Too much of a good thing

Part 2: management of hyperosmolar hyperglycemic syndrome

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A 72-year-old woman presents to the emergency department for left flank pain. She had been experiencing dysuria and increased frequency of urination for 3 days before her visit and was diagnosed with a urinary tract infection at her physician's office yesterday. The left flank pain began a few hours ago, and she now has developed fever and chills. The patient's daughter states that her mother is confused and does not remember her visit to the family physician the day before.

The patient's medical history is relevant for hypertension, a transient ischemic attack 2 years ago, and type 2 diabetes. Current medications consist of 81 mg of acetylsalicylic acid daily, 10 mg of ramipril daily, 75 mg of clopidogrel daily, and 1000 mg of metformin twice daily.

Physical examination reveals a blood pressure of 110/80 mm Hg, a heart rate of 110 beats per minute, a temperature of 38.7°C, a respiratory rate of 18 breaths per minute, and an oxygen saturation of 98% on room air. The patient looks unwell. A grade 2/6 aortic murmur can be heard. The lungs sound clear. Palpation of the abdomen elicits slight tenderness on the left side; renal percussion is unequivocally positive for tenderness on the left side.

A urine dipstick tests positive for low levels of ketones, blood, nitrates, and leukocytes. Laboratory investigations reveal a white blood cell count of 23.7×10^9/L with 80% neutrophils, normal hemoglobin and platelet counts, a sodium level of 148 mmol/L, a potassium level of 3.4 mmol/L, a chloride level of 112 mmol/L, a P_{CO_2} of 24 mm Hg, a blood urea nitrogen level of 17.2 mmol/L, a creatinine level of 172 µmol/L (86 µmol/L at a visit 3 months previously), and a glucose level of 41.2 mmol/L. You have initiated fluid resuscitation and antibiotic therapy. How aggressive should you be in controlling the hyperglycemia? What other information would help your management?

This patient's hyperglycemia raises a red flag for the presence of a hyperglycemic emergency. The normal carbon dioxide level and anion gap reassure us that ketoacidosis is unlikely. What about the other emergency, the hyperosmolar hyperglycemic syndrome (HHS)?

Diagnosis

The term *hyperosmolar hyperglycemic syndrome* replaces *hyperglycemic hyperosmolar nonketotic coma* and *hyperglycemic hyperosmolar nonketotic state* to reflect the facts that alterations of mental status are often present without coma and that HHS might include variable degrees of clinical ketosis.[1] Hyperosmolar hyperglycemic syndrome is characterized by profound hyperosmolality with serum glucose concentrations that are usually higher than those seen in pure diabetic ketoacidosis (DKA).[2] The 2 conditions overlap in about 33% of patients.[2] Management of DKA was outlined in part 1 of this article.[3]

The diagnostic criteria for HHS include an arterial pH greater than 7.3, a serum bicarbonate level greater than 18 mEq/L, and an effective serum osmolality greater than 320 mOsm/kg (normal range 280 to 290 mOsm/kg).[4,5] The glucose level is usually greater than or equal to 34 mmol/L.[6] In the calculation of effective osmolality ([sodium level×2] + glucose level), the urea concentration is not taken into account because it is freely permeable and its accumulation does not induce substantial changes in intracellular volume or osmotic gradient across the cell membrane.[4,5] Ketones can be present in variable quantities in the urine and blood, and the anion gap is also inconsistent.[4]

Hyperosmolar hyperglycemic syndrome is much less common than DKA; its incidence is estimated to be less than 1 per 1000 person-years.[5] The exact incidence is difficult to determine because of the lack of population-based studies and the multiple combined illnesses often found in these patients.[1] Hyperosmolar hyperglycemic syndrome tends to happen in older, obese patients with type 2 diabetes.[5] Its mortality rate, estimated to range from 5% to 17% (as high as 50% in some studies), is considerably higher than that of DKA, and relates to the underlying precipitating illness.[2,4,6,7]

Pathophysiology

The pathophysiology of HHS is similar to that of DKA. Hyperglycemia results from a relative (as opposed to absolute for DKA) insulin deficiency and an increase in counterregulatory hormones.[4,6] Endogenous insulin secretion appears to be greater in HHS than in DKA, in which it is negligible.[4] The absence of ketosis in HHS is thought to be due to lower levels of free fatty acids or higher portal vein insulin levels, or both.[5]

Just as for DKA, precipitating factors include any condition that will induce a stress response, affect carbohydrate metabolism (eg, drugs), or further decrease glucose use (inadequate insulin therapy, discontinuation of oral hyperglycemic medications, pancreatitis, etc). Infection is the most common culprit, in particular pneumonia and urinary tract infection.[2,4,5,7]

The process of HHS usually evolves over several days to weeks, leading to more severe dehydration.

