

CASE REPORT: NEUROLOGICAL ABNORMALITIES DUE TO ACUTE, SEVERE HYPONATREMIA IN A KITTEN ASSOCIATED WITH A SUBCUTANEOUS INFUSION OF 5% DEXTROSE IN WATER

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ABSTRACT

Objective: To describe a case of severe acute hyponatremia in a kitten, as a result of subcutaneous infusion of 5% dextrose in water.

Case summary: A nine-week old male Persian kitten presented with a history of vomiting, depression and tremor of five hour duration, following subcutaneous infusion of 100 ml/kg of 5% dextrose in water (D5W). Severe hyponatremia (109 mmol/l, reference interval 145-158) as well as hyperglycemia, mild hypokalemia and glucosuria were noted. The kitten was diagnosed with feline panleukopaenia. Treatment with intravenous 0.9% and 7.5% saline led to normalization of serum sodium concentration and clinical improvement. The acute, severe, hyponatremia and hyperglycaemia were most likely due to the large subcutaneous volume of D5W which resulted in a rapid water shift into the intravascular compartment. Natriuresis and dilutional hyponatremia with subsequent hypo-osmolality are presumed to be the underlying mechanism for the neurological abnormalities.

New information provided: This case report is the first documented report of an iatrogenic hyponatremia due to subcutaneous fluid administration in any animal species.

Key words: feline, cat, seizures, hypo-osmolality, hypertonic saline

INTRODUCTION

Hyponatremia has been commonly reported in cats, dogs and cattle. Endocrine diseases, gastrointestinal and metabolic diseases as well as effusions into a third space or parasitism are the reported etiologies (1-5). Hyponatremia is the most common electrolyte disorder in hospitalized human patients (6-8). The pathophysiology involves a shift of water from the intracellular compartment to the extracellular space due to accumulation of extracellular solutes other than sodium (e.g., glucose, mannitol), excess body free water retention, sodium loss and an intracellular sodium shift (4).

Clinical signs associated with hyponatremia are related mostly to its onset rate rather than its magnitude or resultant hypoosmolality (4-6). Decreased serum osmolality affects all tissues including the central nervous system (CNS). Fluid shift into the intracellular space results in cerebral edema and neurological signs. Clinical signs may include lethargy, weight gain, vomiting, dyspnea, incoordination, coma, seizures and death (4, 5, 9) and may be absent or mild in cases of chronic hyponatremia, due to compensatory mechanisms which correct intracellular osmolality (1, 4, 5). The decision to

treat hyponatremia and the aggressiveness of the treatment should be based on a careful examination of the history and the presenting clinical signs, as rapid correction of chronic hyponatremia may result in brain osmotic myelinolysis (5, 10).

In dogs and cats, potential iatrogenic causes of hyponatremia include parenteral hypotonic fluid administration and various diuretic or antidiuretic medications (4). This report describes a kitten which presented with neurological abnormalities as a result of acute hyponatremia which developed after subcutaneous (SC) administration of a large volume of 5% dextrose in water (D5W). To the best of our knowledge, iatrogenic hyponatremia due to SC fluid administration, although frequently mentioned as a potential complication in several reviews (11, 12), has never been documented in any animal species, including human patients.

CASE REPORT

A nine-week-old male Persian kitten (body weight 0.5 kg) was admitted to the hospital with a history of anorexia, vomiting, diarrhea, hypersalivation, severe depression and a suspected seizure. He had been in the owner's possession for 4 days, and had received only one inoculation (type and date of vaccination unknown). One day prior to presentation, he became depressed, lethargic and anorexic. He presented to a local veterinarian the next day, and was found to be pyrexic (41°C) and mildly dehydrated. He was treated with SC D5W (50 ml, (100 ml/kg)) and amoxicillin (SC, dose and brand unknown). Five hours after treatment, the status of the kitten had deteriorated and he was observed with vomiting (2 episodes), diarrhea (2 episodes), hypersalivation, severe depression and a suspected seizure. The details of the treatment provided by the local veterinarian became available only a day after presentation to the hospital.

