Hyponatremia: Evaluating the Correction Factor for Hyperglycemia

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PURPOSE: There are no controlled experimental data that assess the accuracy of the commonly used correction factor of a 1.6 meq/L decrease in serum sodium concentration for every 100 mg/dL increase in plasma glucose concentration. The purpose of this study was to evaluate experimentally the hyponatremic response to acute hyperglycemia.

SUBJECTS AND METHODS: Somatostatin was infused to block endogenous insulin secretion in 6 healthy subjects. Plasma glucose concentrations were increased to >600 mg/dL within 1 hour by infusing 20% dextrose. The glucose infusion was then stopped and insulin given until the plasma glucose concentration decreased to 140 mg/dL. Plasma glucose and serum sodium concentrations were measured every 10 minutes.

RESULTS: Overall, the mean decrease in serum sodium concentration averaged 2.4 meq/L for every 100 mg/dL increase in glucose concentration. This value is significantly greater than the commonly used correction factor of 1.6 ($P = 0.02$). Moreover, the association between sodium and glucose concentrations was nonlinear. This was most apparent for glucose concentrations >400 mg/dL. Up to 400 mg/dL, the standard correction of 1.6 worked well, but if the glucose concentration was >400 mg/dL, a correction factor of 4.0 was better.

CONCLUSION: These data indicate that the physiologic decrease in sodium concentration is considerably greater than the standard correction factor of 1.6 (meq/L Na per 100 mg/dL glucose), especially when the glucose concentration is >400 mg/dL. Additionally, a correction factor of a 2.4 meq/L decrease in sodium concentration per 100 mg/dL increase in glucose concentration is a better overall estimate of this association than the usual correction factor of 1.6. **Am J Med. 1999;106: 399–403.** ©1999 by Excerpta Medica, Inc.

Seldin and Tarail (1) described the acute effect of hyperglycemia in lowering serum sodium concentration nearly 50 years ago. They demonstrated that the principal mechanism of glucose-induced hyponatremia was the extracellular shift of water due to the restriction of glucose to the extracellular space (2,3). Although dehydration produced by an osmotic diuresis had been previously recognized, these acute cellular shifts due to hyperosmolarity had not.

Subsequently, a correction factor of a 2.8 meq/L decrease in serum sodium concentration for every 100 mg/dL increase in glucose concentration >100 mg/dL was proposed, based on the assumption that 100 mg/dL of glucose (5.6 mmol) would behave osmotically as 2.8 meq of sodium (5.6 mosm of NaCl; 4). Katz (5) later argued that the movement of water would cease before normal extracellular osmolality was restored, resulting in an equilibrium state of mild hyperosmolarity in both the intracellular and extracellular spaces. Based on this, he proposed the correction factor that is commonly used today: a 1.6 meq/L decrease in serum sodium concentration for every 100 mg/dL increase in glucose concentration (5). With further theoretic considerations, others suggested amended correction factors ranging from 1.2 to 2.0 (6–9), but these have not been widely accepted. Surprisingly, although the 1.6 correction factor is routinely used in the common clinical setting of hyperglycemia, experimental evaluation of its accuracy is lacking.

This report examines the effect of hyperglycemia on serum sodium concentration in healthy subjects who were rendered acutely insulin deficient. Insulin deficiency produces hyperglycemia and also reduces the permeability of most cells to glucose, thus accentuating its osmotic effect. Therefore, we included insulin deficiency in our experimental paradigm to mimic more closely the clinical setting. Our goals were to determine the temporal association between changes in serum sodium and glucose concentrations and to investigate statistical models that quantitatively describe this association.

METHODS

Subjects

Six (5 men, 1 woman) young [32 ± 2 (mean ± SD) years], healthy, normal-weight (70 ± 4 kg) volunteers were studied. None of the subjects were taking any medication or had a family history of diabetes.

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Experimental Protocol

Subjects fasted overnight, and baseline plasma glucose and serum sodium concentrations were obtained. Somatostatin was infused (300 μg/h) throughout the study to suppress endogenous insulin secretion. Glucose (20% dextrose given with 0.45% saline) was infused to increase the plasma glucose concentration to >600 mg/dL within 1 hour. The sodium excretion in patients with diabetic ketoacidosis typically ranges from 60 to 75 meq/L (10,11). Therefore, the inclusion of 0.45% saline in the dextrose infusion was intended to replace urine salt and water losses and minimize any dilutional hyponatremia from the infusate.

