Hypernatremia is often an unanticipated complication in critically ill cats. It can be life-threatening in intensive-care patients with inadequate water intake, renal failure, head injury, respiratory disease, infection, hormone imbalances, or osmotic diuresis from diabetes mellitus or drug therapy. Through rapid loss of intracellular water, hypernatremia acutely and primarily affects the central nervous system, resulting in lethargy, seizures, coma, or death. This article reviews the pathophysiology of hypernatremia in critically ill cats.

**ABSTRACT:**

Hypernatremia is often an unanticipated complication in critically ill cats. It can be life-threatening in intensive-care patients with inadequate water intake, renal failure, head injury, respiratory disease, infection, hormone imbalances, or osmotic diuresis from diabetes mellitus or drug therapy. Through rapid loss of intracellular water, hypernatremia acutely and primarily affects the central nervous system, resulting in lethargy, seizures, coma, or death. This article reviews the pathophysiology of hypernatremia in critically ill cats.

Life-threatening hypernatremia can develop in patients affected by vastly different pathophysiologic processes (see box on page 423). Excessive sodium intake or loss of sodium-free water, the primary reasons for serum sodium elevations, can result either from the pathology of the underlying disease or from therapy. The end results of acute hypernatremia are rapid transcellular fluid shifts and brain dysfunction. These complications may cause neurologic changes ranging from mild depression in mentation to fatal intracranial hemorrhage and cellular death, depending on the rate and level of sodium increase and the presence of concurrent cardiovascular, renal, and neurologic disease. Therefore, profound alteration in a cat’s mentation or level of consciousness warrants immediate evaluation of the serum electrolyte level to detect an elevated serum sodium concentration (values >155 mEq/L merit close monitoring, and clinical signs of hypernatremia are often noted when sodium levels become >160 mEq/L). Although the incidence of acute hypernatremia in cats is poorly described, we have observed the syndrome in critically ill cats.
NORMAL SODIUM HOMEOSTASIS

Function

Sodium, the most abundant electrolyte in extracellular fluid, plays a major role in determining the osmolarity of fluids within each fluid compartment (i.e., intravascular, interstitial, intracellular) within the body. In addition to sodium, glucose and blood urea nitrogen (BUN) contribute to osmolarity in the following way:

\[ \text{Osmolarity} = 2(\text{Sodium}) + \left( \frac{\text{Glucose}}{18} \right) + \left( \frac{\text{BUN}}{2.8} \right) \]

Water moves passively across all compartment membranes in volumes controlled by the osmolarity of the fluid compartments.

Sodium passively moves across the capillary membrane, and its concentration rapidly equilibrates between the interstitial and plasma fluid compartments. In contrast, sodium must be actively transported into and out of the cell. Transcellular sodium gradient is the normal physiologic property that controls water content within a cell (Figure 1).

Like sodium, glucose passes freely across the intravascular membrane but not the cell membrane. Its contribution to water shifts can become significant when the serum glucose concentration rises above the renal threshold (approximate mean threshold: >200 mg/dl in dogs and >290 mg/dl in cats), such as in patients with diabetes mellitus. BUN, however, is freely permeable across all membranes. It is an “ineffective” osmole because it freely passes across the capillary and cell membranes and equilibrates. Normal cats reportedly maintain their plasma sodium concentration and plasma osmolarity (pOsm) within narrow limits (sodium: 145 to 155 mEq/L; pOsm: 308 to 335 mOsm/L).

Acute hypernatremia can occur in critically ill cats that have inadequate water intake, osmotic diuresis, head injury, infection, respiratory disease, hormonal imbalances, or renal disease.

Water Regulation

Plasma sodium concentration is actually a reflection of plasma water content. When the plasma water content increases, the plasma sodium is diluted, and the milliequivalents per liter value decreases. Alternatively, when the plasma water content decreases, the sodium concentration increases. Water is lost continuously through evaporation from the respiratory tract and cellular metab-

Causes of Hypernatremia

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*Osmolarity is the number of osmoles per liter of solution (e.g., plasma); osmolality is the number of osmoles per kilogram of solvent. Because osmoles in the body are dissolved in water (which has a density of 1), osmolar concentrations can be expressed as Osm/L of water, and each osmole is equivalent to osmolarity.
Antidiuretic Hormone

Antidiuretic hormone (ADH) release is stimulated by reduced cardiac output, nausea, and, most important, increased plasma osmolality. ADH, the most potent regulator of body water content, is released when an osmotic gradient develops between the cerebral vessel and the supraoptic and paraventricular nuclei in the hypothalamus (Figure 2). As little as 2% increase in plasma osmolality above the osmotic threshold (280 mOsm/kg water in humans) increases measurements of circulating ADH within minutes. ADH is an arteriole constrictor throughout the body and increases arterial pressure and cardiac output. This response is less important than the renal response to ADH, which is solute-free water reabsorption.

