FOMEPIZOLE FOR THE TREATMENT OF METHANOL POISONING
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WHAT YOU SHOULD KEEP IN MIND AS YOU READ THIS ARTICLE
Methanol poisoning produces significant morbidity, as well as mortality. Although methanol itself is not toxic, it is rapidly bioactivated in a two-step process to formate:

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\text{Methanol} \quad \xrightarrow{\text{Via Alcohol Dehydrogenase}} \quad \text{Formaldehyde} \quad \xrightarrow{\text{Via Aldhehyde Dehydrogenase}} \quad \text{Formate}
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Methanol ingestion produces an elevated osmolal gap; the formate produced by the above reactions produces an anion-gap metabolic acidosis. Formate is especially toxic to the retina, leading to visual disturbances ranging from blurry vision to complete blindness.

Treatment of methanol toxicity should include sodium bicarbonate, to correct the metabolic acidosis and decrease the passage of formate into the CNS, and folate, to promote the metabolism of formate to water and carbon dioxide. Prior to the development of fomepizole, treatment also included ethanol, to “block” alcohol dehydrogenase and prevent the metabolism of methanol to formaldehyde (thus preventing the production of formate), and hemodialysis to correct severe acidosis and remove circulating methanol. This article suggests that the routine use of ethanol and HD may be abandoned in favor of treatment with fomepizole, which effectively blocks alcohol dehydrogenase.

INTRODUCTION
- Prior to the development of fomepizole, methanol-poisoned patients were treated with ethanol
- Ethanol is difficult to dose, difficult to monitor, and may cause liver injury and/or hypoglycemia

METHODS
- In this multicenter trial, 11 patients were treated with fomepizole
- Fomepizole was dosed as 15 mg/kg IV as a loading dose, then 10 mg/kg IV every 12 hours for 48 hours, then 15 mg/kg IV every 12 hours until the methanol level was less than 20 mg/dL
- Patients received other supportive treatments, including hemodialysis (HD); HD performed for arterial pH less than 7.1, decrease in pH of 0.05 units or fall in bicarbonate 5 mmol/L; unable to keep arterial pH > 7.3; serum methanol level above 50 mg/dL; visual symptoms; slowly declining methanol level (see also P. 425).

RESULTS
- The higher the formate level, the more acidemic the patient (i.e. lower arterial pH level)
  - This is logical and expected
- After treatment with fomepizole, plasma formate levels fell
  - This suggests that fomepizole stopped the production of formate, and that levels fell as patients cleared the formate that had already been produced
- As plasma formate levels fell, metabolic acidosis improved, mental status changes improved, and visual changes improved
- Adverse reactions to fomepizole were minor
- The half-life of methanol after treatment with fomepizole was 54 hours
  - This suggests that fomepizole was effective at preventing the rapid conversion of methanol to formaldehyde via aldehyde dehydrogenase. After aldehyde dehydrogenase is blocked, elimination is renal (much slower).

DISCUSSION
- Animal studies have shown that a fomepizole level of 0.8 mg/ml is necessary to inhibit alcohol dehydrogenase; this level was present in 98% of measurements, suggesting that the protocol dosing was appropriate
- In all patients who could be evaluated, visual changes returned to baseline
- Seven patients underwent hemodialysis (HD) in conjunction with fomepizole treatment. HD should be done if:
  - The patient is markedly acidemic (pH < 7.1)
  - The patient has a very high methanol level, and HD is needed to avoid prolonged hospitalization. For example, a patient with a methanol level of 300 mg/dL would need 8 days of fomepizole therapy or one round of HD to reach a level of less than 20 mg/dL.
- This study did not compare fomepizole to ethanol
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TAKE HOME POINTS FROM THIS ARTICLE

- Fomepizole inhibits alcohol dehydrogenase, blocking the conversion of methanol to formaldehyde and preventing the production of formate.
- When methanol poisoned patients were treated with fomepizole, formic acid levels fell, metabolic abnormalities improved, and visual abnormalities improved.
- Hemodialysis (HD) may still need to be performed in many patients (see above)
- Fomepizole has an excellent safety profile, and there were few adverse events associated with its use.
- This article does not establish fomepizole as better than ethanol as a treatment for methanol poisoning; rather, it suggests that fomepizole is an effective way to block alcohol dehydrogenase. Given that fomepizole is much safer than ethanol, it is therefore appropriate to use fomepizole as a first-line agent in the treatment of methanol poisoning.