Bridging the Gap: Understanding "Normal" Osmole Gap in Theory and Clinical Practice

Ravikar Ralph, MBBS, MD*; Jeffrey Brent, MD, PhD

*Corresponding Author. E-mail: ravikar.ralph@rmpds.org.

0196-0644/$-see front matter

https://doi.org/10.1016/j.annemergmed.2025.04.031

A **podcast** for this article is available at www.annemergmed.com.

SEE RELATED ARTICLE, P. 257.

This issue of *Annals* features a study by Marino et al,[1] who examine osmole gaps in a healthy population and assess the effect of ethanol by measuring osmole gaps before and after ingestion. The study contributes to the literature on reference ranges for the osmole gap and offers insights relevant to their clinical interpretation.[1-9] In this context, we discuss the concept of a "normal osmole gap" and its application to osmole gap measurements in clinical practice.

The osmole gap is the difference between measured osmolality and calculated osmolarity.[10] Osmolality reflects the number of particles per kilogram of solvent, whereas osmolarity expresses them per liter of solvent.[11] While osmolality is measured by vapor-pressure elevation or freezing-point depression, calculated osmolarity is derived from measurable, osmotically active serum constituents, including sodium (and its related anions, mostly chloride and bicarbonate), blood urea nitrogen, glucose, and ethanol.[2-4,10,12] Any gap between these two values reflects osmotically active particles not accounted for in the osmolarity calculation.

Ideally, the osmole gap should approach zero under physiological conditions. However, when expressed as 2 SDs from the mean, in prior studies that included healthy and hospitalized individuals unexposed to exogenous osmotically active substances (with the variable exception of ethanol), the range of values span from −14 to +37 mOsm/kg.[2,4,7-9,13] Marino et al[1] demonstrate an even wider range of −7.1 to +53 mOsm/kg in their cohort of healthy volunteers.

This range arises from unmeasured osmoles and deviations from ideal physicochemical properties of serum. Ideal behavior assumes that particles in solution exist independently.[11] However, most particles in serum tend to form physicochemical bonds.[14-16] This putatively reduces particle numbers, leading to lower-than-expected osmolality, overestimated calculated osmolarity, and a smaller or even negative gap. Additionally, errors such as asynchronous blood sample collections for electrolyte and osmolality measurements and use of blood-collection tubes with osmotically active anticoagulants also contribute to gaps.[17]

Osmole gap calculations find frequent clinical application in screening for toxic alcohol exposures, typically treated with fomepizole and optionally with hemodialysis, based on severity.[18,19] As osmotically active agents, toxic alcohols increase the osmole gap, making it a quick, low-cost, and accessible marker of exposure, especially when history is unclear, confirmatory, quantitative tests are unavailable, or both.[17] However, in clinical practice, "normal" shifts from statistical distribution, typically reported as 2 standard deviations from the mean, to arbitrary thresholds, with less than 10 mOsm/kg traditionally defined as "normal" based on older literature.[4] Values of 10 mOsm/Kg and more are often interpreted as indicative of toxic alcohol exposure, although higher cutoffs (20-25 mOsm/Kg and more) have more recently been documented.[4,7,10,20,21]

Patients with negative baseline gaps can develop rising values following toxic alcohol exposure and yet still be below the arbitrary +10 mOsm/kg clinical cutoff, particularly because toxic alcohols produce small osmolal increases at toxic thresholds.[22] This can result in a normal gap and a missed diagnosis. However, the risk of missed diagnoses is often mitigated by additional clinical and laboratory information.[17] Even when not exposed to toxic alcohols, patients with high-baseline gaps (10 mOsm/kg and more) and unrelated encephalopathy risk being misdiagnosed. This risk is further compounded by conditions such as ketoacidosis, critical illness with multiorgan failure, where increased cellular permeability leads to the leakage of cellular contents into the serum, and contracted plasma volumes, all of which increase measured osmolality and hence widen the osmole gap.[17,23,24] The osmole gap can also be increased by exogenous substances besides toxic alcohols such as mannitol, sorbitol, or glycine.[17] Osmole gaps of less than +10mOsm/Kg can

occur in delayed presentations of toxic alcohol ingestion, which typically have attendant metabolic acidosis resulting from toxic alcohol conversion into non-osmotically active acid metabolites.[21-23] Hence, a normal osmole gap by itself cannot rule out toxic alcohol exposures in patients with metabolic acidosis of unknown origin.

In conclusion, Marino et al[1] demonstrate that substantial variability exists in osmole gap values within the healthy population, limiting their accurate interpretation in individual cases.[1] Because premorbid gaps in patients with toxic alcohol exposure are unknown, detecting increments following exposure is challenging when relying on a single cutoff. This difficulty is worsened by factors negatively influencing osmole gap measurements. Given these limitations, we suggest that an osmole gap be interpreted within the individual clinical context. In patients presenting with osmole gap elevations up to 25 mOsm/kg, without attendant metabolic acidosis and history of toxic alcohol ingestion, rule out ketosis and contracted plasma volume and obtain a confirmatory test for toxic alcohol before administering fomepizole. If confirmatory tests are unavailable or delayed, monitor acid-base status and osmole gap every 4 hours. Administer fomepizole with onset of acidosis and osmole gap decline. Conversely, in patients with features consistent with toxic alcohol toxicity such as metabolic acidosis with visual disturbances or oxaluria, promptly initiate fomepizole alongside confirmatory testing, irrespective of the osmole gap. Consult nephrology and toxicology for all patients on fomepizole to guide the need for hemodialysis and treatment duration.

