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Emergency Management of Life Threatening Electrolyte Disturbances

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Disturbances in Potassium

Potassium homeostatsis

Potassium (K^+) is the major intracellular cation. Extracellular concentrations are tightly regulated between 3-6 mEq/L, whereas the intracellular concentration of K^+ is approximately 150 mEq/L. As much as 95% of total body potassium is located in the intracellular compartment and plays an important role in maintenance of cell volume and growth. The remaining 5% is located in the extracellular space, mostly the plasma space.

The most important function of this small but critical amount is to maintain the normal resting cell membrane potential. As you will see, the body attempts to maintain a narrow range of extracellular or plasma K^+ even at the cost of intracellular levels. This explains how we can see a diabetic patient with normal plasma K^+, but assume that total body K^+ is depleted. Potassium is not generated by the body, thus dietary potassium is the sole source of new potassium.

Virtually all of the K^+ is absorbed from the gastrointestinal tract. Canine models show that 90-98% of potassium intake is eliminated by the kidneys and small percent is present in the stool. The balance of K^+ between the extracellular fluid (ECF) and intracellular fluid (ICF) is maintained by insulin and β2 adrenergic receptors as well as the presence of K^+ itself. Insulin and β2 adrenergic receptors facilitate transport of K^+ into the ICF. The presence of K^+ itself influences of electrochemical gradient by which K^+ is transported into the ICF. There is such a positive charge in the ECF attributed to Na^+ that any increase in cations such as K^+ will further enhance movement of K^+ into the cells.

Hypokalemia - Causes and Mechanism of Action

1. Decreased potassium intake: Very uncommon cause for hypokalemia but may be present in cases of starvation or prolonged in-appetence.
2. Translocation of K^+ from ECF to ICF: Albuterol toxicity, alkalosis, insulin, hypokalemic period paralysis (burmese cats, rare), hepatic failure (dogs $>>>$ cats)

3. Urinary loss: Hyperaldosteronism, chronic renal failure (cats > > > dogs), loop diuretics, diet induced hypokalemic nephropathy in cats, renal tubular acidosis, post obstructive diuresis, dialysis, hepatic failure (dogs > > > cats).
4. Gastrointestinal loss.

Hypokalemia - Clinical Signs

1. Musculoskeletal: Weakness seen K^+ < 3.0 mEq/L, pelvic limb > > thoracic limbs, head/neck ventral flexion cats > > dogs, respiratory muscle depression that may require ventilation.

2. Cardiovascular: Supraventricular and ventricular arrhythmias are more commonly seen.

3. Kidney: Hypokalemic nephropathy.

Hypokalemia - Treatment

	Available preparation	Effect
Oral	Potassium gluconate, potassium citrate	Not good for acute severe hypokalemia 2 – 8 mEq/day Low risk of over supplementation Weekly monitoring for effective dose
Parenteral	**KCl** (2mEq/ml) K Phos 4.36 mEq/ml – primarily used for Phos supplementation	Do not exceed 0.5 mEq/kg/hr Very effective, easy to over supplement Monitoring q 4-6 hrs with aggressive supplementation (> 60 mEq/L in fluids)

Quick cheat sheet for potassium supplementation in IV fluids.

Serum K^+ Concentration	**mEq KCl/L additive**	**Max IVF rate Ml/kg/hr**
< 2.0	80	6
2.1 – 2.5	60	8
2.6 – 3.0	40	12
3.1 – 3.5	28	18
3.6 – 5.0	20	25

Hyperkalemia - Causes and Mechanism of Action

1. Pseuohyperkalemia: Thrombocytosis, hemolysis.
2. Increased K^+ intake: Unlikely to result in hyperkalemia with normal renal function.
3. Translocation of K^+ from ICF to ECF: Tumor lysis syndrome, reperfusion injury secondary to thrombolysis of large clot.
4. Decreased urinary excretion: Urinary obstruction, oliguric and anuric renal failure, uroabdomen, chylous effusion with repeated taps, hypoadrenocorticism. Select GI disease (salmonellosis, whipworm, perforated duodenal ulcer – mechanism not clearly understood), ACE-inhibitors and K-sparing diuretics in the face of diminished renal function.

