AAEM/RSA
RESIDENT JOURNAL REVIEW

Neurologic Complications of Correction for Hyperglycemic Hyperosmolar State in the Emergency Department

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Questions

1. What is the preferred therapy for correction of hyperglycemic hyperosmolar states (HHS) in the emergency department, and what potential adverse neurologic effects of these corrective therapies should be considered?
2. What is the incidence of osmotic demyelination syndrome (ODS) or cerebral edema when aggressively correcting hyperglycemic states?
3. Who is at greatest risk for ODS and what can be done to reduce their risk?
4. Who is at greatest risk for cerebral edema and what can be done to reduce their risk?

Introduction

Acute hyperglycemic states are often reasons for presentation to an emergency department. The terminology, classification and approach to these patients, however, are frequently changing. In addition, while correction of physiologic derangements from these states is typically a top priority in emergency care, there remains some concern for negative sequelae secondary to aggressive correction. It is important for EM physicians to understand the optimal therapies and targets when correcting the abnormalities seen with severe hyperglycemia.

Scott AR, The Joint British Diabetes Societies hyperosmolar hyperglycaemic guidelines group. Management of hyperosmolar hyperglycaemic state in adults with diabetes. *Diabet Med.* 2015;32(6):714-24.

In the UK there is no single accepted definition of HHS. This article proposes the following criteria: serum osmolality > 320 mOsm/kg, blood glucose > 30 mmol/L (540 mg/dL), and severe dehydration with a sense of feeling unwell. HHS has a higher mortality than the related condition of diabetic ketoacidosis (DKA) and may be complicated by myocardial infarction, stroke, seizure, cerebral edema, and osmotic demyelination syndrome (ODS). Rapid changes in osmolality may be the cause of the relationship with ODS. This article summarizes the 2015 guidelines on management of HHS from the Joint British Diabetes Societies for Inpatient Care and recommends the following three principals to avoid complications:

1. Monitor the response to treatment
   a. Measure or calculate the serum osmolality regularly (every hour initially)
   b. Aim to reduce osmolality by 3-8 mOsm/kg/hr
2. Fluid and insulin administration
   a. Use 0.9% normal saline
   b. Keep in mind that fluid administration alone will decrease serum glucose
   c. Hold insulin until blood glucose is no longer falling with IV fluids alone (unless ketonemia is present)

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   d. Keep in mind that an initial rise in sodium is expected and should not be an indication for hypotonic fluids
   e. Do not give insulin prior to IV fluids
3. Deliver appropriate care
   a. Early consultation to diabetes team
   b. Disposition patients to a unit familiar with the management of HHS (often an ICU)

Guerrero WR, Dababneh H, Nadeau SE. Hemiparesis, encephalopathy, and extrapontine osmotic myelinolysis in the setting of hyperosmolar hyperglycemia. *J Clin Neurosci. 2013;20(6): 894-6.*

Osmotic demyelination syndrome is a well-described process of myelin destruction. When this demyelination occurs at the center of the basis pontis, it is specifically referred to as central pontine demyelinolysis (CPM). It manifests clinically as a range of devastating neurologic deficits - from a depressed level of consciousness to flaccid quadriplegia. It has typically been described in the setting of rapid correction of hyponatremia. Several reports, however, have now described the occurrence of ODS in the normonatremic setting of HHS.

The case described a 25 year-old man with type 1 diabetes mellitus. After a two-week history of anorexia, nausea, vomiting, abdominal pain and altered mental status, he was found to have a blood sugar concentration greater than 700 mg/dL and pH of 7.0. He was treated for hyperosmolar hyperglycemic coma, but as his anion gap improved and he was being weaned from the ventilator, he developed left sided weakness. A non-contrast head CT showed reduced attenuation in the posterior limb of the right internal capsule. Two weeks later, neurologic deficits which included left sided hemiparesis involving the face, arm, and leg with increased resting tone and reflexes remained present. Additionally, he was only oriented to self, exhibited impaired concentration, word recall difficulties, and frontal lobe function. MRI demonstrated hyperintensities on T2 weighted imaging consistent with demyelination and edema. The patient did not have changes to his serum sodium concentration during his course.

