The Mentally Altered Diabetic

Diagnosis and Management of Hyperosmolar Hyperglycemic Syndrome

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Introduction

When a mentally altered patient arrives on the scene at any veterinary hospital, there is often little information available that might direct a veterinarian down the path toward a diagnosis. In the average patient, part of the initial workup for nonspecific neurologic symptoms would include a basic CBC and blood chemistry – the results of which might point toward a previously undiagnosed hyperglycemic emergency. It is important to note that as many as 50-75% of patients presenting for hyperglycemic emergencies are newly diagnosed diabetics. For those patients the information that follows may prove quite useful but for others the search must go on in other directions! In a patient that is a known diabetic, often the first diagnostic test we reach for is a glucometer which will give us a glucose reading in seconds from a mere portion of a drop of blood.

The results from that glucometer reading will go one of a variety of ways:

- Lo or <60mg/dL lead us on a path of investigating insulin dosing scheduling, eating patterns, concurrent symptoms, etc
- ~60mg/dL-~300mg/dL values may indicate that diabetes and its management are not part of the neurologic impairment of this patient
- ~250mg/dL-~600mg/dL values lead us toward suspicion of complications such as diabetic ketoacidosis
- >~600mg/dL to Hi values are more complicated until a true number can be attached to the blood glucose of a particular patient

These are all approximations and, as with so many problems in veterinary medicine, require a little bit of art in their interpretation combined with reasoning related to insulin dosing history, concurrent symptoms, prior glucose curves/monitoring history, and oral dextrose administration by the owner at home. The scope of this discussion is to hone in on those patients whose glucometer glucose is Hi or whose true glucose value is greater than 600mg/dL – a population that commonly falls into the category of hyperosmolar hyperglycemic patients. These patients are important to understand because their management is NOT exactly the same as diabetic ketoacidotic patients that are seen more commonly. Treatment is not the same because there is some variability in the pathogenesis of the two conditions.

Diagnosis

If we take a walk down memory lane, we will find that hyperosmolar hyperglycemic syndrome (HHS) has worn several names in its past. It was best known as hyperosmolar non-ketotic coma and hyperosmolar non-ketotic diabetes mellitus but more recently both human and animal medicine have come to recognize that diabetic ketoacidosis (DKA) and HHS are hyperglycemic emergencies along a spectrum rather than mutually exclusive. (Trotman, O'Brien)

Diagnosis of hyperosmolar hyperglycemic syndrome is actually just done by simple definition: calculated osmolality greater than 320-350mOsm/kg, and blood glucose greater than ~600mg/dL. However, defining a disease process simply by the numbers does not help us to understand the pathophysiology those numbers represent and subsequently the impact on treatment plan and prognosis for our patients.

Pathophysiology

Diabetic ketoacidosis and HHS share a portion of pathophysiology with each other. Both are a result of absolute or relative insulin deficiency that leads to increased gluconeogenesis, increased glycogenolysis, and decreased utilization of glucose by the tissues. Coexisting disease processes often also contribute increased counterregulatory hormones such as epinephrine, glucagon, catecholamines, cortisol, and growth hormone. Hyperglycemia occurs as glycogenolysis and gluconeogenesis are upregulated and glucose uptake diminishes.

In DKA, increased counterregulatory hormones ultimately result in lipolysis and the release of free fatty acids that are converted to ketones in the liver. In HHS, decreased glomerular filtration rate (GFR) is a primary contributing factor to development of such severe hyperglycemia and subsequently hyperosmolar syndrome. As GFR decreases and hyperglycemia worsens, diuresis is exacerbated. (Koenig) For this reason, patients with pre existing disease such as shock, renal dysfunction, or heart failure are at greater risk of development of HHS. It has been hypothesized that HHS is associated with minimal ketone formation because these patients do have adequate insulin to limit lipolysis but not adequate quantities to control rising blood glucose levels. (Boysen) However, it is also noteworthy that some dogs that develop DKA also have normal insulin levels so it is difficult to assess the accuracy of this hypothesis. (O'Brien)

History and Presenting Symptoms

Some patients presenting with HHS will have a history of therapy for diabetes mellitus that can help to direct us toward diabetic complications as a source of illness. Presenting symptoms can be highly variable ranging from simple polyuria and polydipsia to gastrointestinal symptoms such as vomiting, diarrhea, or anorexia to alterations in mentation. Some patients will have a pre existing history of complicating diseases such as hyperadrenocorticism, chronic renal failure, hepatic dysfunction, chronic infection, pancreatitis, or cardiac dysfunction which are high risk diseases and can contribute to complications of simple or otherwise well-managed diabetes mellitus. Some patients will have a history of treatment with drugs that can contribute to decompensation of diabetes mellitus such as corticosteroids or thiazide diuretics. The main consistent physical examination finding among HHS patients is dehydration.

