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ORIGINAL RESEARCH

The Clinical Utility and Accuracy of Four Equations Predicting Delta Serum Na+ Over Shorter Timeframes (2-4 Hours)

The accuracy of delta Na+ modeling equations revisited over shorter time periods

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Introduction

The Edelman equation is a simple equation that was empirically derived from animal studies showing that serum Na^+ is equivalent to total body exchangeable sodium added to total body exchangeable potassium divided by total body water.[1] From this simple expression multiple, progressively more complex, equations evolved to predict the change in Na^+1 (initial serum Na^+) to Na^+2 (final serum Na^+).[2] The inputs used included all water, fluids, urine, and body fluids and included their volumes, concentrations of sodium, and concentration of potassium.[3] The Barsoum Levine (BL) equation incorporates input and output data in a stoichiometric manner. The Adrogue Madias equation (AM) is an output independent equation, calculating delta Na^+ only on input data.[4] The EFWC equation (EFWC) is an input independent equation, calculating delta Na^+ only on output data.[2] The Nguyen Kurtz (NK) is complex, physiologically rigorous, and accounts the slope (1.03) obtained by applying the Gibbs-Donnan equilibrium, and the Y intercept of -23.8.[5]

In 2016, these equations were tested in 31 patients to determine their clinical utility and accuracy over 11-30-hour time frames.[3] The observed root mean squared errors (RMSE) were between 4.79 and 6.37 mmol/L and the observed average delta Na^+ was about 4 mmol/L. The R^2 parameters were between 0.54 to 0.66 indicating some correlation, as was pointed out in Lindner et al, [2] for individual data points the Na^+2 predicted and observed could be widely divergent. It was posited that these equations are optimally tested under stringent conditions where actual input fluid volume, electrolyte concentration, and all output body fluids are measured in real time for volume and concentration with a high degree of fidelity). Nonetheless, we believe they may perform better over shorter timeframes under clinical conditions. This is likely due to the assumptions of urine electrolytes and volume staying constant is a better approximation over 2-4 hours than 11-30 hours. In addition, tracking inputs accurately is more easily done over shorter timeframes as well.

Subsequent editorials agreed that these equations break down over long time periods, but some authors generalized the findings about the accuracy of equations to all time periods.[6] We did not agree, as appropriate testing over shorter timeframes has been needed and was not yet done.[6] As such a study was undertaken to examine the performance of these equations over 2-4 hours retrospectively to determine the performance of these four equations. All inputs were analyzed at a level of detail including all water intake, intravenous fluid intake, oral potassium and sodium repletion, as well as an accounting of urine output was chosen.

Methods

A retrospective study was designed to compare the predicted Na^+2 with the observed Na^+2 using four equations. An institutional review board protocol was filed with the University of California Los Angeles (UCLA) office of protection of human subjects. The project was approved under UCLA IRB # 18-001859 expiring 12/18/2019. 118 charts were manually reviewed and idetified 20 patients who met criteria. The criteria were the patients needed to have serum Na^+ values 2-4 hours apart, with available urine electrolytes within 4 hours of initial Na^+1 measurement, accurate weights, and accurate ins and outs (Is/Os). Only one data point was calculated for each patient in this study.

To be included in this study patients must have had a serum Na^+ of <135 mmol/L or >145 mmol/L, or be eunatremic with receipt of D5W to attenuate or prevent overcorrection. Receipt of tolvaptan within 24 hours of hyponatremia diagnosis led to exclusion since this guaranteed urine electrolytes would change rapidly. Since this was a retrospective study, the lab orders could not be standardized. The short time frame selected meant patients who warranted more frequent sodium checks were more likely to qualify for inclusion. See Table 1 for inclusion and exclusion criteria.

Our resulting cohort was comprised of 20 data points representing 20 patients. There were 13 females and 7 male patients. 17 patients were hyponatremic, 1 was normonatremic but was receiving D5w (5% dextrose water) for reversal of aquaresis, and 2 were hypernatremic. The causes of hyponatremia were heterogeneous and included 8 patients with hypovolemia, 1 with hypovolemia due to thiazides, 4 with the syndrome of inappropriate anti diuretic hormone secretion/anti diuresis (SIADH/SIAD), 2 with Salt depleted SIADH, 1 with SIADH and reduced water clearance (reduced CH20) due to acute kidney injury (AKI), and 1 with hypervolemic hyponatremia. For this study, total body water was estimated according to clinical situation/volume status physical exam with 0.6 assigned for euvolemia and 0.55 assigned for hypovolemia.