At presentation, he showed depression, weakness, hypothermia (37.4°C), mild tachycardia (200 bpm), tachypnea (56 bpm), hypersalivation, tremor, non-productive tenesmus and pale mucous membranes. There was no evidence of dehydration, and the femoral pulse and the capillary refill time were unremarkable. A mild subcutaneous edema was present at the dorsal trunk and neck areas and was later determined to be the site of the SC fluid infusion administered by the veterinarian.

Complete blood count (CBC) revealed a mild leukopenia and the neutrophil count was at the low reference interval (RI). Serum biochemistry abnormalities included marked hyperglycemia, severe hyponatremia and mild hypokalemia (Table 1). The corrected sodium concentration for glucose concentration (11, 12) was 113 mmol/L. The electrolyte analysis was repeated to exclude a laboratory error, and yielded similar results. Serum creatinine concentration was below the reference interval RI (Table 1). Urinalysis showed marked glucosuria [1000 mg/dl, (55.51 mmol/l)] and urine specific gravity was 1.034. Further laboratory tests were not performed due to insufficient blood sample volume. The calculated serum osmolality, based on the formula $2 \times ([Na^+] + [K^+])$, was 225.2 mOsm/kg and with addition of the contribution of glucose, the calculated plasma osmolality was 246 mOsm/kg.

The tentative diagnosis was feline panleukopenia virus infection with resultant vomiting and diarrhea. Hyponatremia was considered the most likely cause of the neurological abnormalities, and thus no further neurological or diagnostic imaging investigations (e.g., computed tomography and magnetic resonance imaging) were performed.

The kitten was treated with IV 0.9% saline (10 ml/kg/hr) with KCl supplementation (20 mmol/L), ampicillin^a (25 mg/kg q8h), gentamycin^b (6.6 mg/kg q24h), cimetidine^c (10 mg/kg q8h, as an antacid in order to prevent a potential esophagitis due to expected frequent vomiting) and SC metoclopramide (0.5 mg/kg q8h as an antiemetic). Gentamycin was used because septicemia, in particular due to Gram-negative bacteria, is a common sequel in the disease and results from parvovirus induced intestinal lesions and neutropenia.

Three hours after the initiation of treatment, the kitten had a partial seizure and was treated with diazepam (0.5 mg IV) to effect, followed by slow IV bolus of 3.5 ml of hypertonic (7.5%) saline. He appeared disoriented, lethargic and depressed. Six

hours post presentation, clinical improvement in his mental status was noted and he became more alert and active, regained his appetite and had no further signs of vomiting or diarrhea. Blood tests revealed normoglycemia, mild hyponatremia, hypokalemia and hypoproteinemia (Table 1).

Further clinical improvement was observed the next day, as the kitten was even more active and ate willingly; however, severe leukopenia, anemia, mild hyponatremia and mild hypokalemia persisted (Table 1). Treatment with 0.9% saline, metoclopramide, ampicillin and gentamycin remained unchanged for the following 3 days. The kitten improved gradually and progressively. He became increasingly more alert and active, while his appetite progressively increased. No vomiting, diarrhea or further neurological abnormalities were noted, and daily neurological examinations were unremarkable. On day 5, the leukocyte count increased and was within RI (Table 1) and the cat was discharged. He was doing well on follow up examinations at one and four weeks after discharge.

DISCUSSION

Sodium is the primary extracellular cation and osmole in the body and maintains water in osmotic equilibrium (1). Hyponatremia may be associated with low, normal or high plasma osmolality and tonicity, due to presence of other extracellular osmoles and should always be assessed in light of the body water status (i.e., hypovolemia, normovolemia, or hypervolemia), which should be assessed through physical examination findings. Dilutional hyponatremia, by far the most common form of hyponatremia, is caused by water retention which results in dilution of the body solutes, hypo-osmolality, hypotonicity and hypervolemia (6).

Hyponatremia and hypokalemia mostly develop gradually with severe vomiting and diarrhea, and are usually associated with isotonic or hypotonic dehydration (1, 4, 13). Vomiting and diarrhea may have contributed to the hyponatremia in this case, but were too mild to induce this severe hyponatremia. We assume that hyponatremia was the main cause of the transient neurological signs. The onset and rate of progression of hyponatremia must have been acute and rapid in order to induce such severe neurological abnormalities. We speculate that the severe hyponatremia observed at presentation was mainly due to the large SC D5W volume administered by the local veterinarian prior to presentation.