It is important to keep in mind that, depending on the resource, it is estimated that anywhere from 50-75% of patients that present and are ultimately diagnosed with a hyperglycemic emergency are not previously diagnosed diabetics. This means that it will not be uncommon for the diagnosis of a hyperglycemic emergency to be delayed until blood work is available. In many cases stabilizing fluid therapy and other treatments may already have been initiated.

In human medicine it is fairly well established that the duration of symptoms leading up to DKA can pre-exist the diagnosis by a matter of hours whereas symptoms leading up to episodes of HHS are more insidious – occurring over a course of days to weeks. (Chaithongdi) The same finding has not been confirmed in veterinary patients but it is suspected and current therapeutic recommendations take into effect suspected longer-term onset of illness in treatment of HHS when compared to DKA. Koenig et al (2004) hypothesizes that in HHS the hyperosmolar state develops over a long period of time and presents acutely once metabolic derangements become severe whereas in DKA the presence of ketones and their side effects leads to more abrupt presentation.

Koenig et al (2004) reported no significant difference in the onset of symptoms when comparing HHS and DKA in felines though a study size of 17 could be a limiting factor in assessing this factor. The study's definition of

HHS causes further concern with the validity of this outcome because all cats with any urine ketones were excluded from the HHS group regardless of osmolality and included in the DKA group.

Trotman et al (2013) reported a range of onset of symptoms from 0.03-3 months prior to hyperosmolar episode in dogs with a mean of 0.3 +/- 0.39 months. This retrospective study compares hyperosmolar ketotic (HK) and hyperosmolar non-ketotic dogs (HNK), including 66 dogs presenting over a 15-year period. For HK the range of onset of symptoms prior to hyperosmolar episode was 0.03-0.5 months with mean 0.2 +/- 0.14 months. For HNK the range of onset of symptoms prior to hyperosmolar episode was 0.03-3 months with mean 0.38 +/- 0.57 months. It is difficult to extrapolate these results to a comparison between DKA and HHS because all of the dogs in this review were hyperosmolar.

Initial Diagnostic Workup

The initial diagnostic workup on any patient presenting with non-specific symptoms of illness is likely to begin with basic CBC, blood chemistry, and urinalysis and these patients are no different. Even if the patient is a previously diagnosed diabetic who has had normal diagnostics recently when their health seemed fairly normal, diagnostics should be rechecked when they are ill because there could be significant changes.

In the event that in-house blood work is not an option, blood and urine should be collected for submission to an outside laboratory or to a referral veterinary clinic. A bare minimum initial database would include tests that can be done easily in-house: PCV/TS, glucometer glucose, BUN reagent strip, and, if indicated, ketone reagent strip.

For those patients where diagnostics lead us to suspicion of HHS, some other diagnostics that may be indicated in the short or long term would include: blood gas analysis, urine culture, abdominal ultrasound, survey or focused radiographs, etc. While the blood gas analysis is a means to further monitor and adjust therapy for HHS, other testing is generally a search for comorbidities to ensure that everything possible is done to address the underlying cause of the hyperglycemic emergency. Ignoring the precipitating cause of these patients' illness can lead to challenges with glycemic control or stabilization. Having said that, the underlying cause or stimulus for a hyperglycemic emergency is not always identified.

Common Laboratory Findings

Blood Glucose

It is fair to say that, by definition, HHS will be characterized by severely elevated blood glucose. Going the extra distance to dilute samples in chemistry analyzers is very worthwhile to attempt to truly quantify any patient's hyperglycemia. If it is absolutely not possible to do so or the only quantification available is a glucometer, then osmolality can be estimated using the equations discussed below by estimating blood glucose as the high end of the reading range for that device. It is true that blood glucose does not have as much impact on osmolality as sodium but knowing whether your baseline blood glucose is 600mg/dL or 1400mg/dL will certainly make a difference in osmolality calculation as well as assessment of prognosis and development of a treatment plan for the pet owner.

