Nutrición Hospitalaria

Nutr Hosp. 2015;32(6):2757-2762
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original/*Nutrición parenteral*

Agreement between different equations to estimate osmolarity of parenteral nutrition solutions

M.A. Valero Zanuy[1], S. Pablos Bravo[2], A. Lázaro Cebas[2], J. García Sánchez[3], P. Gomis Muñóz[2], J.M. Moreno Villares[1] and M. León Sanz[1]

[1]Clinical Nutrition Unit. Department of Endocrinology and Nutrition. Hospital Universitario 12 de Octubre, Madrid. [2]Department of Pharmacy. Hospital Universitario 12 de Octubre, Madrid. [3]Department of Clinical Biochemistry. Hospital Universitario 12 de Octubre, Madrid, Spain.

Abstract

Background: **our aim was to measure the osmolality of several PN formulas at different component concentrations to determine if equations described in literature to calculate osmolarity accurately predict osmolalality in other experimental conditions different than these used to develop them.**

Methods: **osmolality of 12 different types of PN solutions, 9 for central and 3 for peripheral perfusion were measured by using freezing point depression in cross-sectional study. We evaluated the agreement (Pearson correlation test) and differential bias between measured osmolality and calculated osmolarity for three different equations described in the literature: Pereira Da Silva, ASPEN Practice Manual and ASPEN guidelines.**

Results: **mean ± SD osmolality of PN solutions was 1789 ± 256 (range 1 540 – 2 372) and 751 ± 64 mOsm/kg (range 689 – 817) for central and peripheral infusion, respectively. The osmolality of PN formulations was mainly due to glucose (r = 0.975) and amino acids (r = 0.948). All studied equations had a good correlation in the bivariate analysis (p = 0.000). All equations had a trend to underestimate the osmolality compared with the measured value. However, ASPEN guidelines equation overestimated the osmolality for peripheral PN.**

Conclusions: **measurement of osmolality of peripheral PN solutions is important to reduce the risk of phlebitis. The different equations described previously show a good correlation between them although in general underestimate the osmolality.**

(*Nutr Hosp*. 2015;32:2757-2762)

DOI:10.3305/nh.2015.32.6.9556

Key words: *Osmolality. Osmolarity. Equations. Parenteral nutrition.*

Correspondence: M.A. Valero Zanuy.
Clinical Nutrition Unit.
Department of Endocrinology and Nutrition.
Hospital Universitario 12 de Octubre,
Carretera de Andalucia Km 5,400. 28041 Madrid, Spain.
E-mail: mvalero.hdoc@salud.madrid.org

Recibido: 4-VII-2015.
1.ª Revisión: 19-VIII-2015.
Aceptado: 21-VIII-2015.

ACUERDO ENTRE DIFERENTES ECUACIONES PARA ESTIMAR LA OSMOLARIDAD DE LAS SOLUCIONES DE NUTRICIÓN PARENTERAL

Resumen

Objetivo: **nuestro objetivo era medir la osmolaridad de varias fórmulas de nutrición parenteral (NP) compuestas por diferentes componentes para determinar si las ecuaciones para calcular la osmolaridad de la solución, descritas en la literatura, predicen su osmolalidad en la práctica clínica.**

Método: **se midió mediante osmometría la osmolalidad de 12 fórmulas de NP diferentes: 9 para acceso venoso central y 3 para acceso periférico, en un estudio transversal. Se analizó el acuerdo (test de correlación de Pearson) y las diferencias entre la osmolalidad medida y la osmolaridad calculada mediante tres fórmulas diferentes: ecuación de Pereira Da Silva, ecuación del manual de práctica clínica de ASPEN y ecuación de las guías de ASPEN.**

Resultados: **la media ± desviación estándar de las soluciones era 1.789 ± 256 (rango 1.540 – 2.372) y 751 ± 64 mOsm/kg (rango 689 – 817) para perfusión central y periférica, respectivamente. La osmolalidad era debida principalmente a la glucosa (r = 0,975) y a los aminoacidos (r = 0,948). Todas las ecuaciones presentaban una buena correlación en el análisis bivariante (p = 0,000). Todas las ecuaciones tendían a infraestimar la osmolalidad, en comparación con el valor medido. Sin embargo, la ecuación de las guías de la ASPEN sobreestimaba la osmolalidad de las NP periféricas.**

