the hospital. There was no increase in adverse events or reporting of visual sequelae in the group that was not treated with high-dose folic acid.

Half-life of methanol was similar in both groups. According to Le Chatelier’s principle, supplementation of folic or folinic acid, which drives the oxidation of formic acid into water and carbon dioxide, may shift the equilibrium of methanol toward its metabolic end products thus shortening the half-life [9]. There are two reasons why this may not have any effect. The enzymatic action of 10-formyl tetrahydrofolate synthase (also known as formate-tetrahydrofolate ligase) is slow and requires expenditure of ATP. Second, the use of fomepizole prevents the oxidation of methanol into formaldehyde and, subsequently, formic acid. All of our studied patients received fomepizole within 24 h of ingestion and prior to folic acid administration. This may have obscured a possible effect of folate administration by reducing formate production. In the presence of ADH blockade, methanol clearance in expired breath accounts for 84%–87% of total clearance [8].

Further study of treatments used in infrequent poisonings such as methanol is important to improve the care of poisoned patients. Although folate supplementation confers little risk, therapies that have a clear benefit should be prioritized. We cannot rule out that a larger data set with adequate power to identify harm or one measuring serial levels of formic acid might detect benefit from adjunctive therapy with folic acid. However, the weight of currently

Table 1. Median and IQR of demographic data, laboratory values, and hemodialysis treatment duration between patients in the therapeutic folate and low/no folate groups.

|                        | Overall (N=14) | Folate group (N=9) | Low/no folate (N=5) | p-value |
|------------------------|---------------|-------------------|-------------------|--------|
| Age (y)                | 48 (44–55)    | 48 (30–51)        | 55 (48–55)        | 0.28   |
| Sex (M:F)              | 13:1          | 9:0               | 4:1               | 0.36   |
| pH                     | 7.28 (7.19–7.74) | 7.34 (7.16–7.39) | 7.2 (7.19–7.41)  | 0.94   |
| Bicarbonate (mmol/L)   | 13 (7–24)     | 15 (6–23)         | 10 (9–25)         | 0.84   |
| Lactate (mmol/L)       | 1.5 (1.0–2.1) | 1.6 (1.1–2.1)     | 1.4 (1.0–1.9)     | 0.58   |
| Creatinine (mg/dl)     | 1.0 (0.8–1.2) | 1.1 (0.8–1.2)     | 0.8 (0.8–0.83)    | 0.42   |
| Methanol (mg/dl)       | 119 (48–236)  | 118 (54–246)      | 120 (48–236)      | 0.79   |
| HD duration (h)        | 8 (7–11)      | 8 (8–10)          | 10 (8–11)         | 1.00   |

Figure 2. Scatterplot of bicarbonate concentration (y-axis) over methanol concentration (x-axis).
available evidence is not consistent with a benefit of folate administration [7, 10].

Limitations

Our study was limited by both its retrospective design and small sample size. Dosing regimens of folic acid varied and were subject to the discretion of the treating toxicologist. Though included patients received folic acid at scheduled intervals, frequency of dosing ranged from every three to every six hours. We did not stratify data according to the frequency or cumulative daily dose of folates, thus potentially obscuring dose-dependent effects.

Our retrospective study lacked direct measurement of formate concentrations. Folic acid supplementation may have a more pronounced effect in patients who have delayed presentations with greater accumulation of formate. Although a change in the half-life of formic acid may be more indicative of the effect of folic acid, we relied on the serum methanol half-life and LOS as proxies for successful treatment of methanol toxicity.

A major complication of methanol toxicity is vision loss due to retinal sensitivity to formic acid. However, none of the patients in our study underwent formal ophthalmologic testing (e.g. vision field assessment, fundoscopy, vision acuity testing) during their hospitalization. As a result, clinicians might have overlooked subclinical visual pathology.

Additionally, the small number of patients prevents our ability to detect small differences in adverse effects between groups. Despite including seven years of data at a tertiary care center that accepts transfer of critically ill poisoned patients, we did not collect many patients. A difference could exist, but the study lacked the power to detect it. If the ACMT ToxIC registry were to include data on folate administration and visual acuity testing for methanol poisoned patients, we could potentially collect enough patients to perform an adequately powered study.

Another limitation was the inclusion of a single patient with three total encounters (two in the therapeutic folate group and one in the low/no dose group). This patient could have been either unusually sensitive or resistant to the effects of methanol and/or folate thus biasing the results. However, he showed no sign of increased metabolism of methanol and had variable half-lives with no trend on serial visits (186 min, 201 min, and 159 min).

Conclusion

In this preliminary clinical study on methanol toxicity, we found no difference in methanol half-life or hospital length of stay between high dose folic acid and low/no dose folic acid.

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