Once the hyperglycemic goal was achieved, the glucose infusion was discontinued, and regular insulin was infused (6 U bolus, followed by 6 U/h) until the plasma glucose concentration had decreased to 140 mg/dL. Subjects were monitored until glucose concentrations had returned to baseline. Simultaneous serum sodium and plasma glucose concentrations were obtained in all subjects every 10 minutes from peak hyperglycemia to normalization. Additionally, 3 subjects had simultaneous 10-minute measurements during the induction of hyperglycemia. Subjects voided immediately before the study, and urine samples were collected sequentially to estimate urinary glucose and volume losses. The total volume infused during the study was recorded in 4 of the subjects. The study protocol was approved by the Institutional Review Board, and all subjects gave informed consent.

Analytic and Statistical Methods

Plasma glucose concentration was measured using glucose oxidase, and serum sodium concentration was measured by flame photometry. Data are presented as mean ± SD. Regression models were estimated with sodium concentration as the dependent variable and glucose concentration as the independent variable for each subject. Linear, piecewise linear, and nonlinear models were investigated. To assess the statistical significance of the estimated regression coefficients, and to make comparisons with the standard correction factor of 1.6 meq/L, one-sample *t* tests were used in which the variability of the estimated regression coefficients was based on the variability among the parameter estimates for models estimated within individuals. Statistical testing was confirmed through the use of mixed-effects models. For the within-person piecewise models, ordinary least squares regression was used to estimate the glucose concentration that was associated with a change in the slope of the association between sodium and glucose concentrations. Reported models are based on average parameter estimates between individuals.

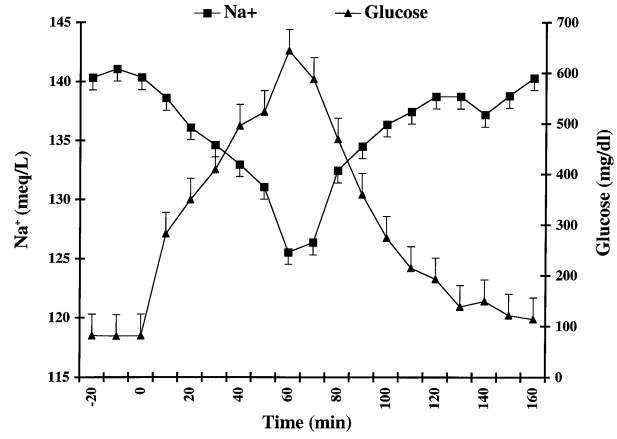

Figure 1. Mean serum sodium (Na+) and plasma glucose concentrations with acute induction of hyperglycemia after rapid recovery with insulin infusion in 6 healthy subjects. Mean ± SD values are depicted for both sodium (meq/L) and glucose (mg/dL) concentrations.

RESULTS

Acute hyperglycemia decreased the serum sodium concentration in all subjects. There was no delay in the hyponatremic effect of hyperglycemia, demonstrating that the extracellular shift of water was essentially immediate (Figure 1). Similarly, normalization of serum sodium concentration mirrored the time course of normalization of serum glucose concentration in the second phase of the study (Figure 1). The volume of fluid infused to increase plasma glucose concentrations averaged 805 mL (n = 4), whereas urinary output averaged 588 mL (n = 6), resulting in a positive balance of approximately 210 mL.

When the data were fit to a simple straight line regression, the average slope was −2.4 ± 0.3 meq/L Na per 100 mg/dL glucose. This value is significantly greater than the conventionally used value of −1.6 ($P = 0.02$). However, the decrement in serum sodium concentration appeared to deviate from linearity. This was most apparent for glucose concentrations >400 mg/dL (Figure 2A). Therefore, we also explored several nonlinear and piecewise linear associations. For the piecewise regression, the slope was −1.6 until the glucose concentration reached approximately 440 mg/dL (Figure 2B), at which level the slope more than doubled to −4.0.

For estimating the baseline sodium concentration at all levels of plasma glucose concentration, the piecewise linear model performed as well as more complex models and better than simple linear alternatives. There was no apparent pattern of either overadjustment or underadjustment throughout the range of glucose concentrations with the piecewise regression (Figure 3).

For the linear 2.4 meq/L Na per 100 mg/dL glucose correction factor, there was a mild overestimation ob-

served in the 300 to 500 mg/dL range of glucose concentration. However, in the clinically important range (≥500 mg/dL), the 2.4 correction factor performed as well as the piecewise model. In contrast, the standard correction factor of 1.6 underestimated the known baseline sodium concentration for glucose concentrations >300 mg/dL in 80% of the samples and underestimated 13 of the 14 samples with glucose concentrations >500 mg/dL (Figure 3).

DISCUSSION

These results demonstrate that hyperglycemia rapidly and profoundly decreases the serum sodium concentration in healthy subjects rendered acutely insulin deficient. Moreover, this hyponatremic effect is quickly reversed with normalization of the glucose concentration (Figure 1). This is consistent with earlier observations that the primary mechanism of hyponatremia is the forced extracellular flux of water induced by acute hyperglycemia (2,3). It is the magnitude of this osmotic shift that Katz (5) tried to predict with a correction factor.

