Estimating excess glucose, sodium and water deficits in non-ketotic hyperglycaemia

Ettore Bartoli¹, Francesca Guidetti² and Luca Bergamasco²

¹Chair of Internal Medicine and ²Dipartimento di Medicina Clinica e Sperimentale, Università degli Studi del Piemonte Orientale ‘A. Avogadro’, Novara, Italy

Abstract

Background. The treatment of solute addition, Na and water losses in hyperglycaemic hyponatraemia is guided by clinical judgement rather than by a quantitative assessment.

Methods. We devised an iteration method to compute glucose appearance (GA) within the extracellular space, to obtain the PNa (plasma sodium concentration) expected by glucose addition only (PNaG). The difference between this and the actual measurement (PNa1) was used to compute the attending Na and/or volume depletion, and the PNa expected during correction. The equations were validated on computer-built models, where the electrolyte derangements were simulated, generating true values of plasma glucose (PG) and Na concentrations, from which surfeit and deficits were back-calculated with our formulas.

We also computed GA and PNaG on 43 patients who were stratified into a group with normal hydration (PNa1 = PNaG), one with prevalent Na depletion (PNa1 < PNaG), and one with prevalent volume depletion (PNa1 > PNaG). The volume conditions established by our computations were compared by logistic regression analysis with those assessed from clinical laboratory data.

Results. The computer simulations demonstrated that the method gave exact results when only one variable changed, clinically useful estimates in the presence of mixed volume and sodium deficits. There was a strongly significant concordance between the clinical and the quantitative method (P < 0.001). The latter predicted the PNa measured after correction of hyperglycaemia (P < 0.001).

Conclusion. This new method more accurately computes the initial conditions, resulting in a useful stratification of patients which improves the quantitative evaluation and treatment of hyperosmolar coma.

Keywords: dehydration; extracellular volume; hyperglycaemia; hyponatraemia; hyperosmolar coma; NIDDM

Introduction

The main derangement of hyperosmolar coma is represented by the accumulation of unmetabolized glucose inside the extracellular space, since the entrance of glucose into cells is blocked. The rise in extracellular osmolarity drives a flow of solvent from cells, diluting the extracellular solutes. Thus, hyponatraemia ensues [1]. It proves difficult in clinical practice to quantitatively analyse this phenomenon, because the osmotic diuresis causes a loss of extracellular fluids that interferes with the quantitative appraisal of glucose addition and sodium losses. In fact, if the osmotic diuresis induces a loss of water exceeding that of solutes, an inappropriately high Na concentration would be measured, unless the patient were to compensate the preferential water losses with an adequate intake. A preferential solute loss alone, and/or coupled with insufficient intake, could instead worsen hyponatraemia.

The present study was undertaken with the aim of improving the quantitative appraisal of the glucose load, and to compute predicted changes in Na concentration capable of helping to understand whether solute or water losses are more important in a single patient. Consequently, the treatment could be focused on the main abnormality, guided to avoid abrupt changes in electrolyte concentrations.

Methods

We will deal with a simplified model, similar to that published by Katz [1], where suffix ₀ refers to normal conditions, ₁ to the presence of the derangement, ₂ to any
### Hyperglycaemic hyponatraemia

**A. Normal condition**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{TBW}_0 )</td>
<td>40 L</td>
</tr>
<tr>
<td>( \text{PNa}_0 )</td>
<td>140 mEq/L</td>
</tr>
<tr>
<td>Osm Tot</td>
<td>4200</td>
</tr>
<tr>
<td>Posm</td>
<td>280</td>
</tr>
<tr>
<td>( \text{ICV}_0 )</td>
<td>25 L</td>
</tr>
<tr>
<td>( \text{ECV}_0 )</td>
<td>15 L</td>
</tr>
</tbody>
</table>

**B. Glucose added: Disequilibrium**

<table>
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<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{TBW}_0 )</td>
<td>40 L</td>
</tr>
<tr>
<td>( \text{PNa}_0 )</td>
<td>140 mEq/L</td>
</tr>
<tr>
<td>Osm Tot</td>
<td>6200</td>
</tr>
<tr>
<td>Posm</td>
<td>413</td>
</tr>
<tr>
<td>( \text{ICV}_0 )</td>
<td>25 L</td>
</tr>
<tr>
<td>( \text{ECV}_0 )</td>
<td>15 L</td>
</tr>
</tbody>
</table>