Conclusiones: **conocer la osmolaridad de la solución de NP periférica es importante para reducir el riesgo de flebitis. Las diferentes ecuaciones descritas en la literatura muestran una buena correlación entre ellas, aunque en general infraestiman la osmolalidad.**

(*Nutr Hosp*. 2015;32:2757-2762)

DOI:10.3305/nh.2015.32.6.9556

Palabras clave: *Osmolalidad. Osmolaridad. Ecuaciones. Nutrición parenteral.*

Introduction

Parenteral nutrition (PN) is an admixture of different components. High concentration of amino acids, dextrose, lipids, electrolytes, trace elements and vitamins are administrated according to weight, height, age, sex and clinical conditions. This results in hyperosmolar PN solutions. It is important to know the final osmolality values of PN formulations because they dictate the type of intravenous access used. High-osmolality PN solutions infused into a peripheral vein will require frequent changes of injection site to decrease the risk of phlebitis. The peripheral vein can not generally tolerate an osmolarity superior to 850 - 900 mOsm/l. It is noteworthy that maximum recommended values are given as osmolarity, not osmolality values. Osmolality and osmolarity are different concepts to quantify the osmotic pressure of a solution. They are erroneously interchanged in the clinical sitting[1]. Osmolality is defined as the number of osmoles for a solute per kilogram of water. It is determined by the freezing point depression method using an osmometer. Osmolarity is defined as the number of osmoles of a solute per litre of solution. It cannot be measured, but it can be calculated from different equations. The equations add up the effect of each component on osmotic pressure per litre of PN formulations[2,3].

The aim of this study was to measure the osmolality of several PN formulations at different component concentrations and to study if three equations described in the literature (Table I) accurately predict osmolalality in other experimental conditions different than these used to develop them.

Material and methods

Over 12000 PN solutions are prepared annually in the Department of Pharmacy at Hospital 12 de Octubre (Madrid, Spain). Around 40% are standardized and 60% individualized formulas. There are 12 different types of standard PN solutions, nine for central and three for peripheral perfusion. The composition of standard PN solutions is shown in table II. The different commercial component used to prepare PN solutions and their osmolarity, according to the manufacturer, are shown in annexe.

Osmolality measurements

Osmolality was measured by the freezing point depression method (ultra supercooling, USC), as previously reported[1], using an automatic cryoscopic osmometer (Osmo Station™ OM-6050, Menarini Diagnostics). This osmometer is programmed to sample of 1 ml volume. Calibration was performed after every 100 measurements at three different points using distilled water (0 mosm/kg) and two standard solutions (300 and 1000 mosm/kg). Interanalysis coefficient of variation of measurements using BIORAD liquid assayed multiqual was 0,61%. All samples were blindly measured by the same investigator.

PN admixtures were prepared in usual conditions to make sure that results reflected daily clinical practice. Samples of 1 ml of final admixture from 12 standard PN solutions were collected. Samples were analysed the same day they were collected. Osmolality was expressed as milliosmols per kilogram.

Estimated and theoretical osmolarity measurements

Estimated osmolarity was obtained by three predictive equations developed for the calculation of osmolarity of PN solutions: Pereira Da Silva equation[2], ASPEN (American Society of Parenteral and Enteral Nutrition) practice manual equation[4] and ASPEN guidelines equation[5] (Table I). All equations use g/l for the concentration of macronutrients, mg/l for phosphate concentration and mEq/l for the rest of electrolytes.

Additionally, we obtained the theoretical osmolarity of each PN solution by summing the number of osmoles contributed by each component of the formulation, according to the manufacturer specifications, divided by the total volume of the solution.

Estimated and theoretical osmolarity were assessed in milliosmoles per litre.