As it is difficult to apply a complex mathematical model at the bedside, we suggest that a decrease of 2.4 meq/L in sodium concentration per 100 mg/dL increase in glucose concentration is a significantly better correction factor for acute hyperglycemia than the value of 1.6 in current use. This is particularly true with marked hy-

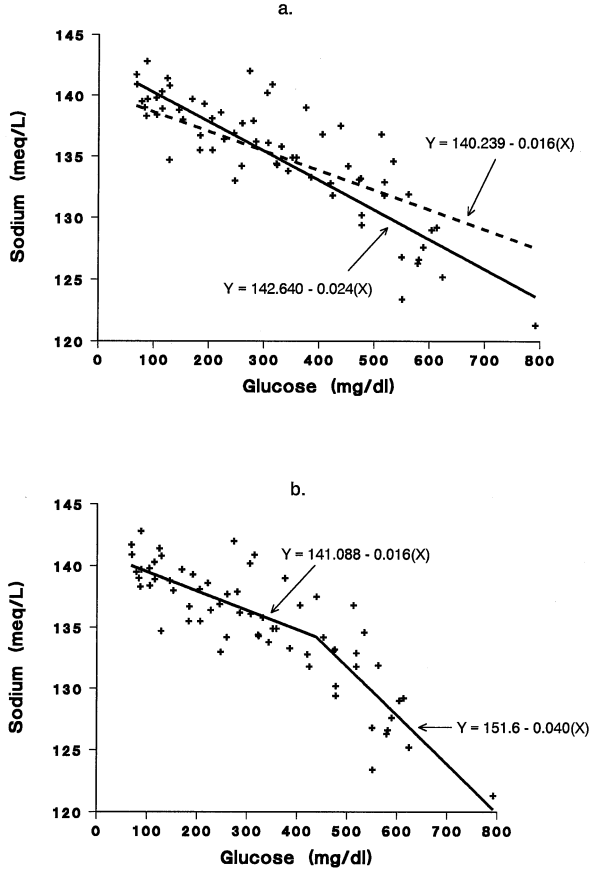

Figure 2. Serum sodium concentrations as a function of plasma glucose concentrations using simple linear regression lines estimated from the mean slope (−2.4 meq/L Na per 100 mg/dL glucose) and intercept for the 6 subjects compared with the regression line when the slope was set at the standard value of −1.6 (**A**). Piecewise linear regression is also shown (**B**).

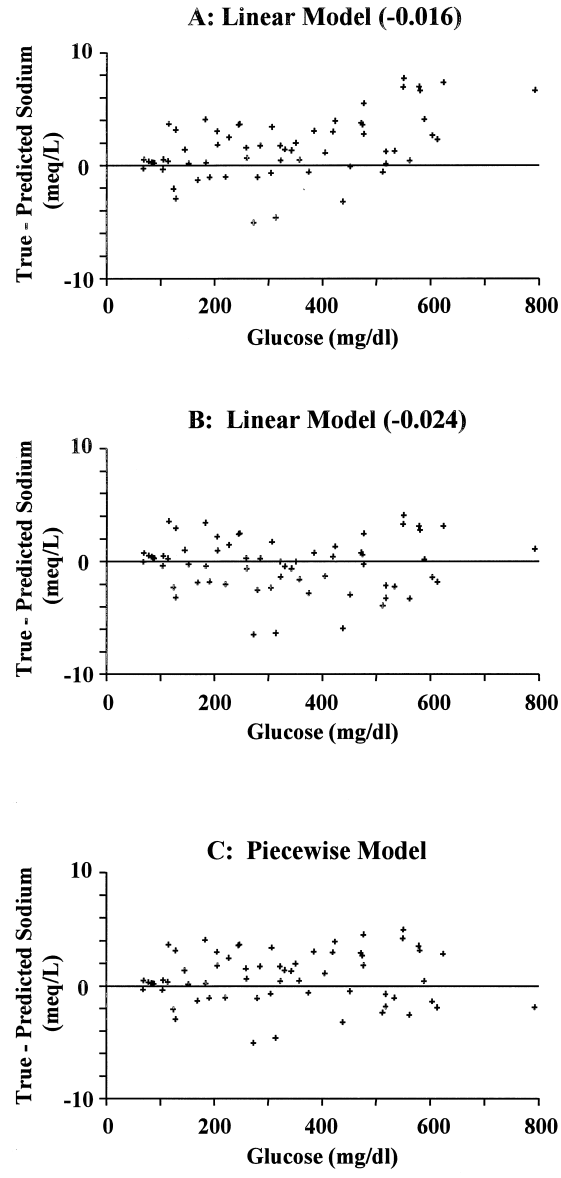

Figure 3. Differences between true (baseline) and predicted sodium concentrations are depicted for the following models: the standard correction factor of 1.6 (**A**), the 2.4 simple linear model (**B**), and piecewise regression (**C**). Predicted sodium concentrations were estimated for each simultaneously measured glucose and sodium concentration.

