Letters to the Editor should be typed double-spaced (including references) with conventional margins. The overall length is limited to five manuscript pages, including not more than one figure or one table.

Chorionic Gonadotropin in Urine or Serum for Detection of Ectopic Pregnancy?

To the Editor:

Daee (1) proposes the use of serum rather than urine as samples for the qualitative measurement of hCG in the detection of ectopic pregnancy. He bases this argument on his observations that in seven of 10 paired patients' specimens, chorionic gonadotropin (hCG) concentrations in serum exceeded those in urine. He also states that urine testing failed to detect hCG in certain of his patients.

As quoted by Daee, we have proposed the qualitative assessment of hCG in urine as the first line test for suspected ectopic pregnancy (2, 3). We based this on our extensive experience with the "Tandem I" urine and serum test (Hybritech, San Diego, CA) and our published adaptation to the urine assay that permits the test to detect 1 in 1,000 units/L (4). In nearly 1000 patients with abdominal pain and symptoms suggestive of ectopic pregnancy, the standard urine test gave results as good as those of radioimmunoassays of the blood (5). In 175 of these patients where the serum I.I test was performed, the sensitivity (98.5%) and specificity (100%) were identical between serum and urine qualitative tests (5). No patient with ectopic pregnancy was missed by either test, and the only false negatives were in four patients with incomplete abortion, where the serum was negative in two instances and the urine in a further two. All these experiments were performed with standard methods sensitive to 25 in 1,000 units/L. Use of the high-sensitivity test (4) now permits detection of concentrations less than that of the most sensitive radioimmunoassays within a few minutes. Furthermore, this can be performed outside of a laboratory by other medical personnel. Apart from the extremely rare cases where no detectable hCG is secreted, urine testing in this manner will detect every patient with hCG regardless of the concentration in serum. Therefore, we continue to support our contention that urine testing is the first line test for suspected ectopic pregnancy because of the convenience of specimen collection and preparation and the suitability for bedside use. Quantitative assessment of hCG is best retained for serum.

References


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What Determines the Degree of Hyponatremia in Hyperglycemia?

To the Editor:

I read with interest the report of hyponatremia in spontaneous hyperglycemia by Strand et al. (1). If they are placed in the proper perspective, I believe that these authors' findings provide some support for Katz's (2) prediction of a 1.6 mmol/L decrease in serum sodium for each 1 g/L increase in serum glucose. For reasons of historical accuracy, it should be noted that Welt (3) first suggested that serum sodium should decrease by 2.8 mmol/L for each 1 g/L increase in serum glucose, and that Goldberger (4) accepted Katz's value of -1.6 mmol/L in subsequent editions of this book. Both values, -2.8 and -1.6 mmol/L, predict the depression of serum sodium that results exclusively from the osmotic shift of intracellular (IC) water into the extracellular (EC) compartment in hyperglycemia. EC hypertonicity resulting from hyperglycemia is the cause of this osmotic fluid shift (5).

In clinical practice, the change in serum sodium during hyperglycemia may be affected by a multiplicity of factors operating either on the magnitude of the osmotic fluid transfer from the IC into the EC compartment or on external fluid and solute balance. Factors affecting the osmotic fluid shift. The osmolality of a 1 g/L aqueous solution of glucose is 5.6 mOsm/kg (1000:180). The approximate osmolality of 2.8 mmol/L NaCl in water is also 5.6 mOsm/kg (2 x 2.8). Therefore, Welt predicted that in hyperglycemia the osmotic shift of water from the IC into the EC compartment is of such magnitude that EC osmolality does not change from baseline. This cannot happen, because IC osmolality rises as fluid is lost from the IC compartment. Net osmotic fluid transfer will stop when the increasing IC osmolality becomes equal to the decreasing EC osmolality. The steady-state osmolality of body fluids, equal between IC and EC compartments, will be higher in hyperglycemia than the baseline osmolality; therefore, the drop in serum sodium will be less than the value of 2.8 mmol/L. This predicted value represents one of the very few conceptual errors in Welt's remarkable book. The significance of Katz's work (2) lies less with the number 1.6 and more with the concept that, in hyperglycemia, body fluid osmolality rises. His work paved the way for all subsequent analyses. Identified factors potentially affecting the magnitude of the osmotic fluid shift from the IC into the EC compartment, and consequently the magnitude of serum sodium depression, include:

(a) The magnitude of hyperglycemia. The magnitude of serum sodium depression becomes progressively smaller with progressive equal increments in serum glucose (6–8).