**C. Final equilibrium**

<table>
<thead>
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</tr>
</thead>
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<td>( \text{PNa}_1 )</td>
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<td>Osm Tot</td>
<td>6200</td>
</tr>
<tr>
<td>Posm</td>
<td>330</td>
</tr>
<tr>
<td>( \text{ICV}_1 )</td>
<td>21.2 L</td>
</tr>
<tr>
<td>( \text{ECV}_1 )</td>
<td>18.8 L</td>
</tr>
</tbody>
</table>

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Fig. 1. Column A indicates normal conditions with assumed normal values of total body water (\( \text{TBW}_0 \)), extra (\( \text{ECV}_0 \)) and intracellular volume (\( \text{ICV}_0 \)), Na concentration and solute contents in the two body fluid compartments. P refers to plasma, \( \text{PNa}_0 \) is the normal plasma Na concentration. Column B: 2000 mM of glucose are added to the extracellular fluid, causing the disequilibrium condition illustrated. Column C: the accumulation of the osmotically active glucose causes a water shift from cells to interstitium, till the final equilibrium situation is established. Indicating with subfix0 the normal conditions, with1 the deranged state, the true numbers are given by: 

\[ \text{Posm}_1 = \text{Posm}_0 + \text{PG}_1 \]

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\[ \text{Posm}_1 = \text{Posm}_0 + \text{PG}_1 \]

\[ \text{ECV}_0 = 15 \text{ L} \]

\[ \text{ICV}_0 = 25 \text{ L} \]

\[ \text{ECV}_1 = 15 \text{ L} \]

\[ \text{ICV}_1 = 25 \text{ L} \]

\[ \text{ECV}_1 = 18.8 \text{ L} \]

\[ \text{ICV}_1 = 21.2 \text{ L} \]

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**The problem is further complicated by the fact that \( \text{BW}_1 \) (the actual body weight) cannot usually be measured in these patients neither is the weight known just before the derangement (\( \text{BW}_0 \)). Inspection of Figure 1 shows that the critical aspect is to correctly compute either \( \text{G}_A \) or \( \text{ECV}_1 \); once one of these values is known, the second can be easily calculated (\( \text{G}_A = \text{PG}_1 \times \text{ECV}_1 \); \( \text{ECV}_1 = \text{G}_A/\text{PG}_1 \)) and the system defined exactly. We therefore approach the problem by computing these values with the following equations:**

\[ \text{TBW}_0 = \text{TBW}_1 - [(2\text{PNa}_1 + \text{PG}_1 - 2\text{PNa}_0) \times \text{TBW}_0 - (2\text{Na})][\text{PNa}_1 + \text{PG}_1]) \] (1); this formula is exact only if neither solvent nor sodium contents change: \( \text{TBW}_0 = \text{TBW}_1 \) and \( \Delta \text{Na} = 0 \). Under these conditions, the numerator of the equation is \( \text{G}_A \). However, this formula computes a volume change even when not present, whilst dividing the same numerator by \( \Delta \text{Posm} \) (given by \( 2\text{PNa}_1 - 2\text{PNa}_0 + \text{PG}_1 \)) gives an exact TBW value. However, \( \Delta V \neq 0 \) is computed as \( \Delta \text{ECV} \).

\[ \text{ICV}_1 = \text{ICV}_0 \times \text{PG}_1/\text{PNa}_0 \] (2); this formula is valid independent from changes in solvent and sodium contents.