Hyperkalemia - Clinical Signs

EKG changes seen in Hyperkalemia

K^+ concentration mEq/L	**EKG characteristics**
5 – 6	Tented T wave
6 -7	Prolongation of PR interval
7 – 8	Widening of QRS, loss of p wave
Over 8 mEq/L	V-fib, V-tach, asystole

These changes are not always seen in this order. Some patients with chronic progressive hyperkalemia may have a normal EKG at high potassium levels.

Hyperkalemia - Treatment

Severe clinical hyperkalemia (>7.5) may need immediate intervention especially if there are concurrent EKG abnormalities. If the pet is moderately hyperkalemic (6.5 – 7.5 mEq/L) with no EKG abnormalities, you may opt to start aggressive fluid therapy and treat underlying cause if identified. If recheck K^+ reveals continued elevation $>$ 7.5 mEq/L then consider interventions as described below.

The goal of immediate intervention is rapid reduction of K^+. Insulin therapy results in the quickest significant reduction in K^+. Care should be taken to give a dextrose bolus with insulin and monitor glucose and K^+ q 1 hour until an improvement is seen and to monitor for hypoglycemia. It is common for fluids, calcium, insulin and dextrose to given concurrently for severe life threatening hyperkalemia.

Therapy	Mechanism of Action	Dose
Calcium gluconate	Membrane stabilizer	0.5 – 1.0 ml/kg IV over 10-15 minutes, monitor EKG 5 – 15 mg/kg elemental calcium
Insulin, dextrose	Potassium shift inducer	Insulin 0.1 u/kg IV or IM Dextrose 0.5 ml/kg 50% IV
Fluid therapy Unblocking	Increased renal excretion	Any isotonic crystalloid is effective but buffered solution may have slight advantages (LRS, NormR) over 0.9% NaCl
Dialysis		

Disturbances in Calcium

Calcium homeostasis

The skeleton holds 99% of total body calcium. It is primarily stored with phosphate in the form of hydroxyapatite. Despite this large amount, less than 1% of skeletal calcium is readily available for exchange with plasma. Virtually all of the non-skeletal calcium resides in the extracellular space (plasma) but is considered the most biologically active. Serum or plasma calcium exists in three forms, ionized (free calcium), chelated or complexed calcium and protein bound calcium. The ionized form is the most important and biologically active form and represents about 50-60% of total serum calcium. The chelated form represents about 10% and is calcium that is complexed with citrate, lactate, bicarbonate and phosphate. The protein bound calcium represents about 30-40% of total calcium. The protein bound calcium is not biologically active and likely serves as a storage pool or buffering for ionized calcium. Only the ionized and complexed calcium are filtered through the glomerulus and 98% is reabsorbed mostly in the proximal tubules. There is a miniscule amount of intracellular ionized calcium and by comparison is 10,000 fold less than serum calcium concentration.

The many roles of intracellular and extracellular calcium are too numerous to cover in a brief overview. Its role is wide ranging from muscle contraction to cell growth and apoptosis, to nerve conduction and hormone secretion. Not to mention intracellular calcium plays a vital role in an unimaginable number of intracellular signaling pathways. Hormones that increase serum calcium include Parathyroid hormone (PTH) and calcitriol. PTH increases ECF calcium by mobilizing calcium from bone, increasing tubular reabsorption and increasing calcitriol synthesis. Calcitriol increases intestinal absorption of calcium. Both calcium itself and calcitriol have negative feedback loop to PTH. Calcitonin is a hormones that decrease serum calcium.

There are two ways of evaluating calcium in the serum, total calcium and ionized calcium. Ionized calcium is the gold standard for determining the true severity of a calcium disorder, however most practices do not have the ability to measure ionized calcium and must make decisions based on total calcium.

There are a few things to consider:

1. There is no algorithm for predicting ionized calcium using total calcium, especially in cats.
2. The corrected calcium formula is not useful for cats and does not accurately predict the ionized calcium.

However, a clinician can use the total calcium in addition to the patient's clinical signs to evaluate whether the calcium could be contributing to symptoms.

Total calcium > 14 mg/dl may result in clinical signs.
Total calcium > 18 mg/dl usually presents as a critically ill patient.

Likewise, patients with total calcium < 7.0 mg/dL can present as a patient with clinical hypocalcemia. Another useful aspect of the total calcium is in evaluating the risk for spontaneous mineralization if the TCa x P product is > 70.

Hypercalcemia

Most causes of hypercalcemia exert their effect through three main routes:

1. Bone resorption (upregulating osteoclastic activity)
2. Increased renal reabsorption or decreased renal excretion
3. Increased intestinal absorption.