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(b) Abnormalities in EC volume. For the same degree of hyperglycemia, edematous patients exhibit a smaller depression in serum sodium than do patients with EC volume depletion (7, 8).

(c) IC solute changes during development of hyperglycemia. These changes have minor effects (7).

(d) Initial body fluid osmolality. This osmolality has also minor effects (8).

(e) Whether osmotic equilibrium between IC and EC compartments is present at the time of blood sampling. Depression of serum sodium is maximal when osmotic equilibrium is achieved (8).

Factors affecting external fluid and solute balance. Hyperglycemia has profound effects on this balance. It produces osmotic diuresis, massive in certain instances, and it stimulates thirst and water consumption. The resulting net changes in body water, sodium, and potassium profoundly affect serum sodium concentration (9, 10). Serum sodium is higher than the value predicted from pure osmotic transfers of water in patients with net loss of body water and less than the predicted value in patients with loss of either sodium or potassium (10). In patients with severe hyperglycemia and coma, loss of body water is so great that the serum sodium concentration may be increased rather than depressed (11). The regression equation for sodium (y) vs glucose (x) in Arieff and Carroll's study (11) is \( y = 137.2 + 0.6x \) \( (r = 0.164) \).

I assume that many of the patients of Strand et al. did not have advanced renal failure, which limits the magnitude of the osmotic diuresis (12), and were, therefore, potentially exposed to influences on both the magnitude of the osmotic fluid transfer and the external fluid and solute balance. Given the multiplicity and opposition to each of these other influences, a correlation of \(-0.556\) between serum glucose and sodium is remarkably good. Even more remarkable is the closeness of the regression coefficient \(-1.9 \text{ mmol/L}\) to Katz's value, which was computed for a serum glucose of 11 g/L (2). Repeating Katz's calculation for a serum glucose of 3.25 g/L, the mean glucose in the study of Strand et al. (1), produces a predicted serum sodium change of \(-1.8 \text{ mmol/L}\) for each 1 g/L increase in serum glucose. I agree with their (1) conclusion that prediction of individual sodium values from the regression equation is erratic. But I suggest that their findings support Katz's value as an approximate prediction of the depression of serum sodium in hyperglycemia. The proper use of Katz's prediction is in identifying the patients who develop large derangements in body fluids as a result of hyperglycemia (7-10). In such patients, the observed changes in serum sodium differ greatly from Katz's prediction.

References

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Jaffé Reaction Interference

To the Editor:
I read with interest the recent paper by Kroll et al. (1) on the mechanism of interference with the Jaffé reaction for creatinine. These authors reach a conclusion concerning the structure of the chromogen different from mine, and I would like to comment on their work.

That carbanions can add to polynitro aromatic compounds, such as picric acid, is well established, and the highly colored products are known as Janovsky complexes (2). In the case of the reaction between acetone and dinitrobenzene, unambiguous 1H NMR (3) and 13C NMR (4) evidence indicates that the structure is as shown:

Creatinine can form a carbanion and so it is not unreasonable to suggest that an analogous complex forms between pикrate and the creatinine carbanion. I have reported evidence to support this view in two papers (5, 6), only one of which was mentioned by Kroll et al. Formation of a Janovsky complex in the Jaffé reaction is a view shared by other workers, including Kovar et al. (7). It is formation of a C-C bond which appears to be the driving force in Janovsky complex formation; acetone does not react with any polynitroaromatic compound as the enolate anion but always as the carbanion.

Any ketone, cyclic or otherwise, with a methane group alpha to the carbonyl will form a carbanion in alkaline solution, so interference in the Jaffé reaction by acetophenone, acetate, phenylacetone, benzylacetone, cyclobutanone, cyclopentanone, cyclohexanone, and acetoxymidazoline, as reported by Kroll et al., is to be expected. The crucial observations for delineating the structure of the chromogen are that dimethylimidazolidinone, aminoantipyrene, ninhydrin, and fenchrome—none of which has the crucial methylene alpha to a carbonyl—also generate chromophores on reaction with alkaline pикrate. The magnitude of the molar absorptivity is critical here, because interactions other than Janovsky complex formation (such as charge-transfer complexation) may occur but the resulting absorbance would be smaller. I quote from the paper of Kroll et al. (1):

The compounds dimethylimidazolidinone, aminoantipyrene, ninhydrin, and fenochrome all reacted with pикrate to form light-absorbing species with spectra identical to that formed by the reaction of pикrate with creatinine. Molar absorptivities, equilibriu m constants, and rate constants were not determined for these compounds.

Possibly noncarbanion-forming carbonyl compounds may interact with pикrate but, if a carbanion can form,