The subcutaneous space may be considered a third body compartment. Movement of water and solutes into or out of this space follow the laws of diffusion. Five percent dextrose in water is an isosmolar although slightly hypotonic (252 mOsm/L) solution which becomes markedly hypotonic in vivo because glucose is rapidly metabolized. It can induce hyponatremia either by dilution or by hyperglycemia-induced natriuresis. Cells in the subcutaneous compartment utilize some of the glucose in this solution; however, glucose also diffuses from the subcutaneous space, where its concentration is high, to the intravascular compartment, where its concentration is lower, leading to hyperglycemia. Free water follows the glucose and the osmotic gradient, diluting other plasma solutes, which results in dilutional hyponatremia, hypochloremia and hypokalemia as well as plasma hypo-osmolality (Fig 1) (14). The sharp decrease in the hematocrit and total plasma protein

that were observed 6 hours post presentation (Table 1) is further evidence of the dilution of the intravascular compartment.

The low sodium, potassium and chloride in the water in the subcutaneous compartment induces sodium, chloride and potassium shift from the extracellular and intravascular compartments into the subcutaneous space following the electrochemical gradient and laws of diffusion and equilibration (Fig 1) (13). In addition, acute rapid hyperglycemia induces natriuresis due to osmotic diuresis (Fig 1) (15). These mechanisms were probably responsible for the severe electrolyte imbalance observed in this case. Excess free extracellular water moves into the relatively hypertonic intracellular compartment and results in cellular swelling and dysfunction.

The calculated osmolality in the kitten at presentation, using sodium and potassium concentrations, was markedly low (225 mOsm/Kg). This value is probably an underestimation. As glucose also contributes to plasma osmolality, and when included in the calculation, yields a total value of 246 mOsm/kg. The contribution of BUN to plasma osmolality could not be assessed as BUN was not measured. It was probably minor in this case due to the absence of renal failure or significant prerenal azotemia (serum creatinine was < 0.5 mg/dl), and because the kitten was anorexic. The maximal contribution of BUN to serum osmolality would not have exceeded 5 mOsm/Kg, and if included would result in a maximal estimated total plasma osmolality of 251 mOsm/kg.

A 30 to 35 mOsm/kg gradient between the plasma and CNS cells can result in water shift from the plasma to the brain cells and lead to swelling and CNS dysfunction (5). Assuming that osmolality was normal in the kitten prior to the SC fluid administration, the calculated osmolar gradient was at least 50 mOsm/kg, making hyponatremia and hypo-osmolality the most likely mechanism for the neurological abnormalities.

Ideally, serum osmolality should be measured rather than calculated, however this is not routinely done in clinical practice because osmometers are not readily available. The difference between measured and calculated serum osmolality is called the osmolal gap. Under normal conditions it ranges between 5 and 15 mOsm/kg. Measurement of serum osmolality is crucial in cases when unmeasured osmoles (e.g., ethylene-glycol) are present (16), however, in the present case all the changes in serum osmolality were probably due to measured osmoles (i.e. sodium, potassium and glucose).

Although the exact impact of vomiting and diarrhea on the severe electrolyte abnormalities in this kitten at presentation cannot be measured as electrolyte concentrations were not determined prior to presentation to the hospital, the proximity of the SC D5W infusion and onset of clinical signs in addition to the concurrent marked hyponatremia, hyperglycemia and glucosuria suggest that administration of D5W was the cause of the neurological abnormalities. The rapid normalization of hyponatremia and hyperglycemia, the improvement of potassium concentration and the resolution of the neurological signs with therapy further support the hypothesis that the onset of hyponatremia was peracute and iatrogenic.