Sodium

Hyponatremia is a common finding in HHS patients, driven primarily by the profound hyperglycemia that causes fluid shifts out of cells and subsequent dilution of sodium. For every 100mg/dL that blood glucose is over normal, sodium is depressed by 1.6mmol/L. In the majority of HHS patients, corrected sodium is actually within the normal range but can also be elevated. The calculation for corrected sodium is:

$$\text{Corrected Na+} = (\text{Uncorrected Na+}) + \left(\frac{[\text{patient's glucose} - \text{normal glucose}]}{\text{normal glucose}} \times 1.6 \right)$$

Potassium

Potassium values on blood chemistry are highly variable in HHS patients but whole body potassium stores are generally severely depleted in these patients. Many patients will have a history of decreased appetite, anorexia, or vomiting that will result in decreased intake of potassium. This combines with the osmotic diuresis caused by profound hyperglycemia to result in loss of significant loss of potassium. Internally, as hyperglycemia pulls fluid out of cells, intracellular potassium concentration increases and extracellular potassium decreases with dilution so potassium subsequently follows the concentration gradient out of the cell. Acidosis further exacerbates extracellular movement of potassium.

Phosphorus

Through similar mechanisms as potassium, whole body phosphorus levels are commonly severe decreased no matter the concentrations reported on initial diagnostics. Failure to address hypophosphatemia can result in hemolytic anemia if not identified and addressed. Both potassium and phosphorus require replacement in the majority of patients either immediately upon starting IV fluid therapy or within the early hours of treatment.

Azotemia

Either renal or prerenal azotemia is common in HHS and severity of azotemia can be highly variable. As with blood glucose, it is worthwhile to dilute renal values if needed for a more accurate assessment of osmolality but also to monitor for patient progress from one day to the next. As with blood glucose, actual values can provide support in discussions with owner about prognosis, length of therapy, and treatment plan.

Magnesium

Magnesium is not frequently monitored but osmotic diuresis may result in hypomagnesemia. It is not generally corrected but hypomagnesemia can contribute to refractory hypokalemia or hypocalcemia or arrhythmias and should be considered in those cases where these issues arise. (Boysen)

Osmolality

Osmolarity is a calculation used to quantify an estimate the body's electrolyte and water balance. Osmolality is essentially the same value but can only be measured directly via an osmometer. The results of these two measurements are usually essentially the same so both terms are used interchangeably. (Wikipedia)

This calculation can be further divided into either total or effective osmolality. Total osmolality is estimated using sodium, potassium, glucose, and BUN while effective osmolality utilizes only sodium, potassium, and glucose. Because BUN freely permeates membranes it does not produce an osmotic gradient and subsequently it has been proposed that effective osmolality estimation may provide a better assessment of patient risk for neurologic complications secondary to HHS though this has not been scientifically established. (Schermerhorn)

Corrected Na+ should be used when calculating either total or effective osmolality to avoid underestimates.

$$\text{Total Osm (mOsm/L)} = 2\,(\text{Na} + \text{K}) + \text{Glu} / 18 + \text{BUN} / 2.8$$

$$\text{Effective Osm (mOsm/L)} = 2\,(\text{Na+} + \text{K}) + \text{Glu} / 18$$

Depending on the source, generally accepted normal ranges for dogs and cats for total and effective osmolality are 290-310 mOsm/L.

Other
Other blood work abnormalities may be present depending on potential underlying disease. Similar to DKA, variable degrees of acidosis may be present along with elevations in total solids, individual proteins, or other factors. Unlike DKA, ketones are usually minimal to absent.

Educate and Plan
Due to the combination of diseases that directly or indirectly interfere with management of diabetes mellitus or the presence of advanced, decompensated metabolic disease by the time of presentation, HHS carries a guarded to grave prognosis. Recovery to discharge from the hospital ranges ~25-35% and survival beyond one to two months is 10-15%.