Thirst Mechanism

Increased pOsm also results in increased water intake via activation of the thirst center. Hyperosmolar fluid bathing the thirst center located near the supraoptic and preoptic nuclei in the anteroventral region of the third ventricle in the brain is a potent stimulator of thirst. Reduced baroreceptor stretch caused by hypovolemia and hypotension also results in stimulating the thirst center. Finally, hypovolemia-induced release of renal angiotensin II directly stimulates the subfornical organ in the diencephalon, which stimulates neural areas associated with the thirst response.

Increased water intake, coupled with ADH-mediated water reabsorption, results in a diluted plasma sodium concentration and decreased osmolarity. A conscious individual with unrestricted access to water can maintain pOsm under most conditions.

MECHANISMS OF HYPERNATREMIA

Stimulation of thirst and water reabsorption from the renal collecting ducts should normally maintain sodium and water balance within an acceptable range. Urine specific gravity (USG) and urine osmolality (uOsm)
Figure 2. Normal ADH release and effect. Increases in pOsm result in an osmotic gradient in the brain, with shrinking of the supraoptic and paraventricular nuclei in the hypothalamus. An action potential is initiated along the nerve cells of the supraoptico-hypophyseal tract to the posterior pituitary. Depolarization at the nerve endings results in release of secretory granules containing ADH into the bloodstream. Circulating ADH binds to V2 receptors on the basolateral aspect of the collecting duct in the nephron. Through adenylate cyclase, aquaporin-2 channels open in the collecting tubules, permitting solute-free water reabsorption as sodium is excreted in concentrated urine. Renal water reabsorption dilutes the plasma sodium, maintaining normal plasma concentration. (Illustration by Barbara Harmon)
reflect concentrated urine during dehydration and water deprivation. When normal thirst and ADH regulatory mechanisms fail to meet rapid changes in plasma sodium and water concentrations or the mechanisms become impaired because of disease, hypernatremia and transcellular fluid shifts occur.

**Normal Regulatory Mechanisms**

Sodium and water regulatory mechanisms may not be adequate during water deprivation when there is ongoing water loss in excess of sodium or when sodium intake exceeds water intake (see box on page 423). Cats may become water deprived if they are denied access to water; have an illness or problem causing immobility; or fail to drink as a result of oropharyngeal disease, nausea, or altered mentation. Hypodipsic hypernatremia due to transient hypopituitarism in a hydrocephalic cat has also been reported.8

Administering isotonic sodium–containing fluids (e.g., 0.9% saline, lactated Ringer’s solution, Normosol-R [Abbott Laboratories], Plasmalyte-A [Baxter]) for extracellular volume replacement should not result in hypernatremia if normal sodium regulatory mechanisms are functioning.9 However, if a cat loses more water than expected (because of tachypnea, diarrhea, or osmotic diuresis) or fails to take in water,
plasma sodium concentration can increase despite normal regulatory responses. Problems such as renal disease, encephalitis, and head trauma can lead to abnormalities within the sodium–water regulatory mechanism.

Abnormal Regulatory Mechanisms

Inadequate water reabsorption from the renal collecting ducts results in loss of sodium-free water, significant hypernatremia, and elevated pOsm when compensatory water intake is either impaired or prevented. Regulatory mechanism abnormalities leading to this life-threatening complication include inadequate ADH production or release from the neurohypophysis or posterior pituitary (central diabetes insipidus), failure of the renal collecting duct cell to recognize and respond to ADH (nephrogenic diabetes insipidus), or a combination of both (see box on page 423 and Figure 3). If this happens in a cat, clinical dehydration or hypotension can be expected to occur along with urine dilution (i.e., USG <1.023 and uOsm <800 mOsm/kg water).^1

Central Diabetes Insipidus

In dogs, hypernatremia has been associated with meningoencephalitis,^10 pituitary malformation, and head injury. Although reports of hypernatremia in cats are rare,^8,11,12 we have treated four cats that developed deteriorating neurologic signs concurrent with hypernatremia 2 to 13 days following head injury.

In humans, encephalitis, vascular disorders, neoplasia, and head injury can directly affect ADH production and release from the hypothalamic–pituitary axis, resulting in hypernatremia.^6,13,14 Approximately 10% of humans with diabetes insipidus have suffered blunt or penetrating cranial trauma. In humans, hypernatremia is reportedly a rare but often fatal complication of severe head trauma when anoxic encephalopathy, skull fractures, and cranial nerve dysfunction have occurred. In addition, hypernatremia has reportedly been a consequence of minor head trauma. In humans, hypernatremia has reportedly been a consequence of minor head trauma.

