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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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

understand the limitations of the osmolal gap, first exclude more common causes of an anion gap metabolic acidosis, and instead consider the entire clinical context when making diagnostic and treatment decisions.

The traditionally taught laboratory findings of acute toxic alcohol exposures are that they present with an initial elevation in the osmolal gap that progressively declines over time as the parent alcohol is metabolized into ion pairs (eg, formate, glycolate, glyoxylate), which contributes to the anion gap. Eventually, as the osmolal gap decreases, the anion gap is expected to increase.[7] This simplistic approach to teaching the concept is not always seen in practice; there may be a temporal overlap between the presence of an increased osmolal gap and the development of an increased anion gap, rarely including a transitional period during which both may be normal. Additionally, the calculated osmolal gap in healthy humans has been described to range from approximately –8 to 11 mOsm/L and –10 to 10 mOsm/L.[8,9] This variability, with some patients having a baseline negative osmolal gap, limits its sensitivity and may yield an osmolal gap within the reference range of $\leq$10 mOsm/L even in cases of toxic methanol poisoning.[10-12] To complicate matters further, there is disagreement regarding the most appropriate method to calculate an osmolal gap and, more specifically, how to assign a molar value to any coingested ethanol.[13] One of the most frequently employed online calculators for the osmolal gap[14] uses the equation derived by Purssell et al[15] that assigns a denominator of 3.7 to convert a serum ethanol concentration to a molar value. Compared to an alternatively referenced denominator of 4.6, the use of a smaller denominator (3.7) is expected to produce a lower calculated osmolal gap value, decreasing the already poor sensitivity, particularly in the setting of markedly increased serum ethanol concentrations. Conversely, using the larger of the conversion factors (4.6) decreases specificity and yields more false positive results.

Beyond the inherent limitations associated with laboratory assay variability in healthy subjects and measurement imprecision, many nontoxicologic medical conditions may present with an increased osmolal gap. Common conditions including starvation ketosis, alcoholic ketoacidosis, diabetic ketoacidosis, renal failure, shock, and lactic acidosis can increase serum osmolality as a result of accumulation of uncharged particles that are not routinely measured.[10] These nonpoisoning associated causes of an increased osmolal gap are encountered far more frequently in clinical practice than methanol and ethylene glycol exposures; in fact, only 576 and 566 cases of each, respectively, were reported to Poison Control Centers in 2022.[16] To complicate the diagnostic evaluation further, a serum osmolality measurement may be ordered and obtained after a period of resuscitation has occurred (rather than submitted as an add-on test from pre-resuscitation labs, where its sensitivity for identifying a toxic alcohol exposure is highest), which can lead to erroneous exclusion of the diagnosis of toxic alcohol exposure. Raising the threshold for initiation of antidotal therapy for a suspected toxic alcohol ingestion to an osmolal gap of >25 mOsm/L or even 30 mOsm/L may increase specificity as it likely excludes most medical causes for the abnormality, but this adjustment further diminishes the test's already poor sensitivity.[6,17] As an example, in a retrospective review of patients presenting to a tertiary medical center who had a measured osmolal gap, a cutoff of osmolal gap of 20 mOsm/L yields a sensitivity of toxic alcohol ingestion of 0.82 and a specificity of 0.85. Moving to a cutoff of 30 mOsm/L yielded a sensitivity of only 0.49 with a specificity of 0.95.[6]

The osmolal gap is an improper diagnostic aid for emergency physicians to use when evaluating an anion gap metabolic acidosis. Routine osmolal gap calculation in patients with anion gap metabolic acidosis with a goal to identify a small subset of patients with a toxic alcohol exposure would lead to the discovery of many elevated osmolal gap without an underlying toxicologic cause risking inappropriate resource allocation (eg, use of a costly antidote, interfacility transfer, hemodialysis), diagnostic confusion, and early diagnostic closure. A markedly increased osmolal gap, for example, more than 50 mOsm/L[6] is more specific for a toxic alcohol ingestion; however, a progressive anion gap metabolic acidosis that does not improve despite treating other nontoxicologic causes will similarly identify the diagnosis. A superior diagnostic strategy to the osmolal gap involves meticulous history-taking, exclusion of alternative diagnoses, and frequent reassessment of patient response to resuscitation. Those patients with a worsening acidosis despite this strategy should be considered for treatments including alcohol dehydrogenase blockade and potentially hemodialysis while awaiting definitive laboratory testing.

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