By the time initial diagnostics are available, you will have an opportunity to assess the severity of your patient's illness. Now is the time to have a very serious conversation with the pet owner and ensure that they are able to commit to the financial and emotional requirements that management of this disease will place upon them and their pets.

Treatment
Treatment of HHS is not dissimilar from treatment for DKA though additional factors require monitoring and priorities are slightly different. Treatment includes but is not limited to:

- Correction of dehydration
- Correction of electrolyte abnormalities
- Managing blood glucose
- Managing underlying diseases

Rehydration
Balanced and buffered crystalloids are the most common choice for rehydration for these animals. Based on calculation of corrected sodium, 0.9% NaCl may also be a fluid option based on its slightly higher sodium concentration but this is not a buffered solution so it will result in a loss of bicarbonate and can worsen any acidosis that is present. While this change is usually transient in a normal animal, compensation may be more difficult for patients with severe illness. While LRS may be a fluid option initially, we can plan ahead for phosphorus supplementation and know that it will not be a long-term option. The calcium in LRS will precipitate with phosphate-containing additives.

Fluid deficits should be estimated based on dehydration and replaced through a combination of shock therapy if needed and relatively slow rehydration. Where DKA patients are generally rehydrated over 18-24 hours, HHS patients should be rehydrated over 36-48 hours to reduce drastic shifts in osmolality (the goal is to drop osmolarity by no more than 0.5-1mOsm/hr) and subsequently reduce the risk of neurologic complications. Depending on concomitant illness, rehydration may need to be even slower. When calculating fluid rates do not forget to allow for maintenance needs and ongoing losses.

Fluid deficit (mL) = % dehydration x body weight (kg) x 1000ml/kg

Because of the degree of dehydration of HHS patients and their known diminished GFR, IV fluid therapy is often the only initial treatment administered for the first few hours. The goals of IV fluid therapy are to begin to restore GFR and subsequently glucose diuresis, restore blood flow to periphery and improve removal of lactic acid, and initiate the shifts of sodium and potassium prior to initiating insulin therapy.

Electrolyte Disturbances

In patients that are not hyperkalemic at presentation, potassium supplementation is generally provided immediately because it is known that potassium will drop significantly with rehydration and even more once insulin therapy is initiated. Depending on the patient, initial supplementation may be 20-40 mEq/L potassium and supplementation may increase from there. Because phosphorus movement echoes potassium movement, some recommend initiating phosphorus supplementation early by replacing half of the potassium in fluids with potassium phosphate and half with potassium chloride. Alternatively, you can calculate phosphorus replacement in the range of 0.03-0.12mmol/kg/hr, making sure to include the potassium in your calculation for supplementation.

Standard potassium supplementation guidelines are:

Serum K in mmol/L	K supplementation in mEq/L	Maximum delivery rate in ml/kg/hr
3.5-5	20	24
3-3.4	30	16
2.5-2.9	40	11
2-2.4	60	8
<2	80	6

Use of this table will prevent administration of more than 0.5 mEq/kg/hr but it is noteworthy that treatment of hypokalemia where K+ is less than 2mEq/L can be treated with 0.5-0.9 mEq/kg/hr potassium for the first 30-60 minutes because these potassium levels can be associated with severe weakness, arrhythmias, and respiratory muscle failure. (O'Brien)

Hypomagnesemia may be a contributing factor in refractory hypokalemia so ionized magnesium should also be monitored and, where necessary, replaced in the form of magnesium sulfate at 0.5-1mEq/kg/day.

Electrolytes should be rechecked every 2-4 hours during initial stabilization and if potassium supplementation was not started at the time of initial fluid therapy it should be started prior to initiating insulin therapy. Once values are more stable, monitoring may decrease to every 8-12 hours depending on the needs of the individual patient.

Glycemic Control

While insulin therapy is an important factor of therapy in HHS, it is often instituted much later than DKA patients and often requires lower rates of replacement. Restoration of GFR will result in fairly rapid drop in blood glucose and subsequent drop in osmolarity. As long as blood glucose continues to drop steadily with IV fluid administration, insulin administration is not necessary so with HHS it often is not started until 8-12 hours or more into treatment. Blood glucose is monitored from every 1-4 hours depending on the patient's progress.