Calculations were performed with Microsoft Excel 2016 © to calculate mean of data points, root mean squared error (RMSE), and the Pearson correlation coefficient (R^2) also known as the proportion of variance. Please see Tables 2 and 3 for the gender of patient, cause of hyponatremia, the input fluids, urine output, urine electrolytes, weights, total body water estimate, and observed Na^+2 in the cohort of 20 patients. All means will be notated as mean ± Standard Error of the Mean (SEM).

Results

The average initial sodium (Na^+1) was 127.6 ± 3.14 mmol/L, including two hypernatremic and one eunatremic patients. Without these, the average Na^+1 was 122.4 mmol/L ± 0.88. The average final sodium (Na^+2) was 128.8 ± 2.8. The average time from Na^+1-Na^+2 was 3.11 ± 0.17 hours. The delta Na^+ range Na^+2-Na^+1 was 0-7 mmol/L, and the average delta Na^+ was 1.7 ± 0.32 mmol/L. The rest of the descriptive statistics are compiled in Table 3 for reference.

The range of error was -3.16 to +4.09 mmol/L for the BL equation, -1.96 to + 5.98 for the AM equation, -4.79 to +4.98 for the EFWC equation, and -3.52 to +4.3 for the NK equation.

The root mean squared errors were 2.17 for the BL equation, 2.36 for the AM equation, 2.2 for the EFWC equation, and 2.35 for the NK equation. The Pearson correlation coefficient (R2) was obtained comparing the predicted delta Na^+ for each equation to the observed delta Na^+. The R^2 was 0.66 for the BL equation, 0.7 for the AM equation, 0.85 for the EFWC equation, and 0.633 for the NK equation. The EFWC had the highest R^2 value indicating the closest correlation between values but the RMSE were otherwise comparable across equations. Please see Figure 1 for the RMSE and R^2 data for the BL, AM, EFWC, and NK equations.

Discussion

It was predicted in Hanna et.al. CKJ 2016, that while it was reasonable to expect these four equations applied over 11-30 hours to fail; it was also reasonable to expect better performance over 2-4 hours.[3] This is because the urine output and urine electrolytes, but also weight were not true constants during the change from Na^+1 to Na^+2 over longer time frames. It is also reasonable to expect record keeping of ins and outs to be more easily accomplished over shorter timeframes.

This cohort produces some evidence that the accuracy of these equations is better over 2-4 hours than 11-30 hours. The range of error from observed and expected serum Na^+ values have narrowed considerably between the initial study and currently. The RMSE have decreased by greater than 50%. The delta Na^+, however, has also decreased dramatically making the RMSE still large by comparison. While the RMSE suggest the equations are equivalent in their predictive power, the R^2 parameter seems to suggest marginally improved correlation with the EFWC equation.

This clinical testing does not produce definitive evidence of the accuracy of these equations. They need to be tested under conditions where input and output values are accurately known as the Edelman equation was, as the ultimate arbiter of their accuracy.[7] Nonetheless, the improved RMSE is encouraging in this cohort testing the equations under a shorter time span under typical clinical conditions.

These equations should not be used with inputs that are assumed to remain constant over long stretches of time, or with the assumption of constant urine flow and urine electrolyte values. This data suggests that these equations can be of some clinical utility in the short term. These equations can be used over 2-4 hours to obtain a general idea of the direction and magnitude of serum Na^+ change. The biggest issue likely to be faced is the difficulty in accurately measuring total body water, which is estimated clinically in this study, and could have a significant impact on accuracy. One method that is not usually used clinically, but can be used in a research setting is the Watson formula.[8] An optimized study for the testing of these equations would likely involve the use of this formula when input and output values are accurately known, to unassailably test the predictive power of these equations.

The EFWC may provide some marginally improved accuracy over the other equations, but they are likely fairly equivalent. Since the RMSE is still larger than the rather small delta Na^+ and since for the other equations the R^2 value is still somewhat low, it suggests that they should not be used exclusively for predicting the serum Na^+ change. Further studies maybe undertaken to examine the effect of serially using these equations over short times as a summation to predict serum Na^+ changes over longer terms (i.e. $Na^+1 \rightarrow Na^+2 \rightarrow Na^+3 \rightarrow Na^+4$). This would involve checking laboratory parameters like urine electrolytes and patient data such as weight every hour or fraction of an hour. Acquiring such data would be rather challenging and impractical in a clinical setting.