\[ \text{ECV}_1 = \text{TBW}_1 - \text{ICV}_1 \] and \( \Delta \text{ECV} = \text{ECV}_0 - \text{ECV}_1 \) (3);

\[ \text{G}_A = \text{ECV}_0 \times \text{PG}_1 \] (4); the problem of how to compute \( \Delta \text{Na} \) requires introducing a new concept, that of \( \text{PNa}_G \), which is the plasma Na concentration that would be measured if there were only \( \text{G}_A \) added to the system. Clearly, \( \text{PNa}_1 - \text{PNa}_G \) should indicate an excess Na content when positive, an Na deficit when negative. Since an Na surfeit is unlikely in hyperosmolar coma, a positive difference indicates a plausible water deficit. It is important to recognize that a negative difference should represent an estimate of Na depletion. \( \text{PNa}_G \) is calculated as if there were no water nor Na changes: \( \text{PNa}_G = \text{pre-existing Na/ECV}_1 = \text{PNa}_0 \times \text{ECV}_0/\text{ECV}_1 \); it is equal to \( \text{PNa}_1 \) of Figure 1, where only \( \text{G}_A \) was added. Thus:

\[ \Delta \text{Na} = (\text{PNa}_1 - \text{PNa}_G) \times \text{ECV}_1 \] (5), where \( \text{ECV}_1 \) is calculated by (3). \( \Delta \text{Na} \) must be fed into the equation (1) to compute \( \text{ECV}_1 \) under these conditions.

\[ \Delta \text{Na} \text{ must be fed into the equation (1) to compute } \text{ECV}_1 \text{ under these conditions.} \]

(vi) When both Na and water contents change, the system does not recognize any exact mathematical solution,
Experiments with computer simulations

Figure 1 exemplifies our computer model, as it illustrates one simulation as an example. The simulations were performed, for a large array of assumed initial normal conditions, by changing  in steps, with or without the imposition of  or , also modified in discrete steps. For each simulation the true and were calculated, as shown in Figure 1, by inserting in the computation formulas the values of  and imposed upon the system each time. These values are then considered as if they were actual measurements during a derangement in a simulated patient, and used to back-calculate, with the formulas detailed above, the deficit of and water, and the surplus of glucose.

To simulate the diagnostic problem, we assume, for each simulation, that we know exclusively the initial conditions (those portrayed in column A for the example shown in Figure 1), and the and values measured during the derangement (generated by the computer), as if we were in column C.

Experiments on patients with hyperglycaemic hyponatraemia

We studied 43 patients admitted with hyperglycaemia to the hospital. Inclusion criteria required  (270 mg/dl), arterial pH > 7.30, plasma bicarbonate >15 mEq/l, urine ketones <2+. Each patient had a complete history and physical examination taken, and the initial measurements of BW (when possible), plasma sodium (PNa mEq/l) and creatinine concentrations (PCR mg/dl), urinalysis, haematocrit (Hct). These measurements were repeated during or at the end of treatment. Although the patients had all routine exams performed, their evaluation for the purpose of the present study was based on 21 clinical lab results independently scored: at least 10 had to be unequivocally present to allow a clinical evaluation. A patient was considered significantly dehydrated if >7 out of 10 measurements indicating low volume were present, rather normally hydrated if <3 were present. The score attributed to normal values was zero. PCR was not corrected, since the correction assumes perfect steady state, probably not present in these patients. The mixed clinical laboratory symptoms, each followed by its score in brackets were: blood pressure mmHg: (1), <100/60 (2), diastolic unmeasurable (3); heart rate per min: ≥84 (1); ≥92 (2), ≥100 (3); appearance of skin and mucosa: dry (3); plasma creatinine: ≥1.5 (1), ≥2.0 (2), ≥2.5 (3); creatinine clearance ml/min: ≤60 (1), ≤20 (3); haematocrit %: ≥40 (1), ≥54 (3); jugular veins and bedside estimate of CVP: low (1); extremities and forehead: sweaty (1); mental state: clouded (3); peripheral veins: flat (1); urine volume/24 h: <400 (1), <100 ml (3).

TBW (litres, l) was computed, in normal conditions, as: TBW0 = 0.6 kg of normal BW when BMI (body mass index) was 25 or unknown, otherwise it was calculated as TBW0 = h2, where h is height in meters, measured in supine position in the hospital bed. This formula subordinates that fat exceeding the amount expected for a normal BMI of 25 is anhydrous and contributes to BW, not to TBW. Thus, TBW0 = 0.6 × lean BW = 0.6 × normal BMI × h2 = 0.15 × h2, taking 25 as normal BMI. The normal ICV was: ICV0 = TBW0 × 0.625; the normal ECV was ECV0 = TBW0 × 0.375; normal plasma sodium concentration (PNa0) was 140 mEq/l. The data of the patients were processed with the same methods used for computer simulations, computing, both with the equations (1)–(5) and the iteration method of the appendix, , and .