Acute hyponatremia is more common in humans than in animals; however, it is a rare clinical problem. Treatment recommendations are based on the physiological mechanisms of ion and water exchange between body compartments

rather than on experimental studies. Rapid correction of acute hyponatremia can lead to serious complications, including brain myelinolysis (also referred to as pontine myelinolysis). Several case reports of this syndrome have been described in people and a single suspected case in a dog has been published (5, 10, 17-19). In addition, this condition has been experimentally induced in rats, dogs and rabbits (20-23). Although the clinical and pathological manifestations of this phenomenon have been described, including magnetic resonance and diffusion-weighted imaging findings, its pathophysiology has never been determined (6, 17). In veterinary medicine, there is limited experience in correction of acute hyponatremia, and primary studies are unavailable. It has been recommended that only conventional crystalloid solutions (e.g. lactated Ringer's solution and 0.9% saline) be used in the treatment of these cases in light of the current limited experience in the management of acute hyponatremia in dogs and cats and with the known risks of overly rapid correction of hyponatremia. The use of 3% NaCl is discouraged (5). In contrast, in people with symptomatic acute hyponatremia and concurrent euolemia or hypervolemia, the use of hypertonic (7.5%) saline has been recommended, and may be required at rates calculated to increase serum sodium levels up to 12 mEq/L/day (6).

In this present case, we have treated this acute hyponatremia with oral water restriction and 0.9% saline IV infusion (10 ml/kg/h) in order to induce a slow and progressive increase in serum sodium concentration and to avoid potential complications. However, when neurological abnormalities worsened and seizures were noted, we concluded that a more aggressive correction of the hyponatremia was necessary. This was achieved with a single IV bolus of hypertonic (7.5%) saline (3.5 ml/cat or 4.5 mEq/cat). Using the Adrogue-Madias formula (6) [change in serum sodium = (infusate sodium – serum sodium) / (total body water + 1)], a single 7.5% saline bolus followed by a 6-hour IV 0.9% saline infusion should have increased the serum sodium concentration by 4.54 mEq/L at 6 hours post presentation. The serum sodium concentration was far higher at that time (136 mEq/L), and this increase can only be explained by a concurrent marked water diuresis that probably resulted from a decrease of serum vasopressin in response to serum hypo-osmolality. Plasma vasopressin concentrations are undetectable when plasma osmolality decreases below 280 mOsm/kg (24). Water diuresis is likely to be the main contributing factor to the normalization of serum sodium concentration, while the IV sodium supplementation had only a minor impact on serum sodium concentration. However, during the critical phase of hyponatremia, when neurological abnormalities worsened, even a relatively small increase in serum sodium concentration due to the IV hypertonic saline bolus was crucial to prevent further deterioration.

Subcutaneous fluid administration (hypodermoclysis) is a common procedure in veterinary practice which is in contrast to human medicine where it is uncommonly used, and is mostly utilized in geriatric patients (25-27). It is considered a safe rehydration technique in mild to moderate dehydration and is used in patients with ongoing fluid losses provided that isotonic or nearly isotonic (200-400 mOsm/kg) balanced electrolyte solutions are used. Large-volume, sodium free solutions are to be avoided in cats and small dogs. The volume that may be infused in a single SC location is limited by the distensibility

of the skin and subcutaneous tissue (28). Approximately 10 ml/kg or 50-200 ml per site has been suggested (13, 29). There is paucity of evidence-based data available of the effectiveness of this technique in the veterinary literature, and further research is warranted to assess its safety and efficacy (28). In people, repetitive SC boluses of 500 ml 2 to 3 times daily have been described as safe. Alternatively, a continuous drip rate of 75-150 ml/hour over extended time-periods (up to 5 days) has been described and was well tolerated (30).

Subcutaneous fluid administration has several advantages. It is minimally invasive, minimizes patient discomfort and is useful in very small veterinary patients in whom venous access is difficult. It is cost-efficient and results in a slow fluid absorption rate. The latter allows administration of a relatively large volume of fluid per body weight, potentially providing fluid requirements for several hours. Disadvantages include some patient discomfort, potential infections and limited usefulness. This technique can be used only in mildly to moderately dehydrated patients (and when absorption from the subcutaneous space is adequate), and is limited to inert isotonic solutions (28). When a large volume of fluid has to be administered quickly, such as in cases of shock, SC fluid administration has a very limited usefulness, and in small veterinary patients, when IV access is difficult, intraosseous catheterization is advised (13, 28).

