Using the Osmolal Gap to Assess Toxic Alcohol Poisoning

Opposing authors provide succinct, authoritative discussions of controversial issues in emergency medicine. Authors are provided the opportunity to review and comment on opposing presentations. Each topic is accompanied by an Editor's Note that summarizes important concepts. Participation as an authoritative discussant is by invitation only, but suggestions for topics and potential authors can be submitted to the section editors.

Editor's Note: *Identifying patients with toxic alcohol exposure can be challenging as assays are not routinely available in most emergency departments. An increased osmolal gap may be the only laboratory indicator of exposure but is an imperfect measure. This Clinical Controversies series presents opposing perspectives on using the osmolal gap as a diagnostic tool for toxic alcohol exposure.*

THE OSMOLAL GAP: A VALUABLE TEST FOR IDENTIFYING TOXIC ALCOHOL-INDUCED ANION GAP METABOLIC ACIDOSIS

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Emergency physicians frequently encounter patients with undifferentiated anion gap metabolic acidosis, some of whom have been exposed to toxic alcohols. In 2022, according to the National Poison Data System, 5,496 cases of non-ethanol alcohol exposure were treated in a health care facility, including 2,920 methanol and ethylene glycol cases.[1] Although toxic alcohol exposures comprise a small proportion of all cases of anion gap metabolic acidosis, timely diagnosis is required to prevent toxic metabolite formation via alcohol dehydrogenase blockade, and guide initiation of hemodialysis in select cases.[2] A screening test called the osmolal gap may facilitate more rapid diagnosis and treatment; however, its use is opposed by some clinicians, who describe it as insufficiently specific and sensitive.[3,4] Yet, as will be discussed, when used to evaluate patients with sufficient pretest probability, the osmolal gap performance characteristics are acceptable and surpass commonly available alternatives.

Unlike ethanol, for which most hospitals possess a rapid assay, definitive identification of toxic alcohols requires gas chromatography. This is not performed at most institutions, which instead refer out samples to reference laboratories that may take hours to days to return.[2] Furthermore, reference laboratories may not test for less common toxic alcohols such as diethylene glycol and 2-butoxyethanol. When non–gas chromatography alternatives to the osmolal gap are considered, they perform poorly. Sensitivity of urine fluorescence for fluorescein-containing antifreeze (a common source of multiple toxic alcohols) was reported at 20% >4 hours after exposure.[5] Likewise, only 63% of ethylene glycol-poisoned patients in 1 case series manifested calcium oxalate crystalluria.[6] False-positive lactate elevations on some assays due to the presence of structurally similar ethylene glycol metabolites are unpredictable.[7]

Anion gap metabolic acidosis, though nonspecific, may suggest toxic alcohol exposure with delayed presentation, particularly with worsening acidosis over time despite resuscitation. However, awaiting development of worsening acidosis for diagnostic purposes may increase risk of morbidity and mortality. A threshold anion gap below which patient risk is negligible is not clearly defined for the undifferentiated toxic alcohol exposure. To this point, Extracorporeal Treatments in Poisoning workgroup guidelines note increased risk of chronic kidney disease and death in ethylene glycol poisoning when the anion gap exceeds 28 mmol/L; however, below this threshold these risks still exist, albeit to a lesser extent.[2] Likewise, "low-risk" anion gaps for less common toxic alcohols such as diethylene glycol are not defined. Thus, this strategy is ideally avoided through initial use of the osmolal gap. Immediate alcohol dehydrogenase blockade, unless a high degree of suspicion for poisoning exists, is problematic as it makes interpretation of subsequent chemistries difficult and may commit patients to prolonged blockade while awaiting referred-out confirmatory testing.

When the osmolal gap itself is examined, performance is comparatively robust. Lynd et al reported an osmolal gap of 10 mOsm/L captures 90% of patients requiring antidotal therapy and 100% requiring hemodialysis in a population with suspected toxic alcohol exposure.[8] In this population, with 26% ultimately positive for ethylene glycol or methanol, the negative predictive value of an osmolal gap <10 mOsm/L was 0.95. Because other osmotically active molecules such as ketones and lactate may also increase the osmolal gap, specificity was 22% utilizing this cutoff.[4,8] Although a certain proportion of false positives must be tolerated to avoid injurious or lethal false negatives, should greater specificity be desired, a higher cutoff of 20 mOsm/L results in 85% specificity and 82% sensitivity.[9] The osmolal gap can also be used, in the absence of gas chromatography, to estimate serum toxic alcohol concentrations through use of conversion factors.[10] This valuable data, in conjunction with markers of end-organ injury, may inform decision-making. For example, the treatment of a mildly acidotic, asymptomatic patient with suspected methanol exposure may be altered by the knowledge that their osmolal gap is 40 mOsm/L, as this suggests the need for (in addition to fomepizole administration) hemodialysis due to expected prolonged pulmonary elimination.

