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NOTES AND COMMENTS I

"Anion-Gap Acidosis" Complicating Diabetic Ketoacidosis

A Commentary on Diagnosis and Management

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A 23-year-old diabetic woman (HFH #1315375) in the seventh month of her second pregnancy was brought comatose to the Emergency Room of the Henry Ford Hospital. Three days previously, she had experienced weakness, fatigue, and increased thirst, followed by nausea and vomiting. Six hours before admission she had become unconscious. Diabetes mellitus was diagnosed at the time of her first pregnancy three years ago. One week before the onset of this present illness, her private physician had reported a normal fasting blood sugar.

Physical examination showed an obese, dehydrated, unresponsive patient. Her blood pressure was 140/80 mmHg, pulse 100 per minute, and temperature 100°F. Respirations were of the Kussmaul type, 40 per minute. Optic fundi showed no papilledema, hemorrhages, or microaneurysms. The neck was supple. The deep tendon reflexes were hypoactive bilaterally. The uterus was enlarged to a seven month size of gestation.

With the preceding description, a multitude of diagnoses are conceivable. To narrow the possibilities, we need a few modifying details. Her symptoms developed suddenly. There was no preceding fever, edema, or hypertension. Knowing these facts influences the early management of any patient with a comparable problem. Diagnostic considerations include: eclampsia, ketoacidosis, hypoglycemia, central nervous system diseases, and drug ingestion. A normal blood pressure and absence of convulsions makes eclampsia unlikely. Did the initial laboratory study guide us toward the correct diagnosis?

The data included a hemoglobin of 16.7 gm per 100 ml and a serum urea nitrogen of 32 mg per 100 ml, while the urinalysis showed 4+ glucose and acetone. The blood sugar was 315 mg per 100 ml with a serum bicarbonate of 5 mEq per liter. A determination of the serum ketones was strongly positive (4+) in three successive dilutions. The arterial pH was 7.22.

These findings support a diagnosis of ketoacidosis. The mere finding of serum ketones does not imply a state of acidosis. Acidosis does ensue with massive ketosis and uncompensated base deficiency. Technically, we like to crush the reagent tablet to assure optimal chemical interaction. Aqueous dilutions are carried out when the undiluted serum on the scale of 0-4 records strongly positive. A 4+ reaction represents roughly 50 mg of ketones per 100 ml serum.[1]

The acidemia of ketoacidosis is due to excess proton-donating ketoacids,

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especially beta-hydroxybutyric acid. Accelerated lipolysis and the consequent base depletion bring about the serious pH change we see. All the blood buffers are eventually consumed in the compensatory effort.

In treatment, we gave 100 units of crystalline insulin initially and three liters of hypoosmolar saline (230 mOsm) and 176 mEq of sodium bicarbonate.

Depending upon the age of the patient, the duration of the diabetes, the height of the initial blood glucose level and the degree of ketonemia, we recommend an initial dose of 50-100 units of crystalline insulin to patients with ketoacidosis. One system for judging the initial dose of insulin advises 50-100 units for each strongly positive (4+) reaction in the serum ketone test. Modesty on the first dose is certainly justifiable; the degree of effect will be seen within two hours and can be further adjusted.

Intracellular deficits in patients with ketoacidosis include water, salt, bicarbonate, potassium and glucose.[2] We delay the infusion of exogenous glucose until an insulin effect clearly develops and the blood glucose falls below 200 mg per 100 ml. Premature use of glucose only aggravates intracellular dehydration and allows continuing osmotic diuresis, which accentuates potassium and water loss. It also spoils a fine guide of insulin effect.

Pregnancy complicating ketoacidosis demands especially aggressive correction of the acidotic state since acidosis is lethal to the fetus. Adequate bicarbonate therapy will correct the alkali deficit. The fetal mortality in any given episode of acidosis will approach 50%.[3]

Gastric lavage and suctioning were performed early in our patient. The material aspirated was blood-flecked and copious.