Table I
Equations used to calculate theoretical and estimated osmolarity (mOsm/l) of parenteral nutrition solutions

Theoretical osmolarity	∑ *osmolarity components/volumen*
Pereira Da Silva Equation[2]	(A (g/l) × 8) + (G (g/l) × 7) + (Na (mEq/l) × 2) + (P (mg/l) x 0.2) - 50
ASPEN practice manual equation[4]	(A x 100 mOsmol/% final concentration) + (G x 50 mOsmol/% final concentration) + (F × 1.7 mOsmol/g) + (1,4 x Ca gluconate mOsmol/mEq) + (1 x Mg sulfate mOsmol/mEq) + (K chloride, acetate o phosphate salt x 2 mOsm/mEq) + (Na chloride, acetate o phosphate salt x 2 mOsm/mEq)
ASPEN guidelines equation[5]	(A (g/l) × 10) + (G (g/l) × 5) + (F (g/l)× 0.7) + (E (mEq/l) × 1)

A= amino acids, G = glucose, Na = sodium, P = phosphorous, Ca = calcium, Mg = magnesium, K = potassium, F = fat, E = electrolytes.

Table II
Composition of standard parenteral nutrition (PN) solutions studied

Component	*Peripheral PN*	*Central PN*
Amino acids (g/l)	22,6 ± 3,2	48,8 ± 6,7
Dextrose (g/l)	51,8 ± 4,9	130,7 ± 25,8
Fat (g/l)	21,8 ± 1,5	33,0 ± 7,3
Sodium(mEq/l)	50,2 ± 10,1	64,0 ± 15,4
Potasium (mEq/l)	21,1 ± 3,0	35,9 ± 10,7
Chlorine (mEq/l)	56,5 ± 10,4	73,4 ± 18,7
Magnesium (mEq/l)	5,2 ± 0,7	10,1 ± 2,0
Calcium (mEq/l)	5,2 ± 0,7	9,0 ± 2,6
Phosphorous(mmol/l)	6,2 ± 0,6	11,9 ± 2,4
Acetate (mEq/l)	38,9 ± 11,9	67,3 ± 10,7

Statistical analysis

Results are shown as mean ± standard deviation (SD). Pearson correlation test was used to determine the relationship between the measured osmolality and each component of final PN admixture. We included all components of PN solutions: amino acids, dextrose, lipids, sodium, potassium, chlorine, calcium, magnesium, phosphate and acetate having statistical significance in a lineal multivariate regression analysis. A $p < 0,05$ was considered as statistical significance. Additionally, we analyzed the agreement between the measured osmolality and the osmolarity obtained by summing the number of osmoles contributed by each component according to the manufacturer formulation (theoretical osmolarity) and the agreement between measured osmolality and estimated osmolarity obtained by different equations. The discrepance between the measured osmolality and estimated osmolarity was analyzed by assessing the difference and relative error of the values obtained from the three equations. That represents the differential bias.

Statistical analysis was performed with SPSS 15.0 version.

Results

Mean ± SD osmolality of PN solutions for central and peripheral infusion solutions was 1789 ± 256 (range 1540 – 2372) and 751 ± 64 mOsm/kg (range 689 – 817), respectively. The measured maximum value was 2036 mOsm/kg and the minimum was 664 mOsm/kg.

Strong lineal relations were found between the measured osmolality and the components of PN admixture (Table III). In decresing order of importance, the osmolality of PN formulations was due to glucose ($r = 0.954$), amino acids ($r = 0.932$) and fat ($r = 0.555$). Lineal correlation was also found for electrolytes: sodium, potassium, magnesium, calcium, phosphorous and acetate in bivariate analysis. Using "step by step" method, our lineal multivariate analysis included the number of milliosmols provided by dextrose and amino acids but not lipid and electrolytes.

Measured osmolality and theoretical and estimated osmolarities had good correlation in the bivariate analysis (Table IV). The ASPEN Practice Manual had the best Pearson correlation coefficient when

Table III
Equations describing the bivariate analysis correlation between components and osmolality of parenteral nutrition solutions