The SC administration of D5W as a single solution, especially in a large bolus, is contraindicated in small animals (13, 28). This solution has been evaluated in human patients recently, and has been found to be as safe as other types of solutions (25-27). However, in these reports, D5W was always supplemented with NaCl (one third 0.9% NaCl with two thirds D5W [288 mOsm/kg], or 5% dextrose in 0.45% NaCl [406 mOsm/kg]) (26), and in addition, the rate and relative volume of such infusions were considerably lower (75-150 ml/hour per patient) than the volume and rate in this case (30).

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FOOTNOTES

^aPenibrin, Teva, Israel ^bgeneric, Teva, Israel ^cTagamet, GlaxoSmithKline, Germany ^dPramin, Rafa Laboratories, Israel ^eAssival, Teva, Israel

20. Laureno, R.: Central pontine myelinolysis following rapid correction of hyponatremia. *Ann. Neurol.* 13: 232-242, 1983.
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TABLE

Table 1: Clinical pathology measures during hospitalization in a kitten with neurological abnormalities due to acute, severe hyponatremia following a subcutaneous 5% dextrose in water infusion

Parameter	Time post presentation					Reference interval
	0	6 hours	24 hours	Day 3	Day 5	
White blood cells (x10 ³ /mm ³) [10 ⁹ /L]	4.10 [4.10]	NA ¹	1.63 [1.63]	2.40 [2.40]	6.12 [6.12]	5.00-18.00 [5.00-18.00]
Neutrophils (x10 ³ /mm ³) [10 ⁹ /L]	3.69 [3.69]	NA ¹	NA ¹	NA ¹	NA ¹	3.00-12.00 [3.00-12.00]
Hematocrit (%) [L/L]	33 [0.33]	23 [0.23]	21 [0.21]	19 [0.19]	21 [0.21]	27-45 [0.27-0.45]
Sodium (mEq/IL, mmol/L)	109	136	140	138	NA ¹	145-158
Potassium (mEq/IL, mmol/L)	3.60	3.60	3.40	3.5	NA ¹	3.80-5.30
Glucose (mg/dL) [mmol/L]	371 [20.59]	69 [3.83]	NA ¹	94 [5.22]	NA ¹	70-110 [3.89-6.11]
Total plasma protein (g/dL) [g/L]	6.3 [63]	5.0 [50]	4.2 [42]	6.8 [68]	6.2 [62]	5.5-7.5 [55-75]
Creatinine (mg/dL) [μmol/L]	<0.5 [44.2]	NA ¹	<0.5 [44.2]	<0.5 [44.2]	NA ¹	0.5-1.6 [44.2-141.4]