Gastric lavage lowers the chance of bronchial aspiration, decreases the associated gastric atony, and generally hastens oral intake during the convalescent stage. Unfortunately, gastric lavage is often ignored when treating this condition. Incidently, we have shown by gastrocamera that hemorrhagic gastritis is a frequent complication of ketoacidosis.[4]

Twenty hours after admission, we had given our patient 500 units of insulin, five liters of hypoosmolar saline, and 250 mEq of bicarbonate. The blood sugar was 150 mg per 100 ml and the serum was free of ketone bodies. However, the blood CO_2 remained 8 mEq per liter and the arterial pH 7.20. The BUN was 30 mg per 100 ml and the rectal temperature 102°F. The blood pressure was 118/80 mmHg. Clinically, she was comatose and had dramatic Kussmaul respirations. She was well-hydrated. At this time, a macerated fetus weighing five pounds presented in the birth canal and was delivered without difficulty.

Generally, when insulin resistance is overcome and the blood glucose approaches normal, the serum will be free of ketones and the patient will show clear evidence of improvement. In our patient, metabolic acidosis persisted without ketosis. With this lack of response, we consider inadequate insulin, too little potassium, or cerebral edema.

On further testing, we found that our patient's cerebrospinal fluid was sterile, acellular, and of normal pressure. Blood and urine cultures were negative. The fibrinogen was 130 mg per 100 ml. Urinalysis demonstrated no sugar, casts, RBC's, or albumin. The BUN was 40 mg per 100 ml. Hourly output was 20 ml with blood pressure as low as 50 mmHg systolic. Aramine was required for support.

Diminished glomerular filtration is known to occur in patients with ketoacidosis.[5] Ordinarily this does not cause oliguria if hydration is maintained. In our patient, multiple factors,

including electrolyte imbalance, acidosis, fever, shock, and a precipitous delivery contributed to the oliguria.

The serum electrolytes were: Na 145 mEq/1, K 3.6 mEq/l, Cl 108 mEq/l; arterial pH 7.20. Blood lactate was not available at this time for our use.

The difference of the sums of cations and anions is normally less than 10: $(Na + K) - (Cl + HCO_3 + 12) \leq 10$. This is a raw number which tests electrochemical neutrality.[6] The factor of 12 accounts for a group of fixed anions present in the blood. In any case of acidosis, a "gap" will exist in the anion side of the equation which is filled by either ketoacids, renal acids, or by lactic acid. This situation implies an excess of H+ ions, that is, dissociative ions which characterize any acid with a known dissociation constant. Calculation of our patient's "anion-gap" after the treatment of ketoacidosis showed a figure of 32. Since lactic acidosis sometimes follows severe ketoacidosis, we considered this possibility. Some authors have also suggested that the intrauterine dead fetus is a potent source of lactic acid,[7] which clears following delivery of the fetus. In our patient, however, acidosis followed the obstetric delivery.

Lactic acidosis subsequent to poor tissue perfusion is uniformly fatal. Huckabee separates lactemia (class I) from lactic acidosis (class II).[8] The former condition is common and occurs in many disease states. Acidosis does not occur because lactate disposal is maintained through the pyruvate system. In class II, however, lactate accumulates in large amounts, consumes all available buffers and causes irreversible acidosis.

Determination of blood lactate in our patient was not possible at this time. Because of her general clinical state and the known association with shock, blood loss, and fever, we made a presumptive diagnosis of lactic acidosis.

Peritoneal dialysis was done, using 1.5% Impersol buffered with 44 mEq $NaHCO_3$. After 24 hours of dialysis, the urea nitrogen was 20 mg per 100 ml; the arterial pH was 7.4, the serum bicarbonate 28 mEq/l. We recalculated the anion-gap as: $(148+4.0) - (104+28+12) = 8$. The patient was awake, breathing slowly, and was in metabolic balance.

She went home on the fourteenth hospital day and has been well since.

Recently we treated a confirmed case of lactic acidosis in a similar manner by dialysis. This patient (HFH #1328308) also survived despite known statistics to the contrary. In proposing this form of therapy, we believe the advantage of dialysis is probably the massive and rapid effusion of H+ ions. This form of acid excretion replaces usually deficient renal function caused by lowered renal perfusion.

We are aware of the presence of lactate in commercial Impersol. Lactate is a known buffer in the salt form and may act in the same way in the dialysate. The *endogenous* lactate acts as an acid in lactic acidosis. Preferably, a bicarbonate dialyzing material would provide a more efficient buffering system, but such a material is not available at this time.

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