Typically, the overall goal clinically is to correct the serum Na^+ sufficiently quickly to reverse and prevent neurological complications, as well as chronic sequelae of hyponatremia such as osteoporosis and falls.[9] Optimally prevention of hyponatremia should be a clinical goal to avoid the risk of over

correction[10] which is associated with morbidity and should be treated as a medical emergency.[11] Desmopressin use with hypotonic fluid has been shown to be effective in preventing osmotic injury by reversing the rise in serum Na^{+}[12]. Newer modalities like vasopressin antagonists also have their own risk of Osmotic demyelination syndrome (ODS),[13,14] but agents like urea have promise in correcting SIADH with a theoretical lower risk of ODS.[15]

While ODS is uncommon, it is a devastating and preventable iatrogenic complication,[16] that should be prevented as much as possible. The most useful approach currently is frequent checks of serum Na^{+}, and urine electrolytes. It is important to note that serum Na^{+} values are more accurately measured from blood chemistry samples than arterial blood gas analyzers for optimal accuracy.[17]

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Figure 1

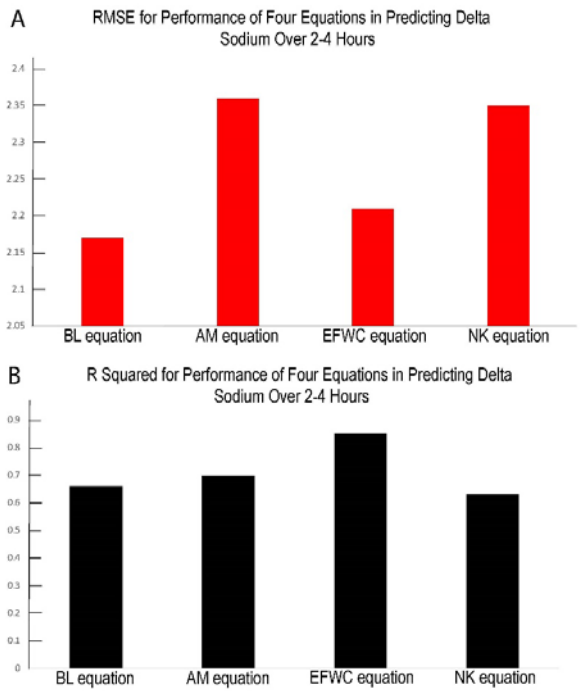

Figure 1: AM=Adrogue Madias equation, BL=Barsoum Levine equation, EFWC=Electrolyte Free Water Clearance equation, NK=Nguyen Kurtz equation, RMSE=root mean squared error, R^2=Pearson correlation coefficient for predicted delta Na^+ compared to observed delta Na^+

Table 1

Inclusion and Exclusion Criteria
Inclusion
sNa1 < 135
sNa1 > 145
Normal sNa but D5w to bring down delta sodium
Serum sodium checks 2-4 hours apart
Strict Is/Os
Weight available
Urine electrolytes [uNa+ and uK+] available within 4 hours of sNa 1
Exclusion
Incomplete charting of Is/Os weight etc.
Incomplete lab data of above
Tolvaptan administration within 24 hours of sNa1

D5W, 5% dextrose water; Is/Os, Ins and Outs; sNa1, initial serum Na; uK, urine potassium; uNa, urine sodium