The clinical picture is similar to that of DKA (polyuria, polydipsia, weight loss, vomiting); however, the mental status changes are much more pronounced in HHS and can include seizures and stroke-like symptoms that might resolve once osmolality returns to normal.[6] There is a direct correlation between osmolality and mental obtundation; the occurrence of mental status changes in a patient with diabetes in the absence of hyperosmolality demands immediate consideration of another cause.[4]

Treatment

The mainstays of treatment for both HHS and DKA are the same: correction of fluid deficits, electrolyte imbalances, and hyperglycemia. In addition, it is particularly important in HHS to identify and correct the underlying trigger condition.

Fluid replacement. Fluid losses typically amount to 7 to 12 L, causing severe volume contraction.[5,6] Rapid reexpansion has been associated, although inconsistently, with an increased risk of cerebral edema. In adults, the Canadian guidelines recommend 1 to 2 L/h of normal saline to correct shock; otherwise, 500 mL/h for 4 hours, then 250 mL/h.[6] These recommendations are the same as those for the treatment of DKA. Once euvolemia is restored, switch to half-normal saline to match the usual hypotonicity of osmotic diuresis.

Correction of potassium deficit. The typical potassium deficit ranges from 3 to 15 mmol/kg (about the same as in DKA).[5,6] The recommended replacement regimen also follows the DKA guidelines: for a potassium level greater than 3.3 mmol/L but less than 5.0 mmol/L, give 10 to 40 mmol of potassium chloride per litre of normal saline once diuresis has been established; for a potassium level of less than 3.3 mmol/L, give 40 mmol/L of potassium chloride until the potassium level reaches 3.3 mmol/L.[6] Remember to omit insulin until the potassium level reaches 3.3 mmol/L.

Correction of hyperglycemia. The role of insulin in HHS is to correct hyperglycemia and thus lower osmolality. Short-acting insulin (0.1 unit/kg/h) is recommended; this is the same dose used to treat DKA.[6] The decrease in plasma glucose concentration is predominantly due to the expansion of extracellular space and osmotic diuresis; insulin has been withheld successfully in HHS but generally its use is recommended.[6] Insulin should be continued until the target glucose level is reached, hyperosmolality is corrected, and the patient's mental status improves.

Because of the risk of cerebral edema with rapid reductions in osmolality, it is recommended that plasma osmolality be lowered no faster than 3 mOsm/kg/h (ie, glucose reduction of 2 to 3 mmol/L).[5,6] If osmolality falls too rapidly, glucose can be added to the saline.[5,6]

Your patient's serum osmolality is 332.2 mOsm/kg/h; her anion gap is 22 mmol/L. An arterial blood gas test shows a pH of 7.35 with a bicarbonate level of 22 mmol/L. Therapy is initiated concomitantly for HHS and urosepsis. After several days, the patient returns home in good condition.

BOTTOM LINE

- Hyperosmolar hyperglycemic syndrome is often masked by the precipitating condition and comorbidities; it must be actively sought. Identify and treat precipitating condition.
- Hyperosmolar hyperglycemic syndrome has a high mortality rate. The fluid deficit is double that seen in diabetic ketoacidosis.
- Continue insulin therapy until the patient's mental status improves, hyperosmolality resolves, and the target glucose level is reached.

POINTS SAILLANTS

- Le syndrome d'hyperglycémie hyperosmolaire est souvent masqué par le problème déclencheur et les comorbidités; il faut activement les chercher. Identifiez et traitez le problème déclencheur.
- Le syndrome d'hyperglycémie hyperosmolaire est associé à un taux élevé de mortalité. Le déficit en volume liquidien est le double de celui observé dans l'acidocétose diabétique.
- Continuez la thérapie à l'insuline jusqu'à ce que l'état mental du patient s'améliore, que l'hyperosmolarité se règle et que le taux de glucose visé soit atteint.

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Competing interests
None declared

References

1. Kitabchi AE, Umpierrez GE, Murphy MB, Barrett EJ, Kreisberg RA, Malone JI, et al. Management of hyperglycemic crises in patients with diabetes. *Diabetes Care* 2001;24(1):131-53.
2. Gaglia JL, Wyckoff J, Abrahamson MJ. Acute hyperglycemic crisis in the elderly. *Med Clin North Am* 2004;88(4):1063-84, xii.
3. Blouin D. Too much of a good thing. Management of diabetic ketoacidosis. *Can Fam Physician* 2012;58:55-7.
4. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care* 2009;32(7):1335-43.
5. Chiasson JL, Aris-Jilwan N, Bélanger R, Bertrand S, Beauregard H, Ekoé JM, et al. Diagnosis and treatment of diabetic ketoacidosis and the hyperglycemic hyperosmolar state. *CMAJ* 2003;168(7):859-66. Erratum in *CMAJ* 2003;168(10):1241.
6. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. *Can J Diabetes* 2008;32(Suppl 1):S65-70. Available from: **www.diabetes.ca/files/cpg2008/cpg-2008.pdf**. Accessed 2012 Aug 24.
7. Stoner GD. Hyperosmolar hyperglycemic state. *Am Fam Physician* 2005;71(9):1723-30.

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