An immediate treatment was started by infusing regular insulin (Humulin R-Lilly, or Acrapid-Novon Nordisk Farmaceutici) at an initial rate of 20 IU/h, plus maintenance infusions calculated to replace the external losses of Na and water. During treatment which lasted on average, 12 h, the rate of insulin administration was progressively reduced, according to plasma glucose measurements, to an average of 8 IU/h. As glucose is metabolized, its corresponding osmoles disappear from the extracellular fluid, causing a shift of water into cells; PNa consequently increases. This phenomenon is the reverse of that portrayed in Figure 1. The PNa rise can be calculated, at an unchanged TBW, by the equations reported at the end of the appendix.

The data were analysed statistically. Means and standard errors of the means (M ± SE) were computed, and their differences tested by paired or unpaired t-tests. Correlations and regressions between variables were computed by least square methods, using a ‘Stat Soft’ software package commercially available.

Results

The computer simulation experiments establish the validity of the equations and their range of applicability, being built with assigned values and yielding true numbers on which to base our calculations.

Table 1 displays the true values of and generated by the computer, and their paired values calculated with the iteration method of the appendix and the formulas (1)–(5) of the methods. The data of the first horizontal lines refer to simulations where there was neither nor . The methods give exact values. The regression equations between true and calculated data are in unity with the formulas (1)–(5) and nearly in unity with the appendix method. When only the TBW changes, the iteration slightly overestimates the true ECV and , while correlation...
and regression are significant. Instead, the ‘one-step method’ strikingly underestimates both, while regression and correlation are not significant.

The data obtained when there was a change in Na while not in water contents, are reported in the three lines that follow. The values of ∆Na are shown together with their paired values calculated with the formulas. The iteration method calculates more useful data as the intercept is more reliable than that given by the ‘one-step procedure’.

The two bottom lines of Table 1 display the true values generated by the computer, plotted against the paired values calculated by each method when both water and Na were lost. The ECV regression is negative, as it computes large volumes when the true ones are small, and vice versa, when the ‘one-step method’ is used. Instead, the data are more reliable using the iteration method of the appendix, which, however, underestimates the true value.

Therefore, we applied to patients, who were very likely suffering from mixed disorders, the iteration method of the appendix to compute the entity of Na and water derangements, and the critical value of PN_{NaG}. The data obtained in each patient are reported in Table 1, together with the clinical score of the volume conditions. The PNa calculated by G_{A} (PN_{NaG}), and the difference between this value and the actual PNa measurement performed at the same time (∆PNa) are included.

Seventeen out of 43 patients with PN_{A}–PN_{NaG} within 3 mEq/l, belonged to group 1. They should have had an ECV compatible with the water shift from cells, which remained either stable or was partly depleted iso-osmotically by the osmotic diuresis.
However, patient 12 was comatose, anuric, with important dehydration. Patient 2 had mild dehydration, a rise in PNa to 2.4 mEq/l and a heart rate of 92 bpm. Patients 25 and 27 had mental clouding and dehydration. All other patients of this group had normal volume and circulatory conditions by clinical examination, were alert, had normal BP, no renal failure, indicating an intake of hypotonic fluids capable of balancing the losses due to the osmotic diuresis. In this group, the mean PNa was 2.24 ± 2.3 mEq/l, systolic BP 141 ± 8 and diastolic BP 84 ± 5 mmHg.

Seven out of the remaining 25 patients (numbers 5, 6, 11, 16, 22, 28, 41) had PNa1 – PNaG > 3 mEq/l; they belonged to group 2, where there was a significant volume loss. They exhibited clinical signs of dehydration. The PGI averaged 30.6 ± 1.5 mEq/l, systolic BP 131 ± 16, diastolic BP 78 ± 12 mmHg.

The remaining 19 patients had PNa1 – PNaG ≤ 3 mEq/l. Therefore, they belonged to group 3, which should have suffered from a significant Na depletion caused by the prolonged osmotic diuresis, compensated by a water intake larger than that of Na. They did not show clinical signs of dehydration. Their average PGI was 25.9 ± 2.2 mEq/l, systolic BP 145 ± 4, diastolic 92 ± 5 mmHg.

