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Choice of the best equation for plasma osmolality calculation: Comparison of fourteen formulae

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ABSTRACT

Background: Many different equations have been previously described to estimate plasma osmolality. The aim of this study is to compare 14 of these equations, in order to determine which results agree best with measured osmolality.

Objectives: Our aim is to elucidate which is the most accurate equation for osmolality calculation among the fourteen that were previously described.

Methods: We measured osmolality by the freezing point depression method, and glucose, urea, sodium, potassium, calcium and magnesium concentrations with Unicell DXC 800 analyzer. Goodness-of-fit rates were calculated using the Passing–Bablok regression model and the t-paired sample test. In addition, we used survival curves in order to find the percentage of cases in which the difference between measured and calculated osmolality was under 10 mOsm/kg. Data were plotted using the Bland–Altman graphical approach.

Results: The equation that provides the best fit between measured and calculated osmolality is $1.86(Na + K) + 1.15(Glu / 18) + (Urea / 6) + 14$, followed by $2Na + 1.15(Glu / 18) + (Urea / 6)$.

Conclusions: According to our results, the Dorwart–Chalmer's equation should not be used for osmolality calculations. The equation $1.86(Na + K) + 1.15(Glu / 18) + (Urea / 6) + 14$ is the most accurate. The widespread use of the equation $2(Na + K) + (Glu / 18) + (Urea / 6)$ is also acceptable.

Introduction

Osmolality is a colligative property of a solution whose value depends on the number of dissolved particles per kilogram of water (osmoles/kg or miliosmoles/kg), which can be measured by the freezing point depression method. In normal serum or plasma, osmolality depends mainly on the concentration of the five major osmotic solutes, three of which are of ionic nature (Na^+, Cl^-, HCO_3^-), and two that are non-ionic (glucose and urea). Activity coefficients of the latter are close to 1, hence their contribution to osmolality is equal to their molar concentration, whereas the contribution of ionic solutes to osmolality equals about 0.9 times their concentration [1]. Since sodium ions can be assumed to be counterbalanced by an anion, the dependence of serum osmolality on electrolyte concentration may be considered to be a function of sodium alone. Many equations for osmolality calculation have been proposed [1–10]. Most of them take into account the aforementioned endogenous factors. The difference between measured (OSMm) and calculated (OSMc) osmolality is referred to as osmolal gap (OG) or delta osmolality. Some substances such as xenobiotics, and especially alcohols increase plasma osmolality. For instance, the osmolal contribution of 100 mg/dL of methanol is 34 mOsm/kg (miliosmoles per kilogram of water), while this contribution is 24 mOsm/kg for ethanol, 18 mOsm/kg for isopropanol and 17 mOsm/kg for ethylene glycol [11]. Consequently, the calculation of the OG can be used as a rough screening method for toxic alcohol ingestion (ethanol, methanol, ethylene glycol and propylene glycol), since an elevated OG implies the presence of unmeasured osmotically active substances, mainly alcohols [4,11].

Despite the wide variety of equations that have been proposed for osmolality calculation, there are few studies that determine which one of them provides the best results. Dorwart and Chalmers [1] measured osmolality in 715 serum samples and used linear regression analysis to devise an equation for calculating serum osmolality. The Dorwart–Chalmers is written as follows: $OSMc = 1.86[Na^+] + [Glu] + [Urea] + 9$, where Glu is glucose (if glucose and urea are expressed in molar concentrations) or $OSMc = 1.86[Na^+] + [Glu] / 18 + ([Urea] / 6) + 9$, when glucose and urea appear in conventional units (mg/dL). This equation has been the most popular for years [2,3], being its use recommended in the Tietz's Clinical Chemistry Textbook [12], and it has been

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Table 1
Equations evaluated in the study.

Number	Equation	Reference
1	2Na + (Glu / 18) + (Urea / 6)	[5]
2	2(Na + K) + (Glu / 18) + (Urea / 6)	[6]
3	1.75Na + (Glu / 18) + (Urea / 6) + 10.1	[7]
4	1.86Na + (Glu / 18) + (Urea / 6)	[8]
5	1.86Na + (Glu / 18) + (Urea / 6) + 5	[9]
6	1.86Na + (Glu / 18) + (Urea / 6) + 9	[1]
7	1.86(Na + K) + (Glu / 18) + (Urea / 6) + 9	[3]
8	1.85Na + 1.84 K+(Glu / 18) + (Urea / 6) + Ca + 1.17 Mg + 1.15	[10]
9	2Na + 1.15(Glu / 18) + (Urea / 6)	[4]
10	1.86(Na + K) + 1.15(Glu / 18) + (Urea / 6) + 14	[4]
11	1.89Na + 1.38 K + 1.08(Glu / 18) + 1.03(Urea / 6) + 7.45	[3]
12	1.86(Na + K) + (Glu / 18) + (Urea / 6) + 10	[3]
13	1.897(Na) + (Glu / 18) + (Urea / 6) + 13,5	[2]
14	1.90(Na + K) + (Glu / 18) + (Urea / 6) + 5	[2]

Equations evaluated in the study, where Glu indicates glucose. The reference is indicated on the right column.

incorporated into commercial analyzers. However, several reports have shown that the use of this equation underestimates true osmolality [2,3,13].