Component	*Equation Osmolarity (Osm mosm/l)*	*Pearson correlation coefficient (r)*	*p value bivariante analysis*	*p value multivariate regression analysis*
Amino acids (A) (g/l)	Osm = 37,8 x A – 71,2	0.932	0.000	0.013
Glucose (G) (g/l)	Osm = 11,9 x G + 204,6	0.954	0.000	0.011
Fat (F) (g/l)	Osm = 47,9 x F + 79,8	0.555	0.005	0.135
Sodium (Na) (mEq/l)	Osm = 19,9 x Na + 323,2	0.377	0.034	0.077
Potassium (K) (mEq/l)	Osm = 34,0 x K + 433,6	0.564	0.005	0.426
Chlorine (Cl) (mEq/l)	Osm = 14,1 x Cl + 552,4	0.248	0.099	0.167
Magnesium (Mg) (mEq/l)	Osm = 154,7 x Mg + 149,1	0.711	0.001	0.500
Calcium (Ca) (mEq/l)	Osm = 136,8 x Ca + 426,7	0.567	0.005	0.056
Phosphorous (P) (mmol/l)	Osm = 135,2 x P + 106,7	0.756	0.000	0.104
Acetate (Ac) (mEq/l)	Osm = 22,4 x Ac + 180,0	0.513	0.009	0.055

estimated osmolarity was compared with measured osmolality.

The results of predictive performance analysis are shown in table V. All equations underestimated the osmolality, except ASPEN guidelines equation, than overestimated the osmolality for peripheral PN. The theoretical formula and ASPEN guidelines equation had lower relative error for peripheral PN.

Discussion

PN can be infused via a peripheral venous catheter into a peripheral vein or via central venous catheter into a central vein. PN is associated with different complications. It is well know that peripheral infusion of hypertonic solutions may cause phlebitis[6,7,8]. Many factors are involved in the development of this complication. Specifically, the role of pH and osmolality has been described[9]. ESPEN[10] and ASPEN[11] guidelines recommend that osmolarity should be < 850 – 900 mOsm/l for peripheral venous access. It is important to know the final osmolality of PN solutions in order to choose the access route and to decrease the rate of phlebitis. The freezing point depression method is the preferable way to measure the osmolality. With this method, the mean osmolality of our PN solutions was 751 ± 64 mOsm/kg for peripheral and 1789 ± 256 for central formulations.

PN solutions are obtained from the mixture of many components, including amino acids, dextrose, fat, electrolytes, trace elements and vitamins. The final dextrose and amino acids concentration was the major determinant of osmolality of PN solutions in our study. The major role of amino acids and dextrose in the increased of osmolality of PN solutions is well described in the literature and it is shown in osmolarity equations. In our study other components as fat and electrolytes contributed little to the final osmolality value of PN solutions.

Osmolality and osmolarity are physical terms to quantify the osmotic pressure of a solution. Different concepts are behind those words although they are erroneously interchanged in the clinical setting. Osmolality is defined as the number of osmoles of a solute per kilogram of water. It is determined by the

Table IV
Pearson correlation coefficient (r) between measured osmolality, theoretical and estimated osmolarities (p = 0,000)

	Measured	*Theoretical*	*Pereira Da Silva equation*	*ASPEN practice manual equation*	*ASPEN guidelines equation*
Measured	-	0,963	0,927	0,948	0,936
Theoretical	0.963	-	0.955	0,996	0,988
Pereira Da Silva equation	0.927	0,955	-	0,964	0,959
ASPEN practice manual equation	0.948	0,996	0,964	-	0,993
ASPEN guidelines equation	0.936	0,988	0,959	0,993	-

Table V
Predictive performances of the different models compared with measured osmolality (mean ± SD)

	Peripheral infusion		*Central infusion*	
	Difference	*Relative error (%) (CI 95 %)*	*Difference*	*Relative error (%) (CI 95 %)*
Theoretical	- 31 ± 6,0	4,1 ± 0,4 (2,9 – 5,2)	- 294,4 ± 80,7	16,6 ± 4,4 (13,2 – 20,0)
Pereira Da Silva equation	- 212 ± 93,8	28,1 ± 25,9 (-36,3 – 92,6)	- 432,5 ± 104,3	24,2 ± 5,1 (20,3 – 28,2)
ASPEN practice manual equation	- 73,0 ± 31,2	9,5 ± 3,6 (0,4 – 18,7)	- 369,5 ± 105,6	20,8 ± 5,5 (16,5 – 25,1)
ASPEN guidelines equation	+ 35,6 ± 40,5	4,9 ± 5,9 (- 19,8 – 9,8)	- 31,6 ± 151,6	2,0 ± 8,2 (-4,2 – 8,3)