1 – Not assessed

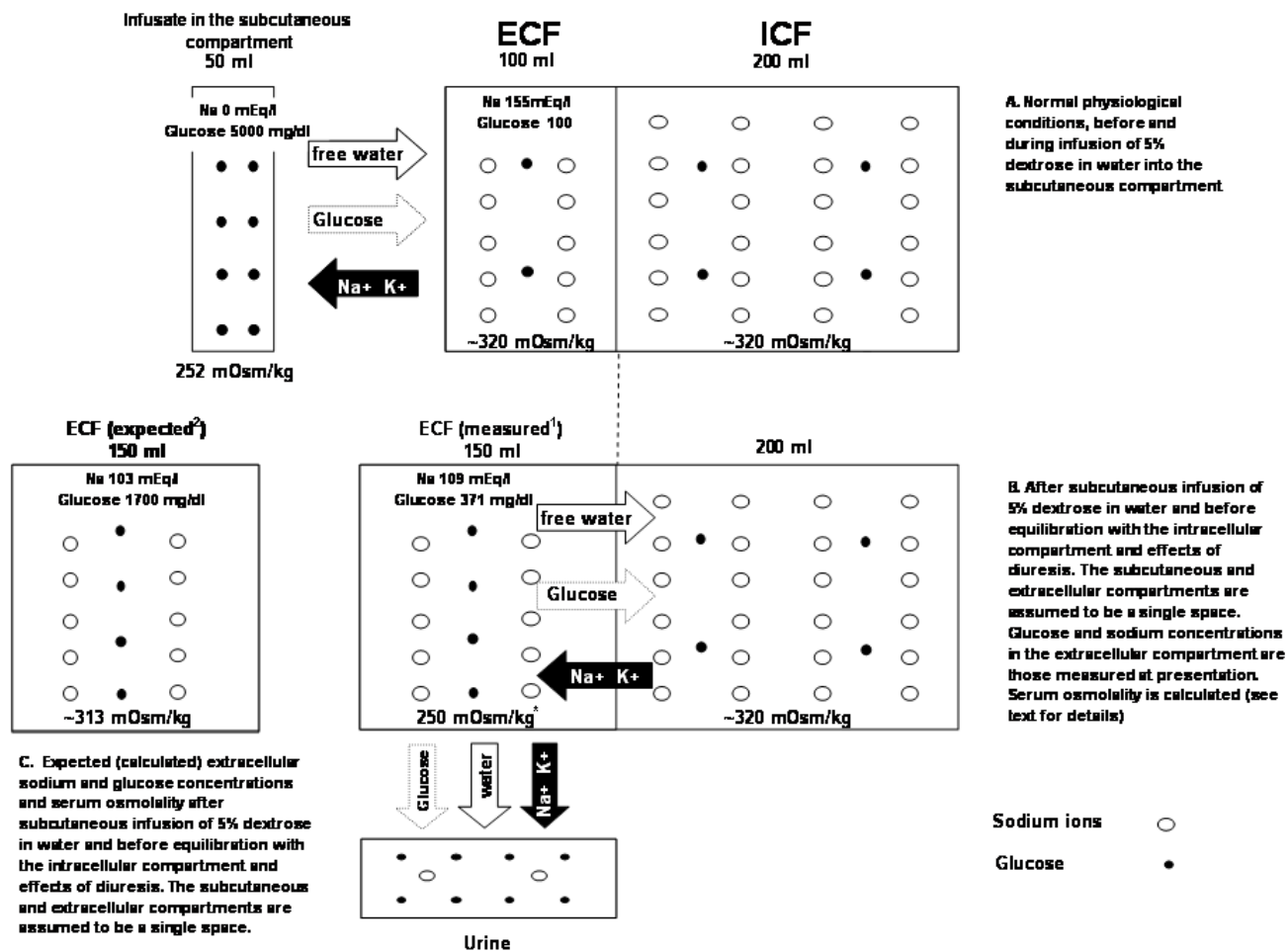


Fig.1

A simplified diagram depicting the movement of sodium and potassium ions, glucose and free water between body compartments in the kitten (body weight 0.5 kg). A. The distribution of body fluids between the extracellular and intracellular compartments under physiological conditions, before the subcutaneous (SC) infusion of 5% dextrose in water (D5W). The approximated concentrations of sodium and glucose and serum osmolality are based on their reference intervals in healthy cats, as these were not measured in this case. B. The distribution of body fluids after the SC D5W infusion (50 ml), assuming that the SC and extracellular compartments are a single space and that equilibration with the intracellular fluid (ICF) and diuresis have yet to occur. The concentrations of sodium and glucose are their actual measured concentrations at presentation. Serum osmolality is calculated based on sodium, potassium and glucose concentrations, while the maximal contribution of blood urea nitrogen to serum osmolality is assumed to be 5 mOsm/kg (see text for details). In this diagram, the SC infusion is assumed to move first as a whole into the extracellular fluid (ECF) and only later to equilibrate with the ICF. C. Expected ECF sodium and glucose concentrations and serum osmolality based upon the composition of D5W and normal ECF, with their respective volumes. The difference between the expected and measured sodium concentration is small, however there is a large difference between the expected and measured serum glucose concentration, and the resulting calculated serum osmolality. This can be explained by the one way glucose movement out of the ECF (into the ICF and urine) that led to a rapid and marked decrease in its serum concentration. Glucose movement into the ICF was likely induced due to an increase of insulin concentration, and its urine excretion was marked because its serum concentrations were above the renal threshold and diuresis was markedly increased. In contrast, the measured and expected ECF sodium concentrations were similar. ECF sodium concentration is influenced by several mechanisms, including dilution and free water movement, natriuresis and equilibration of ICF and ECF sodium concentrations.