Once blood glucose stabilizes or begins to stabilize with IV fluid therapy, insulin administration can be done via either IM or IV administration of regular insulin. There is no scientific evidence that one approach is better than another but there is concern that variable hydration may make the results of IM regular insulin injections difficult to predict where, as in HHS, careful control over dropping blood glucose is necessary. IV regular insulin CRI can be more carefully titrated to manage blood glucose and maintain decreasing glucose concentrations from 50-75mg/dL/hr.

To make regular insulin CRI, add 2.2 units/kg for dogs or 1.1 units/kg for cats to 250ml of 0.9% NaCl and administer as needed to drop glucose at the desired rate. The following table outlines common use in management of ketosis and similar guidelines may be necessary for those HHS patients that do have ketones:

Blood glucose in mg/dL	IV fluids	Insulin solution (ml/hr)
>250	0.9% NaCl	10
200-250	0.9% NaCl with 2.5% dextrose	7
150-200	0.9% NaCl with 2.5% dextrose	5
100-150	0.9% NaCl with 5% dextrose	5
<100	0.9% NaCl with 5% dextrose	stop

With rehydration and clinical improvement, hopefully patients will begin eating and start long acting insulin as soon as possible.

A recent study by Marshall et al (2013) suggests that management of feline DKA with a combination of IM and SC glargine may be a viable treatment option for this condition but it is unknown whether glargine would function similarly in canines or in HHS so more information is needed before making sweeping changes to therapeutic recommendations.

Underlying Diseases

Part of management of either DKA or HHS is a search for comorbidities. In those patients that presented for hyperglycemic emergency without a prior diagnosis of diabetes mellitus or those that have a history of poor control of diabetes, there may not be an underlying precipitating illness but it is still important to be thorough in the search for any problems. Treatment of either DKA or HHS is associated with significant financial and emotional investment on the part of pet owners so any intervention that may be able to decrease the likelihood of recurrence is also a valuable investment.

Other Factors

Acidosis is commonly noted in HHS patients but usually resolves with IV fluid therapy alone. In humans, acidosis associated with DKA is not treated unless pH remains less than 7 after one hour of IV fluid therapy. When treated it is treated with bicarbonate but this carries its own risk of side effects such as worsening hypokalemia, decreasing oxygen release at the tissue level, central nervous system acidosis, lactic acidosis, persistent ketosis, and cerebral edema. (O'Brien)

While all of the math and fidgeting and adjusting associated with management of HHS are important, it is also important not to get too caught up in the numbers and fail to note changes or issues in the patient. Monitor for issues such as fluid overload, ensure that adequate nutrition is being taken in or supplement it, control pain, vomiting, or any other symptoms that may arise.

Anticipated Monitoring

Here is a summary of factors that will most likely be monitored in all HHS patients and their frequencies. In general, each will be monitored more frequently early in the management of the disease and less frequently as they stabilize. Any other abnormalities noted on initial diagnostics should also be scheduled for monitoring.

- Glucose q1-4 hours
- Electrolytes (Na, K, and Cl) q2-12 hours
- Phosphorus q12-24 hours
- BUN/Creatinine q6-24 hours
- Magnesium q8-24 hours
- Calcium q8-24 hours
- PCV/TS q8-24 hours
- Where applicable, ketones q24 hours

Goals of Therapy

This monitoring is the primary means to assess patient progress and they are monitored so frequently with the following goals in mind:

- Osmolality decreasing at a rate of no more than 0.5-1mOsm/hr
- Blood glucose decreasing at a rate of 50-75mg/dL/hr
- Maintain potassium greater than 3.5mmol/L
- Maintain phosphorus greater than 2mg/dL
- Maintain ionized magnesium to avoid refractory hypokalemia
- Maintain calcium to avoid symptoms associated with hypocalcemia
- Eliminate any ketones that were present
- Address anemia or hypoproteinemia that may develop

Summary

As the information provided above clarifies, management of HHS is complex, challenging, and often associated with generally poor prognosis but that does not make treatment impossible. The decision about whether to treat these patients requires an informed and serious conversation with pet owners about the commitment being made and treatment itself requires significant input and resources on the behalf of the veterinarian as well. Unlike a mild DKA, these are not patients that can be treated on an out patient basis or treated during the day and sent home at night. In the absence of in house testing capabilities and 24 hour monitoring, referral should be considered.