CI = confidence intervals
SD = standard deviation

freezing point depression method using an osmometer. Osmolarity is defined as the number of osmoles of a solute per litre of solution. An osmolarity value obtained by the freezing point depression is directly proportional to the osmolarity[12]. In the clinical setting, as the equipment for osmometry is expensive, osmometers are usually not available and direct measurement of osmolalities of PN solution is not routinely undertaken. If a valid equation for the calculation of osmolarity of PN solutions can be derived of osmotically active components, this equation would decrease the likelihood of phlebitis and other complications associated to PN. In the literature different equations have been proposed for the estimation of osmolarities of PN solutions. These equations allow for a practical prediction of the measured osmolality to estimate osmolarity. However, it is not known which equation adjusts best to measured osmolality of PN. Our results show a correlation very close to linearity between measured osmolality and

Annexe

Characteristics of components used to prepare parenteral nutrition solutions

Nutrient	*Manofacturer formulations*	*Composition*	*Manofacturer osmolarity (mOsm/l)*	*Pharmaceutical laboratory*
Amino acids	Tauramin 12,6%	500ml/bottle	1096	Laboratorios Grifols, S.A. (Spain)
	Synthamin 9	500ml/bottle	520	Baxter S.L. (Spain)
	Synthamin 14	500 – 1000 ml/bottle	880	Baxter S.L. (Spain)
	Synthamin 17	500 – 1000 ml/bottle	1060	Baxter S.L. (Spain)
	Aminoven 15%	500 ml/bottle	1505	Fresenius Kabi Deutschland GmbH (Germany)
Dextrose	Glucosa 5%	250 - 500 ml/bottle	278	Laboratorios Physan S.A. (Spain)
	Glucosa 10%	100 ml/bottle	555	Laboratorios Grifols, S.A. (Spain)
		250 - 500 ml/bottle	556	Laboratorios Physan S.A. (Spain)
	Glucosa 30%	500 ml/bottle	1665	Laboratorios Grifols, S.A. (Spain)
	Glucosa 40%	500 ml/bottle	2220	B. Braun Medical, S.A. (Spain)
	Glucosa 50%	100 ml/bottle	2777	Laboratorios Grifols, S.A. (Spain)
		500 ml/bottle	2775	Baxter S.L. (Spain)
	Glucosa 70%	250 ml/bottle	3890	B. Braun Medical, S.A. (Spain)
Lipids	Smof 20%	100 - 250 ml/bottle	270	Fresenius Kabi España S.A.U (Spain)
	Lipoplus 20%	100 - 250 ml/bottle	410	B. Braun Melsungen AG (Germany)
Electrolytes	Hyperlite 75	75 ml/bottle	4200	B. Braun Medical, S.A. (Spain)
	Glycophos	20 ml/bottle	2540	Fresenius Kabi España S.A.U (Spain)
	Sulfato de Magnesio Genfarma 150 mg/ml	10 ml/bottle	700	Genfarma Laboratorio S.L. (Spain)
	Cloruro de Sodio B.Braun 20%	10 ml/bottle	6844	B. Braun Medical, S.A. (Spain)
Trace elements	Addamel	10 ml/bottle	2500	Fresenius Kabi España S.A.U (Spain)
Vitamins	Cernevit	5 ml/bottle	1000	Baxter S.L. (Spain)

predicted osmolarity using different equations. The ASPEN practice manual equation had the best agreement when estimated osmolarity was compared with measured osmolality. All equations, except ASPEN guidelines equation for peripheral PN, underestimated the osmolality. According to our results measured osmolality values tend to be 5 – 20 % higher than those of osmolarity. This difference may be at least partly responsible for the occurrence of complications when equations are used to know milliosmoles of PN solution.

Some limitations of our study need to be considered in the interpretation of the results. First, PN solutions are admixtures of different components. The nature of the components may vary. For example, solutions of amino acids contain other components such as chloride and acetate in different concentrations depending on the commercial manufacturer solutions. These components are considered when the osmolality is measured but they are not when osmolarity is predicted by equations. Second, different salts can be used to administer electrolytes. For example, sodium lactate or sodium chloride do not have the same osmolality. For the same concentration of sodium, these salts have the same osmolarity but different osmolalities[13]. The same phenomenon could be found with other electrolyte solutions used to elaborate PN admixtures. These two aspects explain why equations present an overall bias in predicting osmolality. This is shown when we compared our measured osmolality with estimated osmolarity by equations. Equations may not be able to predict osmolality in other conditions than those in which they were developed, depending on local practice. In spite of that, we have found that the equations have acceptable predictive performances.