Common causes and mechanism of action are listed below.

Common Causes Ionized Hypercalcemia	**Bone resorption**	**Intestinal absorption**	**Renal reabsorption**
Hyperparathryoidism	+ + +	+ + +	+ + +
Vitamin D Toxicosis	+	+ + +	+
Hypcalcemia of malignancy	+ +	+	+ +
Granulomatous disease	+/-	+ + +	+
Idiopathic Feline dz	?	?	?

Less common causes of clinically significant hypercalcemia include hypoadrenocorticism, acute renal failure, osteomyelitis, and vitamin A toxicosis.

Hypercalcemia - Clinical Signs

There are two factors that contribute to severity of clinical signs:

1. Chronicity of the hypercalcemia and the degree of hypercalcemia. In general, slowly progressive hypercalcemia tends to have more subtle symptoms compared to acute hypercalcemia.
2. The degree of hypercalcemia is associated with worsening clinical signs. Mild signs may be vague and include anorexia, lethargy, weakness, and vomiting. Specific signs that are seen in acute or worsening cases of hypercalcemia include PU/PD, and azotemia (renal or prerenal). Severe acute cases can result in cardiac arrhythmias, tremors, seizure or death.

Hypercalcemia - Treatment

For the purposes of this lecture, we will focus on treatment of acute severe hypercalcemia. Often simple aggressive IV fluid therapy can help rehydration, correct acid base disturbances which help promote hypercalcemia and promotes renal excretion of calcium. Any fluid that causes volume expansion and increased renal filtration can be effective.

However, 0.9% NaCl may be most effective due to the higher sodium content. Due to the complex interaction between Na^+, Ca^{2+} and water at the level of the renal tubules, fluids that are higher in sodium facilitate excretion of Ca^{2+} in the urine. Once rehydration has been achieved, furosemide may be given as a targeted way to promote calciuresis. In an acute setting, fluids and furosemide work most quickly.

Steroids can also be a very effective way to decrease calcium. Hypercalcemia related to diseases such as lymphoma and granulomatous disease have a very good response to steroids. Consideration should be made for obtaining a definitive diagnosis prior to the initiation of steroid therapy. Sodium bicarbonate can be used if severe ionized hypercalcemia is present with severe metabolic acidosis. Once a neutral or alkaline pH is achieved, continued bicarbonate therapy may not have benefit. Bisphosphonates are a potent inhibitor of osteoclastic activity. Bisphosphonates are expensive and can take days to exert their effect. They have been used to manage hypercalcemia secondary to osteosarcoma and multiple myeloma and also for severe cholecalciferol toxicosis that is refractory to fluids, furosemide and steroid therapy.

Summary of recommended therapy is below.

Therapy	Dose	Notes
0.9% NaCl	3-5 ml/kg/hr or higher if needed	Any isotonic crystalloid is useful but 0.9% NaCl is more effective
Steroids	Prednisone 1 – 2 mg/kg/day Dexamethasone 0.1 – 0.2 mg/kg/day	May be more effective for granulomatous disease or lymphoma Consider definitive sampling prior to initiating therapy
Furosemide	1 – 4 mg/kg q 12 hrs	
Bisphosphonate	Pamidronate 1.3 – 2 mg/kg IV Aledronate 1 – 2 mg/kg PO Given every 1 – 2x/wk	Expensive May require multiple doses Risk of permanent damage to osteoclasts
Calcitonin	4 – 6 u/kg SC q 8 hr	Risk of refractory hypercalcemia Short lived effect
Bicarbonate	1 mEq/kg IV slowly	May only be useful if patient is concurrently acidotic

Hypocalcemia - Causes

There are only a few causes of severe clinical hypocalcemia in dogs and cats, notably post partum eclampsia, hypoparathyroidism and citrate toxicosis (secondary to large volume, rapid blood transfusion). The many conditions that are common that cause mild ionized hypocalcemia that may be accompanied by mild or no clinical signs. These include chronic renal failure, acute renal failure, acute pancreatitis.