Supervising editor: Andrew A. Monte, MD. Specific detailed information about possible conflict of interest for individual editors is available at https://www.annemergmed.com/editors.

Author affiliations: From the Rocky Mountain Poison & Drug Safety (Ralph), Denver Health & Hospital Authority, Denver, CO; and the Departments of Medicine & Emergency Medicine (Brent), University of Colorado School of Medicine, Aurora, CO.

All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding and support: By *Annals'* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that no such relationships exist.

REFERENCES

1. Marino R, Sidlak A, Scoccimarro A, et al. Ethanol and the limitations of the osmol gap. *Ann Emerg Med*. 2025;86:257-261.
2. Geller RJ, Spyker DA, Herold DA, et al. Serum osmolal gap and ethanol concentration: a simple and accurate formula. *J Toxicol Clin Toxicol*. 1986;24:77-84.
3. Purssell RA, Pudek M, Brubacher J, et al. Derivation and validation of a formula to calculate the contribution of ethanol to the osmolal gap. *Ann Emerg Med*. 2001;38:653-659.
4. Hoffman RS, Smilkstein MJ, Howland MA, et al. Osmol gaps revisited: normal values and limitations. *J Toxicol Clin Toxicol*. 1993;31:81-93.
5. Carstairs SD, Suchard JR, Smith T, et al. Contribution of serum ethanol concentration to the osmol gap: a prospective volunteer study. *Clin Toxicol (Phila)*. 2013;51:398-401.
6. 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.
7. Aabakken L, Johansen KS, Rydningen EB, et al. Osmolal and anion gaps in patients admitted to an emergency medical department. *Hum Exp Toxicol*. 1994;13:131-134.
8. Glasser L, Sternglanz PD, Combie J, et al. Serum osmolality and its applicability to drug overdose. *Am J Clin Pathol*. 1973;60:695-699.
9. Worthley LI, Guerin M, Pain RW. For calculating osmolality, the simplest formula is the best. *Anaesth Intensive Care*. 1987;15:199-202.
10. Smithline N, Gardner KD. Gaps–anionic and osmolal. *JAMA*. 1976;236:1594-1597.
11. Koga Y, Purssell RA, Lynd LD. The irrationality of the present use of the osmole gap: applicable physical chemistry principles and recommendations to improve the validity of current practices. *Toxicol Rev*. 2004;23:203-211.
12. Dorwart WV, Chalmers L. Comparison of methods for calculating serum osmolality form chemical concentrations, and the prognostic value of such calculations. *Clin Chem*. 1975;21:190-194.
13. Osterloh JD, Kelly TJ, Khayam-Bashi H, et al. Discrepancies in osmolal gaps and calculated alcohol concentrations. *Arch Pathol Lab Med*. 1996;120:637-641.
14. Matsuo H, To ECH, Wong DCY, et al. Excess partial molar enthalpy of 1-propanol in 1-propanol−NaCl−H2O at 25 °C: the effect of NaCl on molecular organization of H2O. *J Phys Chem B*. 1999;103:2981-2983.
15. Westh P, Haynes CA, Koga Y. How dilute is the Henry's law region? *J Phys Chem B*. 1998;102:4982-4987.
16. Tu S, Lobanov SS, Bai J, et al. Enhanced formation of solvent-shared ion pairs in aqueous calcium perchlorate solution toward saturated concentration or deep supercooling temperature and its effects on the water structure. *J Phys Chem B*. 2019;123:9654-9667.
17. Purssell RA, Lynd LD, Koga Y. The use of the osmole gap as a screening test for the presence of exogenous substances. *Toxicol Rev*. 2004;23:189-202.
18. Jacobsen D, McMartin KE. Methanol and ethylene glycol poisonings. Mechanism of toxicity, clinical course, diagnosis and treatment. *Med Toxicol*. 1986;1:309-334.
19. McMartin K, Jacobsen D, Hovda KE. Antidotes for poisoning by alcohols that form toxic metabolites. *Br J Clin Pharmacol*. 2016;81:505-515.
20. Gennari FJ. Current concepts. Serum osmolality. Uses and limitations. *N Engl J Med*. 1984;310:102-105.
21. Hovda KE, Hunderi OH, Rudberg N, et al. Anion and osmolal gaps in the diagnosis of methanol poisoning: clinical study in 28 patients. *Intensive Care Med*. 2004;30:1842-1846.
22. Kraut JA. Diagnosis of toxic alcohols: limitations of present methods. *Clin Toxicol (Phila)*. 2015;53:589-595.
23. Inaba H, Hirasawa H, Mizuguchi T. Serum osmolality gap in postoperative patients in intensive care. *Lancet*. 1987;1:1331-1335.
24. Hirasawa H, Odaka M, Sugai T, et al. Prognostic value of serum osmolality gap in patients with multiple organ failure treated with hemopurification. *Artif Organs*. 1988;12:382-387.