The classic understanding of ODS involves the sudden shrinkage of brain cells caused by a rapid increase in serum osmolality, as occurs due to over-rapid correction of hyponatremia. Two theories exist to explain oligodendrocyte shrinkage and myelinolysis associated with rapid rises in serum osmolality. The first is that injury to the blood-brain barrier results in local inflammatory demyelination. The second suggests that oligodendrocyte apoptosis is triggered as a result of hypertonic stress caused by serum osmolality that changes too quickly for idiogenic osmolytes. These are organic solutes that shift across the cell membranes to protect the cells from osmotic injury.

Cellular accommodation involves a shift of potassium ions and idiogenic osmolytes from the intracellular to the extracellular space. This process, referred to as "regulatory volume decrease" can take up to 48 hours to achieve equilibrium. Therefore, rapid changes in serum osmolality does not allow the body's natural accommodation mechanism to take effect. This supports the concept that ODS can occur during rapid changes in osmolar state as with HHS, even with normal sodium concentrations. An awareness of this complication is necessary for treating providers.

O'Malley G, Moran C, Draman MS, et al. Central pontine myelinolysis complicating treatment of the hyperglycaemic hyperosmolar state. *Ann Clin Biochem.* 2008;45(4):440–3.

The authors here describe another case of HHS during which CPM/ODS developed. They describe a 49 year-old woman who presented with drowsiness and was found to have a serum glucose of 106 mmol/L (1,908 mg/dL). Her presenting serum sodium was 135 meq/L. Over the first 6 hours of her treatment, she was given IV insulin and normal saline, which resulted in a drop in her glucose to 60 mmol/L (1,080 mg/dL) and a rise in sodium concentration to 159 mmol/L. She was subsequently noted to have flaccid quadriparesis and pseudobulbar palsy. MRI showed lesions consistent with CPM. The patient eventually recovered to near normal functional capacity.

HHS leads to a reduction in serum sodium due to the dilutional effect of water shifts. Over time this hyponatremia is corrected by our body by extruding sodium and potassium (over a period of hours) and by generating organic osmolytes (over a period of days). If the hyponatremia is corrected more rapidly than these compensatory mechanisms would have allowed, there is a rapid drop in the neuronal intracellular volume which can lead to shrinkage and demyelination. Calculation of a corrected sodium allows assessment of the degree of derangement in sodium homeostasis (this patient's corrected sodium on presentation was 178 meq/L). In cases where the corrected sodium is significantly elevated, serum glucose should be corrected more cautiously and serum sodium should be closely monitored for excessive rebound. Hypotonic fluids should be considered instead of isotonic fluids to avoid extreme sodium rebound upon glucose correction.

Siwakoti K, Giri S, Kadaria D. Cerebral edema among adults with diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome: Incidence, characteristics, and outcomes. *J Diabetes*. 2017;9(2):208-9.

Although cerebral edema is a feared complication of DKA treatment in children, its incidence in adults with hyperglycemic states is unknown. This study used a large claims database covering US patients to examine ICD codes. They examined 252,645 adult hospitalizations for severe hyperglycemic states; they did not differentiate HHS from DKA. Of this set, 80 patients (0.03%) had a diagnosis of cerebral edema which did not appear to be attributable to another cause aside from treatment of their hyperglycemic state. The mortality of patients with cerebral edema was 35% versus 1.1% mortality for those without. The authors also cited an incidence of about 0.5-0.9% for cerebral edema in pediatric DKA patients for comparison.

This study has several limitations but may serve as a starting point in identifying how common a complication such as cerebral edema may be in the treatment of adult hyperglycemic patients. This study suggests that while cerebral edema may occur with treatment of adults with HHS, it is likely relatively rare.