Figure 2 shows the plot between the actual measurements of PNa1 and the values calculated from GNa (PNaG). Regressions and correlations are significant only for groups 1 and 3. The intercepts indicate that, extrapolated to a measurement of zero,
there is an overestimate of PNa in group 3 > 1, suggesting the existence of Na depletion in both, although significantly (P < 0.001) larger in group 3. Group 2 did not show any significant correlation.

Figure 3 shows a similar plot between the actual measurements obtained at the same time point during correction (PNa2), and the values computed by the associated changes in PG by equations (17)–(20). Correlations and regressions are highly significant.

Figure 4 portrays the changes in PNa during correction, plotted against the associated changes in PG. As expected, PNa rises in all patients, parallel to the fall in plasma glucose concentration.

The slope indicates that the rate of PNa rise, with respect to the fall in PG, averaged 2.2 mEq/l/100 mg% drop in glucose concentration.

The logistic regression analysis was executed between the scores of the mixed clinical laboratory signs reported in the methods, and the groups stratified according to the PNa1–PNaG difference intended as an independent appraisal of their volume conditions. There is a significant concordance between the clinical evaluation and the results of the quantitative analysis of volume conditions derived from the mathematical formulas. The overall F-value is 7.33, P < 0.002. The difference between groups shows the following: group 1 vs group 2, P < 0.02; group 2 vs group 3, P < 0.02; group 1 vs group 3, P = n.s.

The prediction of clinical signs in suggesting the volume status gave the following results: mental state (F = 112, P < 0.001); appearance of skin and mucosae (F = 68, P < 0.001); blood pressure (F = 60, P < 0.001); urine volume (F = 56; P < 0.001); haematocrit (F = 51, P < 0.001); creatinine clearance (F = 51, P < 0.001); temperature of extremities and forehead (F = 49, P < 0.001); filling of peripheral veins (F = 40, P < 0.001).

Discussion

The present work represents an initial effort in the direction of a quantitative assessment of hyperosmolar...
coma, providing reliable predictions on the desired modifications of electrolyte concentrations. For this purpose, we built a simplified mathematical model that considers only acute changes, affecting exclusively the content of ECV. It yields exact results when $G_A$ alone changes, whilst it performs less efficiently in the presence of altered Na or water content and in mixed derangements. However, the iteration method described in the appendix circumvents some of these problems, yielding reliable estimates even with mixed derangements, at least on computer simulated patients. Unfortunately, real patients are different from their computer counterparts, since the rising glucose concentration dictates the onset of an osmotic diuresis attended by important losses of solvent and Na $[4]$. Furthermore, the normal BW preceding the onset of the alteration is seldom known in the emergency room, where even the actual BW is difficult to measure, limiting the applicability of more reliable formulas for estimating the normal TBW $[5]$.

The critical point of the patient evaluation must then rely on a derived value, rather independent from these confounding problems, represented by $PNa_G$. It is calculated, as shown in Figure 1, with the equations of the methods and of the appendix. It represents the plasma Na concentration that would be attained if only $G_A$ had been added, without Na and/or water loss, as could happen, ideally, in anephric patients. The patient becomes hyponatraemic because of dilution of his unchanged content of extracellular Na by the water shifted from cells because of the osmotic effect of added glucose. Thus, when measured and calculated $PNa$ are the same ($PNa_1 = PNa_G$), the patient should have no Na and/or water deficit, the ECV expanded, good clinical and circulatory conditions, and above all, he would need only insulin plus reintegration of urinary losses to correct the disorder. The data of group 1, reported for each patient in Table 2, as well as those of the logistic analysis, strongly support our contention. However, four patients appeared dehydrated at physical examination (patients 2, 12, 25 and 27 of Table 2). It is very likely that these subjects had incurred in a negative Na balance quantitatively corresponding to that of water, by a combination of osmotic diuresis and oral intake. Thus, the usefulness of our calculations cannot be separated from that of the clinical reasoning, because the $PNa_1 - PNa_G$ represents, in most instances, the correct clue to a preserved ECV and Na content, while, in a few cases, it could be the fortuitous combination of important, although casually balanced, losses of both solvent and solutes.