Hypocalcemia - Clinical signs

Similar to hypercalcemia, the severity of clinical signs for ionized hypocalcemia are dependent upon duration and magnitude as well as the rate of decline. Dogs and cats with chronic mild hypocalcemia may not have any clinical signs at all. Most of the typical signs we attribute to ionized hypocalcemia are secondary to increased neuromuscular excitability. Tremors, seizures, panting and restlessness are classic signs of ionized hypocalcemia. Hyperthermia is commonly noted in severely tremoring patients and is likely secondary to increased muscle activity. Lethargy and weakness is a more commonly reported clinical sign in cats compared to dogs with hypocalcemia.

Hypocalcemia - Treatment

Treatment for acute severe hypocalcemia is parenteral calcium. Calcium comes in two main parenteral forms, calcium gluconate and calcium chloride. Although they come in similar percent concentrations, their *elemental calcium* differs. Calcium gluconate 10% has 9.3mg elemental calcium per ml whereas calcium chloride has 27.2 mg elemental calcium per ml. The *dose* is the *same* for both however, 5 – 15 mg/kg elemental calcium. This translates into approximately 0.5 – 1.5 ml/kg 10% CaGluconate and 0.18 – 0.56 ml/kg 10% CaCl. Both preparations can be administered intravenously, however only CaGluconate is labeled for subcutaneous use as well. As a constant rate infusion both preparations can be used. The recommended dose is 0.25 – 0.35 mg/kg/hr. For conditions where oral supplementation will be needed once the urgent phase is past, calcium carbonate is readily available over the counter. Summary of emergency management of hypocalcemia is below.

Therapy	Dose	Notes
Calcium gluconate **Calcium chloride**	5 – 15 mg/kg bolus 0.25 – 0.35 mg/kg/hr CRI	Bolus given over 15 minutes with EKG monitoring! Best to monitor ionized calcium
Fluid therapy	As needed for shock or to reduce fever	LRS has small amount of Ca^{2+} however any balanced crystalloid is appropriate
Calcium carbonate	50 – 100 mg/kg/day depending on cause for hypocalcemia	Oral supplementation not appropriate for emergency management

Disturbances in Sodium

Sodium homeostasis

Sodium is the major extracellular cation in the body and may be the most important single electrolyte in the body. We cannot discuss sodium without discussing water balance because the most important function of sodium is regulating water balance in the body. Sodium is also crucial for transport (co-transport or antiport) of other major anions and cations such as K^+, Mg^{2+}, Ca^{2+}, H^-, Cl^- and HCO^-_3. Because of the adage "wherever sodium goes, water follows", sodium and water balance are achieved simultaneously using a multitude of sensors and effectors in different parts of the body. Their interactions and effects are complex and could fill an entire book. But in brief there are low pressure and high pressure volume sensors in the cardiac atria, carotid sinus and aortic arch.

Simply, if there is too much volume detected atrial natriuretic peptide promotes renal excretion of Na^+ and water and there is down regulation of renin. If there is too little volume, renin is upregulated which in turn has numerous effects one of which is to stimulate aldosterone which promotes Na^+ and water reabsorption from the distal tubule and collecting ducts.

In addition to volume receptors there are osmoreceptors which are less well characterized. These are sensors of plasma osmolality, meaning the concentration of solutes within the blood. Most animals must operate within a fairly narrow osmolality range in order to maintain adequate hydration, neurologic, musculoskeletal, and cardiac function. Out of all of the particles in the blood, only a few are deemed "osmotically active" because they cannot move freely across a cell membrane and therefore can influence osmosis.

There are a few different osmolality equations, but many clinicians use the following due to its simple nature and recent validation against measured osmolality:

$$[2Na + 2K] + BUN/2.8 + Glucose/18$$

Due to potassium's small contribution to the equation it can further simplified to:

$$2Na + BUN/2.8 + Glucose/18$$

The 2.8 and 18 are conversion factors which standardize the units between the particles.

Dogs and cats normal osmolality ranges between 290 – 310 mOsm/L which is slightly higher than humans. Cats may naturally have a slightly higher osmolality than dogs because of their obligatory carnivorous diet.

As stated above, there are osmoreceptors in the liver and CNS that contribute to sodium homeostasis. Osmoreceptors in the hypothalamus detecting plasma hyperosmolality are the primary stimulator for release of vasopressin or antidiuretic hormone. Vasopressin is unique in its action as it causes pure water reabsorption through water channels in the collecting ducts that occurs independently of sodium reabsorption. The macula densa cells of the juxtaglomerular apparatus sense sodium and chloride concentration and influence renin release accordingly.