Within hours to days, injury to the central osmoreceptors, hypothalamus, supraopticohypophyseal tract, or posterior pituitary and altered ADH synthesis and secretion can result in acute sodium imbalances (Figure 3). Impaired water intake may also contribute to hypernatremia in patients with these injuries. Recovery of the injured hypothalamic–pituitary tract may take days to years or may not occur at all.

Nephrogenic Diabetes Insipidus

The presence of primary (familial) or secondary (acquired) nephrogenic diabetes insipidus is characterized by lack of response to ADH by renal receptors. Pri-
mary nephrogenic diabetes insipidus has not been reported in cats. Secondary nephrogenic diabetes insipidus results from disruption of the corticomedullary osmotic gradient or inhibition of ADH action by the kidneys (Figure 3). Disruption of the corticomedullary osmotic gradient can occur in the presence of infection, hypokalemia, or hypercalcemia. Endotoxins produced by Escherichia coli may produce renal V2 receptor resistance to ADH and can be seen as a result of pyelonephritis and pyometra. Hypercalcemia damages ADH receptors in the tubules, and hypokalemia can decrease renal responsiveness to ADH. Certain drug therapies have also reportedly caused partial impairment of renal concentrating ability through partial inhibition of ADH receptors.

CONSEQUENCES OF ACUTE HYPERNATREMIA

In humans, the rate and degree that pOsm increases determine the severity of the resulting clinical signs. Slowly progressive increases in pOsm caused by hypernatremia may result in no signs. Acute hypernatremia causes rapid fluid shifts from the intracellular to extracellular compartment (Figure 1). Clinical signs of hypernatremia primarily involve the central nervous system. Neurologic signs range from lethargy and weakness to twitching, seizures, coma, and death. Brain cells respond to hypernatremia and cell shrinkage by increasing intracellular osmolarity to make it equal to pOsm. In rabbits and rats, experimentally administered intraperitoneal and IV hypertonic saline solution result in a process of accommodation in brain cells. Extracellular hypernatremia initially promotes water loss from brain cells. Within 30 minutes, sodium and potassium ion concentrations increase in brain cells. Within hours to days, the idiogenic osmole (amino acids, glutamine, and inositol) concentration increases, reestablishing transcellular osmotic gradient and intracellular water content (Figure 4).

Few reports pertain to symptomatic hypernatremia in cats. Mortality rates of more than 70% have been reported in adult humans when serum sodium levels acutely increased over 160 mEq/L in less than 24 hours. We have observed hypernatremia as a severe complication of diabetes mellitus, chronic respiratory disease with upper airway discharge, and head trauma in cats. When hypernatremia occurred in association with diabetes mellitus or respiratory disease, treatment, including careful manipulation of fluid balance, was usually successful; development of hypernatremia is presumably slowly progressive in these cases. When acute hypernatremia occurred in four cats with head injury (sodium concentration: 171 to 209 mEq/L), concurrent neurologic deterioration developed. Three of the cats were humanely euthanized because of continued neurologic deterioration, and one recovered after 10 weeks of supportive care.

REFERENCES


**4. Which condition can result in hypernatremia through renal osmotic diuresis and free water loss?**

- diabetes mellitus
- diabetes insipidus
- head trauma
- pneumonia

**5. Why does hypernatremia occur in patients with central diabetes insipidus?**

- The kidneys are not responsive to ADH, resulting in renal free water loss in excess of solute.
- There is minimal to no circulating ADH to allow solute-free water resorption in the kidneys, and water is lost in excess of solute.
- More sodium is reabsorbed by the kidneys.
- Excessive aldosterone is released, resulting in sodium gain.

**6. Clinical signs of acute hypernatremia primarily affect the________ system.**

- gastrointestinal
- cardiopulmonary
- musculoskeletal
- central nervous

**7. The brain responds to chronic hypernatremia by**

- producing idiogenic osmoles.
- becoming hyperplastic.
- releasing calcium.
- shrinking.

**8. Hypernatremia can occur as a complication of**

- diabetes mellitus.
- renal failure.
- diabetes insipidus.
- all of the above

**9. Acute hypernatremia leads to neurologic dysfunction because it**

- alters potassium levels.
- causes rapid fluid shifts from the intracellular to extracellular compartment.
- inhibits the sodium–potassium pump.
- causes hypocalcemia.

**10. *E. coli* may cause nephrogenic diabetes insipidus by**

- directly binding to ADH molecules.
- causing hypercalcemia.
- producing endotoxins that cause V2 receptor resistance to ADH.
- altering BUN levels, thereby causing renal medullary washout.