When $PNa_1 > PNa_G$, the osmotic diuresis must have caused a loss of water in excess of that of Na, as happened in a patient belonging to group 2. The solvent lost can be calculated as: $\Delta$Volume = improved-ECV$_1 \times (PNa_1 - PNa_G)/PNa_1$ (16). We calculated an average volume loss of 1.1 ± 0.3 l, significantly higher than that of the other groups ($P < 0.001$).

When $PNa_1 < PNa_G$, there is a clear indication that the Na deficit prevails over that of water. Since Na is lost through the kidney, this means that the volume depletion caused by the osmotic diuresis is being counterbalanced by an appropriate intake of tap water, restoring the volume while not the salt deficit. While non-hyperglycaemic hyponatraemia is attended by ECV contraction, this hyperosmolar form is accompanied by preserved or even expanded ECV. The clinical data of group 3 patients and the logistic regression analysis strongly supports this interpretation. The Na deficit can be calculated as: $\Delta$Na mEq = improved-ECV = $\times (PNa_1 - PNa_G)$ (15). We calculated an average Na loss of 100 ± 12, significantly higher than 19 ± 8 mEq of group 1, $P < 0.001$. Since (15) underestimates, on average, the salt loss, the quantity so calculated should be considered a minimum estimate.

The prediction of the results after treatment constitutes an additional important aspect of our view of hyperosmolar coma. In fact, the formulas of the appendix allow us to compute the predicted $PNa_2$ after correction. Figure 3 shows the paired data, predicted vs measured, for $PNa_2$. The significance of the correlation coefficient confirms the validity of the model on which the predicted values rest.

Our method also allows a prediction on the ratio between the rise in $PNa$ and the fall of $P_G$ during treatment. This problem has been debated in the literature $[6-11]$. Previous estimates are based on the fact that 100 mg% glucose are equivalent, osmotically, to 2.8 mEq of Na$^+$; hence, the rate of rise in $PNa$ was assumed to be 2.8 mEq/l/100 mg% fall in $P_G$ by Welt $[9]$. Katz $[1]$, on a single model and with one single simulation based on TBW of 42 l and a $G_A$ of 1000, calculated a theoretical rate of 1.6 mEq/l/100 mg% fall in $P_G$. Nguyen and Kurtz $[10]$ assumes the rate of 1.6 mEq/l/100 mg% fall in $P_G$ in his study as a constitutive element of the equation for calculating $PNa_2$. Hillier instead $[11]$ calculated empirically a rate of 2.4 mEq/l/100 mg% fall in $P_G$, which is similar to ours. This rate, shown in Figure 4, is predicted by our model, since our calculated $PNa_2$ is strongly correlated with that measured, as shown by Figure 3, and its value is included in the ordinate of Figure 4.

The present article was undertaken with the aim of introducing an important aid to the physician, that is, a guide to compute the quantitative estimates of the losses to be reintegrated, allowing the critical appraisal of clinical data with mathematical calculations. Even though the model yields exact estimates when certain conditions are fulfilled, our data support its usefulness in more extended conditions. The data suggest that the physician should compute the $PNa_1 - PNa_G$ difference with a suitable software. From this he will gain an immediate diagnostic indication, that he can translate into proper therapeutic options. He could replace the ongoing urinary losses with the infusion of hemitonic saline at a rate equal to that of the urine output, an acceptable approximation to urine Na content during osmotic diuresis. He will only add the insulin treatment when the $PNa_1 - PNa_G$ difference is within 3 mEq/l, provided the patients do not show signs of dehydration.
and mental clouding. He will infuse more hypotonic solutions when the difference is positive, isotonic saline when the difference is negative. He might consider re-measuring PNa and PG after the calculated deficits have been replaced: these values could still be below those predicted, as the method, on average, underestimates the losses. Nevertheless, he would know that his procedure is correct, and replace the missing amounts of salt and/or water. Even during treatment the clinical judgement remains at least as important as the quantitative calculations, although their combined use will significantly improve the effectiveness of the correction.