Hypernatremia - Causes

1. Pure water loss: Diabetes insipidus, hypodipsia, fever, lack of water intake
2. Hypotonic water loss: Gastrointestinal loss, thermal injury loss, third spacing
3. Sodium gain: Salt ingestion, hypertonic saline administration, hyperaldosteronism

Hypernatremia - Clinical Signs

Signs of severe hypernatremia are primarily neurological; behavior change, stupor, weakness, ataxia, seizures but also can include signs of the underlying disease process such as vomiting, diarrhea or PU/PD (in the case of diabetes insipidus). The degree of clinical signs has as much to do with how rapidly the change occurred as well as the actual sodium value. A patient with a Na^+ acutely of 170 mEq/L could have as severe of signs as a patient who developed a Na^+ of 180 mEq/L over a longer period of time. The brain has a protective mechanism against dehydration in chronic gradual increases in plasma sodium. Through a mechanism that is poorly understood, the brain has the ability to produce intracellular particles called idiogenic osmoles whose sole purpose is to counteract extracellular increases in osmolality so as to not lose intracellular water.

Hypernatremia – Treatment

Acute or chronic mild hypernatremia (< 170 mEq/L) from GI loss, third space loss or renal disease probably represents the majority of pets we treat with hypernatremia. This type of hypernatremia is usually attributable to interstitial and to a lesser extent intracellular dehydration.

It is extremely rare for these patients to have neurologic signs attributed to their degree of hypernatremia. These pets can usually be effectively treated with balanced crystalloid replacing dehydration over 18-24 hours without major concern for decreasing sodium too rapidly. There may be an argument for cardiac patients or CRF patients to use a lower sodium fluid such as 0.45% saline. In the vast majority of cases of mild hypernatremia (<170 mEq/L) it is unnecessary to use a pure water replacement fluid such as 5% dextrose.

Acute and chronic severe hypernatremia (> 175 mEq/L) requires more careful treatment. Most clinicians find it helpful to calculate the free water deficit to determine the volume of pure water that should be replaced.

$$0.6\ (kg) \times [(Na\ present / Na\ normal)] - 1 = Liters\ of\ free\ water\ to\ replace$$

The goal is to replace fluids *slowly*, and not to reduce Na^+ more than 0.5 mEq per hour. Too quick reduction in sodium can lead to cerebral edema if idiogenic osmoles do not have time to be removed from intracellular space. Recommended electrolyte recheck interval when correcting a severe sodium disorder is q 4-6 hours. Realistically it can take days to safely correct severe chronic hypernatremia, not to mention identification and treatment of underlying condition. There is an argument for more rapid correction of acute instances of hypernatremia (< 1 day duration) due to the unlikelihood of development of idiogenic osmoles, therefore decreased risk of cerebral edema with rapid changes. Ideal fluid type for pure water replacement is 5% dextrose in water, however if

too rapid change in sodium is occurring you may slow down the fluid rate or switch to 0.45% saline solution.

Hyponatremia – Causes

1. Normal Plasma osmolality: Hyperlipidemia, hyperproteinemia, considered lab error and sample should be rechecked on different machine
2. High plasma osmolality: Hyperglycemia, each 100 mg/dL increase in glucose results in 1.6 mEq/L decrease in Na^+
3. Hypervolemia: Advanced severe liver disease, congestive heart failure, nephrotic syndrome
4. Normovolemia: Psychogenic polydipsia, syndrome inappropriate ADH, myxedema coma
5. Hypovolemia: GI loss, third space loss, hypoadrenocorticism.

Hyponatremia - Clinical Signs and Treatment

Hyponatremia as a whole does not cause significant morbidity and uncommonly carries clinical effects on its own. The most common cause for acute severe hyponatremia for which a patient is clinical is water intoxication. This is rare outside of experimental cases in veterinary medicine. Clinical signs attributed to acute severe hyponatremia (< 120 mEq/L) would be neurological.

The vast majority of cases of hyponatremia in veterinary patients is mild to moderate and usually not specifically treated depending on the cause or corrected with isotonic solutions. If correcting severe hyponatremia, similar guidelines for increasing Na^+ as for decreasing Na^+, not more than 0.5 mEq/hr change with fluid therapy. Ideally 0.9% NaCl is used or another isotonic solution. Hypertonic solutions are not recommended to treat hyponatremia.

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