Table 2

Point #	Gender	Weight (kg)	TBW est	Fluids given (L)	Other	[Na], mmol/L	[K], mmol/L	UOP (L)	uNa (mmol/L)	uK(mmol/L)	Serum glucose (mg/dL)
1	M	37	55%	0.36L D5W	1 packet K-phos-neutral	19.17	19.72	1	22	11	96
2	F	71.7	55%	1L 0.9NS	none	154	0	0.74	33	32.4	94
3	F	63.6	60%	0.13L D5w, 0.1L 0.9NS, 0.101L Na Acetate, 0.2L oral water	none	57.42	0	0.675	99	73	116
4	F	73.1	60%	0.5L 0.9NS	none	154	0	0.2	36	19.7	83
5	M	72.6	60%	1L 0.9NS	none	154	0	0.3	69	46.4	121
6	F	44.5	55%	0.1 L 0.9NS	40mmol oral KCL	154	400	0.2	24	6.7	160
7	F	54.4	55%	0.308 L 0.45 D5NS, 0.104 L D5W, 0.104L 12mmol NaPhos packed in 0.9 NS	none	69.4	0	0.15	45	37.8	136
8	F	91.1	55%	0.06L free water, oral	none	0	0	0.18	48	11.4	83
9	F	68	55%	1L 0.9NS	none	154	0	0.75	13	8.7	119
10	F	68.2	55%	0.42L 0.9NS	none	154	0	0.16	15	64	113
11	F	55	55%	0.1 L 0.9 D5NS, 0.125L 20mmol NaPhos packed in 0.9 NS	none	287.33	0	0.2	9	43.4	115
12	M	90.7	60%	0.075L D5W, 0.22L oral water	20 mmol KCL tab	0	67.8	0.4	15	13.4	128
13	F	65.8	55%	0.25L 0.9NS	none	154	0	0.48	53	14.3	87
14	F	41.9	60%	0.12L oral kayexalate (123mmol Na)	1g Nacl tab (17.11 mmol Na)	1166.67	0	0.35	61	31.3	151
15	M	77.1	55%	1L 0.9NS	none	154	0	0	0	0	116
16	F	41	55%	0.18L 0.45NS+40mmol NaCl, 0.32L D5W, 0.041L Zosyn in NS (7.7 mmol)	none	53.39	0	0.54	7	6	109
17	F	67.6	60%	0.24L oral water, 0.475 D5W	none	0	0	0.4	12	9.9	111
18	M	95.3	55%	0.2L D5W (amiodarone drip)	none	0	0	0.36	15	14.6	152
19	M	91	60%	0.056L 0.9 NS (drips), 0.060L water flush via Nasogastric tube	none	74.34	0	0.032	5	54.1	147
20	M	80.5	55%	0.2L water (oral)	none	0	0	0.1	13	38.9	176
MN±SEM	N/A	67.5±3.94	56.8±0.5%	N/A	N/A	147.9±52.7	24.4±18.3	0.36±0.05	29.7±5	26.9±4	120.7±5

D5W,5% dextrose water; est, estimate; F, female; K, potassium; Ki, concentration of potassium total in fluids and electrolytes-"infusate" sodium; Kg, kilogram; mmol, millimoles; L,liter; MN, mean; N/A, not applicable; Na, sodium; Na_1,initial sodium; Na2,final sodium; Na_i, concentration of sodium total in fluids and electrolytes-"infusate"; SEM, standard error of the mean (for n=20) [Standard deviation/ square-root (n)]; sodium; NS, normal saline; M, male; phos, phosphorous; TBW, total body water; uK, urine potassium; uNa, urine sodium; UOP, urine output

Table 3

Point #	Cause of HypoNa	Na_1	Na_2	Time elapsed (hours)	Delta (Δ) Na
1	Hypovolemia	127	127	3.8	0
2	Hypovolemia	123	126	2.2	3
3	SIADH	121	123	3.2	2
4	SIADH	118	120	3	2
5	SIADH	118	121	3.5	3
6	Hypovolemia-due to HCTZ	125	125	1.8	0
7	Hypernatremia	169	169	4.1	0
8	Hypovolemia	125	126	4.5	1
9	Hypovolemia	115	122	2.17	7
10	Hypernatremia	163	160	4	3
11	Salt depleted SIADH	122	122	3	0
12	Hypervolemia	128	127	2.5	1
13	Hypovolemia	126	127	4.66	1
14	SIADH	122	125	3.33	3
15	Salt depleted SIADH	118	120	2	2
16	Hypovolemia	121	121	3.67	0
17	D5W to reverse aquaresis	137	137	3.25	0
18	Hypovolemia	120	124	2	4
19	SIADH, Reduced CH20 due to AKI	129	128	1.75	1
20	Salt depleted SIADH	124	125	3.78	1
MN±SEM	N/A	127.6 ± 3.14	128.8 ± 2.8	3.11 ± 0.17	1.7 ± 0.32

Delta Na (Δ),change between Na_1 to Na_2; HCTZ, hydrochlorothiazide; HypoNa, hyponatremia; MN, mean; N/A, not applicable; Na, sodium; Na_1,initial sodium; Na2,final sodium; SEM, standard error of the mean (for n=20) [Standard deviation/Square-root of (n)]; SIADH, syndrome of inappropriate antidiuretic hormone secretion/syndrome of inappropriate antidiuresis.