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Conclusions

Structural neurologic complications such as cerebral edema or ODS may occur in the treatment of adult hyperglycemic states, including HHS. However, these are probably exceedingly rare complications. While the available literature and evidence for the incidence and risk factors for these complications are limited, the pathophysiology and the data suggests that risk increases when development of the hyperosmolar state or correction of the state is undertaken extremely rapidly.

To avoid ODS, providers caring for HHS patients with exceedingly elevated glucose values should calculate a corrected sodium, consider frequent monitoring of serum glucose, sodium, and osmolality levels, and consider switching to hypotonic fluids or decreasing fluid rate when rapid rebounding of serum sodium occurs upon glucose correction. The optimal method to avoid cerebral edema in adult HHS patients is unknown, but extrapolating from the pediatric DKA literature it may be reasonable to slightly reduce the aggressiveness of fluid administration in patients.

Answers

Aggressive restoration of euvolemia by administration of IV fluids (typically isotonic fluids) remains the mainstay of therapy for HHS. Providers should be aware of the possibility of neurologic complications such as ODS and cerebral edema developing in these patients.

Cerebral edema may complicate approximately 0.03% of DKA/HHS admissions. The rate of ODS is unknown, but is likely exceedingly low based on the limited literature.

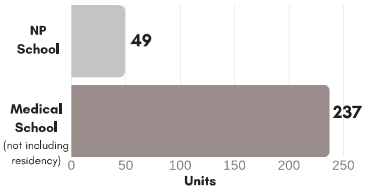
Patients with an elevated corrected sodium concentration on presentation are likely at increased risk of ODS. In these cases, serum glucose, sodium, and osmolality should be measured regularly and should be slowly corrected (goal correction 3-8 mosm/kg/hr).

It is unknown what factors increase risk for cerebral edema in adult patients treated for HHS. Extrapolating from the pediatric DKA literature, it may be reasonable to be less aggressive with fluid resuscitation in patients with elevated potassium and/or urea levels, but it should be kept in mind that cerebral edema is likely a very rare complication of adult HHS treatment and should not dissuade clinicians from providing appropriate therapy. ●

WHAT IT TAKES TO MAKE A DOCTOR

The Educational Differences between Medical Doctors and Nurse Practitioners

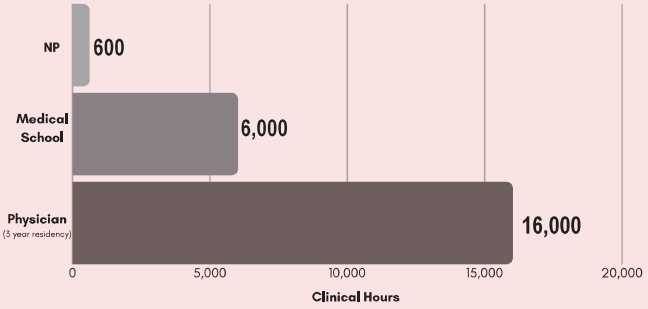
CERTIFICATION BY UNIT REQUIREMENT[1,2]



- Even without accounting for residency, which is an additional 3–7 years of training, physicians who just graduated medical school had to take nearly 5x the amount of units for their degree compared to NPs.

**Example programs are listed that state their specific unit requirements for graduation. These sources closely resemble other programs of their same degree.*

CLINICAL HOURS REQUIRED FOR CERTIFICATION



- While some nurse practitioner degrees can be completed 100% online in as little as 5 years including college, physicians must complete at least 11 years and more than 16,000 hours of hands-on training before treating patients independently.[3]
- An NP has less than 4% of the clinical hour training of an MD/DO (with the minimum 3 years residency training).[4]
- **A medical student, who is not allowed to treat a patient independently, would have undergone nearly 5x the amount of unit requirements and 10x the amount of clinical training that a fully licensed NP has.**

With the vast amount of education, training, and clinical hours required to produce a single physician (the most of any healthcare team member), physicians can rely on a much larger breadth of knowledge in each of the medical decisions they make. This is why we at AAEM/RSA believe that all healthcare team members, including nurse practitioners, should be under the supervision of a physician in order to ensure the safety and proper health care of our patients.

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