The osmolal gap should not be indiscriminately calculated in every patient with an anion gap metabolic acidosis. Acceptable test characteristics are predicated upon its application to a population with sufficient pretest probability of toxic alcohol exposure.[4,8,9] For example, a history of possible toxin exposure, alcohol use disorder, prior suicide attempt, or at-risk occupation may inform clinician gestalt. Exclusion of alternative causes of anion gap acidosis such as alcoholic ketoacidosis also increases pretest probability.[4] If the osmolal gap is elevated in a patient with sufficient pretest probability, treatment may be initiated; if not, and clinical suspicion remains high enough, the anion gap can be further trended to exclude toxic alcohol poisoning with normal osmolal gap.

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REFERENCES

1. Gummin DD, Mowry JB, Beuhler MC, et al. 2022 Annual report of the National Poison Data System® (NPDS) from America's Poison Centers® : 40th annual report. *Clin Toxicol (Phila)*. 2023;61:717-939.
2. Ghannoum M, Gosselin S, Hoffman RS, et al. Extracorporeal treatment for ethylene glycol poisoning: systematic review and recommendations from the EXTRIP workgroup. *Crit Care*. 2023;27:56.
3. Glaser DS. Utility of the serum osmol gap in the diagnosis of methanol or ethylene glycol ingestion. *Ann Emerg Med*. 1996;27:343-346.
4. Kraut JA. Diagnosis of toxic alcohols: limitations of present methods. *Clin Toxicol*. 2015;53:589-595.
5. Winter ML, Ellis MD, Snodgrass WR. Urine fluorescence using a wood's lamp to detect the antifreeze additive sodium fluorescein: a qualitative adjunctive test in suspected ethylene glycol ingestions. *Ann Emerg Med*. 1990;19:663-667.
6. Brent J, McMartin K, Phillips S, et al. Fomepizole for the treatment of ethylene glycol poisoning. Methylpyrazole for Toxic Alcohols Study Group. *N Engl J Med*. 1999;340:832-838.
7. Poirier-Blanchette L, Simard C, Schwartz BC. Spurious point-of-care lactate elevation in ethylene glycol intoxication: rediscovering a clinical pearl. *BMJ Case Rep*. 2021;14:e239936.
8. Lynd LD, Richardson KJ, Purssell RA, et al. An evaluation of the osmole gap as a screening test for toxic alcohol poisoning. *BMC Emerg Med*. 2008;8:5.
9. Krasowski MD, Wilcoxon RM, Miron J. A retrospective analysis of glycol and toxic alcohol ingestion: utility of anion and osmolal gaps. *BMC Clin Pathol*. 2012;12:1.
10. Greene HR, Krasowski MD. Correlation of osmolal gap with measured concentrations of acetone, ethylene glycol, isopropanol, methanol, and propylene glycol in patients at an academic medical center. *Toxicol Rep*. 2020;7:81-88.

THE OSMOLAL GAP HAS A LIMITED ROLE IN THE EVALUATION OF POSSIBLE TOXIC ALCOHOL POISONING

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In the evaluation of a patient with an anion gap metabolic acidosis, the differential diagnosis frequently includes ingestion of toxic alcohols, such as ethylene glycol and methanol. The osmolal gap, defined as the difference between the measured serum osmolality and calculated osmolality, has been suggested as a diagnostic test to allow early identification of these substances.[1,2] Unfortunately, this is neither sufficiently specific nor sensitive enough to be routinely used in cases of toxic alcohol exposure. For example, severely poisoned patients who require hemodialysis may present with a normal osmolal gap.[3-5] Furthermore, many nontoxicologic etiologies and states of critical illness may cause an increased osmolal gap, which can be misleading without appropriate clinical context.[6] Clinicians suspicious of toxic alcohol poisoning must