In conclusion, this study represents the first step into a way to quantitatively evaluate and treat hyperosmolar coma. The method we propose is exact in a good number of clinical situations, while it is capable of furnishing useful estimates of solvent and solute losses, as well as glucose accumulation, in all other conditions.

Conflict of interest statement. The computer program necessary to perform the calculations is copyrighted (SIAE registration n° 0604311) but not presently marketed.

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Appendix

Iteration method to compute GA, PNaG and ∆Na. The iteration steps are numbered progressively.

(i) Posm1 = (Posm0 × TBW0 + PG1 × ECV0)/TBW0; this calculation will underestimate the true Posm, because PG1 × ECV0 underestimates the glucose appearance, given by GA = PGI × ECV;
(ii) ECV1 = ECV0(Posm0 + PG1)/Posm1; this calculation will give a better estimate of the ECV, because the underestimate of the numerator (caused by PG1 × ECV0) and that of the denominator (caused by Posm1), compensate each other;
(iii) PNaG (the Na concentration expected only by glucose) = PNa0 × ECV0/ECV1 (8);
(iv) Improved-Psm1 (improved by the initial estimate of ECV) = [(Posm0 × TBW0) + (PG1 × ECV1)]/TBW0 (9);
(v) Improved-ECV1, improved by the second estimate of Posm1, is given by: Improved-ECV1 = [(ECV0 × Posm0) + (PG1 × ECV1)]/Improved-Psm1(10);
(vi) Glucose appearance within the ECV, GA (better estimate) = PG1 × Improved-ECV1 (11);
(vii) PNaGfe1 (final estimate) = PNa0 × ECV0/Improved-ECV1 (12);
(viii) PosmG predicted by glucose addition only = PG1 + 2 × PNaGfe1 (13);
(ix) ∆PNa (the difference between the actual PNa1 and PNaGfe1) = PNa1 – PNaGfe1 (14); PNa1 – PNaGfe1 = 0 indicates no volume and/or Na depletion, and the above formulas are exact; when PNa1 < PNaGfe1, the formula: (PNa1 – PNaGfe1) × Improved-ECV1 = ∆Na (15), represents an exact estimate of Na depletion when ∆V = 0, while it represents a minimum estimate when ∆V ≠ 0; when PNa1 > PNaGfe1, the formula: (PNa1– PNaGfe1) × Improved-ECV1/ PNa1 = ∆ECV (16), estimates exactly the ECV contraction when ∆Na = 0, while it represents a minimum estimate of its change when ∆Na ≠ 0.

These calculations were performed in an iterative mode, whereby each subsequent computation utilized the value yielded by the preceding equation, following their progressive numeration.

In the example of Figure 1, the iteration method yields, at the first run, the following equation: GA = 1988.5 while the true value is 2000, a 99.4% approximation; Posm = 329.7 mOsm/kg, while the true value is 330; ECV = 18.81, equal (within the rounding off) to the true value; PNa = 112 mEq/l, equal (within the rounding off) to the true value; PNa1 – PNaGfe1 = 0, which means that the TBW is unchanged and ∆Na = 0.

If GA were estimated by PG1 × ECV0, it would be computed as 106 × 15 = 1590 mM, a 79%
approximation (a 21% error). The PNa_G1 would be calculated, by consequence, as 116 mEq/l, indicating a non-existing water loss.

During treatment, as glucose is metabolized and its osmotic effect fades away, water shifts into cells and the contraction of ECV is attended by a rise in PNa. Subfix 1 indicates the values before treatment, while 2 indicates values measured either during or at the end of treatment:

Glucose disappeared during treatment up to the time of measurement = (P_G1 - P_G2) × Improved-ECV_1 (17); Posm_2 = (Posm_0 × TBW_0 + P_G2 × Improved-ECV_1)/TBW_0 (18); ECV_2 = [(ECV_0 × Posm_0) + (P_G2 × Improved-ECV_1)]/Posm_2 (19); PNa_2 = PNa_1 × Improved-ECV_1/ECV_2 (20). This ‘predicted’ PNa_2 can be compared to that actually measured, to check the accuracy of prediction, which depends upon that of the equations. An appropriate software is available to help with these calculations (SIAE registration 8/16/06, number 0604311, informations from sonbartoli@libero.it, quoting reference program number 0602).