perglycemia. Piecewise linear regression performed best throughout the range of glucose concentrations and may be a useful alternative. However, in the clinically important ranges that we studied, using the overall 2.4 correction factor and using piecewise linear regression provided nearly equivalent results. For example, in a patient with a glucose concentration of 600 mg/dL, the sodium correction is $(600 - 100) \times (2.4/100$ mg/dL glucose$) = 12$ meq/L with the 2.4 correction; with piecewise regression, the sodium correction is $\{[(400 - 100) \times (1.6/100)] + [(600 - 400) \times (4.0/100)]\} = 12.8$ meq/L).

The source of the deviation that we observed from Katz's prediction, particularly with increasing hyperglycemia, is not clear. Dilutional hyponatremia from the infused glucose and saline could have overestimated the degree of hyponatremia. However, the inclusion of 0.45% saline in the infusate to match the sodium excretion seen in diabetic ketoacidosis (10,11), such that the volume infused approximately matched urine output, makes a dilutional effect unlikely. The net increment in body fluid volume (approximately 210 mL) would not have a substantial effect on serum sodium concentration in these adults with an estimated total body water >40 liters. Even if the total fluid intake were free water, and the approximately 600 mL lost in the urine were normal (0.9%) saline, only approximately a 2% decrease in serum sodium concentration would be expected. Furthermore, as all subjects' sodium concentrations normalized with return of euglycemia, there was no evidence of substantial dilution.

Our experimental design could have increased antidiuretic hormone (ADH) release, which would worsen hyponatremia. Because our subjects were neither volume contracted nor severely hyperosmolar, potent stimulation of ADH from the usual mechanisms is unlikely. It is possible that somatostatin could have stimulated ADH secretion (12,13). However, severe hyperglycemia with hyponatremia as occurs with diabetic ketoacidosis is accompanied by both volume contraction and hypertonicity, and ADH levels are typically markedly elevated (14).

We included insulin deficiency in the current study, because it is a common clinical accompaniment to hyperglycemia and hyponatremia. The insulin deficiency induced by somatostatin likely accentuated the hyponatremic effect of glucose. The mass of tissue that requires insulin for glucose transport represents approximately 83% of body weight and accounts for the majority of intracellular water volume (8). In a study that examined the effect of acute glucose infusion without suppressing endogenous insulin secretion, the decline in serum sodium concentration was less than in the current study (15). This suggests that insulin deficiency decreases the distribution space available to glucose, increasing the osmotic effect of a glucose load.

We caution that our study evaluated the effect of acute hyperglycemia on serum sodium concentration in healthy subjects, and this may be very different than the effect of chronic hyperglycemia. Neither the current work nor the theoretical estimation by Katz accounts for the additional effect of dehydration that usually accompanies severe hyperglycemia. However, in outpatients with presumably long-standing hyperglycemia, the decrement in serum sodium concentration ranged from 1.9 to 2.3 meq/L for every 100 mg/dL increase in glucose concentration (16,17). Thus, the correction factor for serum sodium concentration may exceed 1.6 even with chronic increases in plasma glucose concentration.

In their studies of diabetic acidosis, Seldin (2) and Seldin and Tarail (3) noted that the magnitude of water depletion may be underestimated if the sodium concentration is either low or normal. Therefore, a markedly hyperglycemic patient who presents with a sodium concentration in the normal range is substantially volume depleted. Furthermore, once the hyperglycemia is corrected, the patient's hypernatremia will manifest. Thus, the correction factor with marked hyperglycemia is pertinent regardless of the initial sodium concentration.

In summary, these experimental results indicate that the degree of hyponatremia varies among individuals with acute hyperglycemia and becomes more pronounced with marked hyperglycemia. Furthermore, we suggest that a correction factor of a 2.4 meq/L decrease in sodium concentration per 100 mg/dL increase in glucose concentration is practical and more accurate than the accepted 1.6 value that was derived from theoretical predictions. Because of the curvilinear association, the true correction factor may be even greater than 2.4 for glucose concentrations >400 mg/dL. The more hyperglycemic the patient, the more the 1.6 correction factor diverges from the actual sodium concentration. Therefore, it is the markedly hyperglycemic patient that benefits most from using the 2.4 correction factor.

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