The purpose of this study is to compare osmolality calculated by the use of 14 previously proposed equations with osmolality measured by the freezing point depression method, and elucidate which calculated results fit best with actual osmolality.

Materials and methods

Patients

One hundred and forty six healthy volunteers (96 male and 50 female) were selected among blood donors of our hospital. The average age was 41.4 years (standard deviation 11.73, median 42). Drug abusers, smokers and alcohol drinkers were excluded from the study. Included individuals had no history of disease and no prescription medications documented. Blood was collected in lithium heparin tubes and plasma samples were obtained after centrifugation at 1700 ×*g* for 5 min.

Biochemical analysis

Plasma osmolality was measured by the freezing point depression method using an Advanced Instruments Model 3300 Micro-Osmometer (Advanced Instruments® Inc, Needham, MA, USA). Glucose, urea, sodium, potassium, calcium and magnesium were measured with the Unicell DXC 800 analyzer (Beckman Coulter® Inc, Brea, CA, USA). Sodium, potassium and calcium were analyzed with ion selective electrodes, glucose with a polarographic method which involves glucose oxidation with glucose oxidase (EC 1.1.3.4), urea with a conductimetric method which uses urease (EC 3.5.1.5) to produce ammonium ions, and magnesium by complex formation with calmagite and subsequent spectrophotometric measuring.

Table 2
Passing–Bablok non-parametric analysis for each formula.

Formula	Regression equation	CI for intercept	CI for slope
1	Y = −34.005 + 1.1X	−136.58 to 45.2	0.833 to 1.44
2	Y = −25.06 + 1.098X	−128.3 to 52.65	0.84 to 1.44
3	Y = −11.51 + 0.94X	−96.93 to 55.38	0.71 to 1.23
4	Y = −25.26 + 1.004X	−119.07 to 46.68	0.76 to 1.32
5	Y = −20.26 + 1.004X	−114.07 to 51.68	0.76 to 1.32
6	Y = −16.26 + 1.004X	−110.07 to 55.68	0.76 to 1.32
7	Y = −8.95 + 1.006X	−101.94 to 61.03	0.77 to 1.32
8	Y = 12.02 + 1.022X	−102.39 to 56.75	0.79 to 1.33
9	Y = −39.5 + 1.12X	−148.26 to 41.77	0.85 to 1.49
10	Y = 9.98 + 1.03X	−106.076 to 60.75	0.79 to 1.35
11	Y = −18.34 + 1.04X	−115.76 to 53.09	0.8 to 1.37
12	Y = −7.95 + 1.006X	−100.94 to 62.03	0.77 to 1.32
13	Y = −13.36 + 1.027X	−110.57 to 60.08	0.78 to 1.35
14	Y = −15.33 + 1.033X	−109.27 to 56.89	0.79 to 1.35

Regression equations obtained with Passing–Bablok analysis. Confidence intervals for the slope and intercept are shown.

Table 3
Results of Student t-test.

Formula	Mean difference	Standard deviation	95% CI	†	p
1	4.31	5.23	3.45 to 5.17	9.95	<0.0001
2	−3.7	5.10	−4.53 to −2.86	−8.76	<0.0001
3	29.34	4.92	28.54 to 30.15	72.04	<0.001
4	23.98	5.06	23.16 to 24.81	57.32	<0.0001
5	18.98	5.06	18.16 to 19.81	45.37	<0.0001
6	−14.98	5.06	−15.81 to 14.16	−35.81	<0.0001
7	7.53	4.93	6.73 to 8.34	18.46	<0.0001
8	5.62	5.01	4.80 to 6.44	13.56	<0.0001
9	3.27	5.28	2.41 to 4.13	7.49	<0.0001
10	1.49	4.97	0.68 to 2.31	3.63	0.0004
11	6.09	5.01	5.27 to 6.91	14.67	<0.0001
12	6.53	4.93	5.73 to 7.34	16.02	<0.0001
13	5.29	5.10	4.45 to 6.12	12.52	<0.0001
14	5.75	4.98	4.94 to 6.57	13.97	<0.0001

t-Test for paired samples. The results for the three best equations are bold. The fields corresponding to the equation which provided the best results are in bold and shaded.

Equations

Fourteen equations for the calculation of osmolality were selected from the literature [1–10]. The variables included in these equations were measured on plasma samples as indicated above. Glucose (Glu),

Table 4
Kaplan–Meier survival analysis for each formula.

Formula	% cases with OG <10 mOsm/kg
1	99.83
2	99.89
3	None
4	None
5	99.03
6	99.18
7	99.71
8	99.78
9	99.88
10	99.97
11	99.77
12	99.75
13	99.80
14	99.79

Percentage of cases with an osmolal gap less than 10 mOsm/kg, obtained with Kaplan–Meier survival analysis. The results for the best equations are bold and they are bold and shaded for equation 10