In summary, to measure the osmolality of PN solutions is a clinical issue. Osmolality > 900 mOsm/kg is above the acceptable range for peripheral venous access. Knowing osmolality value of the solution may reduce the risk of phlebitis. Osmolality and osmolarity are not similar concepts. Osmolality must be measured using osmometry. In clinical sitting, osmolarity equations have been used to know milliosmoles of PN solutions. The different equations proposed in the literature show a good correlation between them although in general they underestimate the osmolality. Our recommendation therefore is that predicted equations obtained by lineal multivariate analysis should be used in strict accordance with the practice of their authors in terms of preparing PN solutions. Nevertheless, they are a helpful tool for PN prescription.

Conflict of interest statement

None of the authors have any conflict of interest to declare.

Author's contributions

MA Valero Zanuy: was responsible for the study design, interpretation of the results and writing manuscript. S. Pablos Bravo and A. Lázaro Cebas were responsible for colleting data and statistical analysis of data. J. García Sánchez was responsible for biochemical measurements and coding data. P. Gomis Muñóz and J.M. Moreno Villares were responsible for the interpretation of results and critical revision of manuscript.

M León Sanz had primary responsibility of final content.

All authors read and approved the final manuscript.

References

1. Deardorff DL. Osmotic strength, osmolality, and osmolarity. *Am J Hosp Pharm* 1980;37:504-509.
2. Pereira-da-Silva J, Virella D, Henriques G, Rebelo M, Serehla M, Videira-Amaral JM. A simple equation to estimate the osmolarity of neonatal parenteral nutrition solutions. *JPEN* 2004;28:34-37.
3. Wei Kuo Chan and Ming Kung Yeh. Prediction of parenteral nutrition osmolarity by digital refratometry. *JPEN* 2011;35:412-418.
4. Strausburg K. Parenteral Nutrition admixture. In: *The ASPEN Nutrition Support Practice Manual*. 1998: Section III, capter 8, 1-8.
5. Mirtallo J, Canada T, Johnson D, Kumpf V, Petersen C, Sacks G, et al. Safe practices for parenteral nutrition. *JPEN* 2004;28:S39-S70.
6. Bayer-Berger M1, Chioléro R, Freeman J, Hirschi B. Incidence of phlebitis in peripheral parenteral nutrition: effect of the different nutrient solutions. *Clin Nutr* 1989;8:181-186.
7. Timmer JG1, Schipper HG. Peripheral venous nutrition: the equal relevance of volume load and osmolarity in relation to phlebitis. *Clin Nutr*. 1991;10:71-75.
8. Kuwahara T. Infusion phlebitis and peripheral parenteral nutrition. *Nutrition* 1999;15:329.
9. Kuwahara T, Asanami S, Tamura T, Kaneda S. Effects of pH and osmolality on phlebitic potential of infusion solutions for peripheral parenteral nutrition. *J Toxicol Sci* 1998;23:77-85.
10. Pittiruti M, Hamilton H, Biffi R, MacFie J, Pertkiewicz M. ESPEN guidelines on parenteral nutrition: central venous catheters (access, care, diagnosis and therapy of complications). *Clin Nutr* 2009;28: 65–377.
11. Boullata JI, Gilbert K, Sacks G, Labossiere RJ, Crill C, Goday P et al. A.S.P.E.N. clinical guidelines: parenteral nutrition ordering, order review, compounding, labeling, and dispensing. *JPEN* 2014;38:334-377.
12. Khajuria A, Krahn J. Osmolality revisited deriving and validating the best formula for calculated omolality. *Clin Biochem* 2005;38:514-519.
13. Petitcollin A, Duval S, Bouissou A, Bourgoin H. Reproducible and individualized method to predict osmolality of compounded pediatric parenteral nutrition solutions. *JPEN* 2015; DOI: 10.1177/0148607115570695.