

Hypertonic (3%) Sodium Chloride for Emergent Treatment of Exercise-Associated Hypotonic Encephalopathy

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Abstract

Exercise-associated hyponatraemia (EAH) is an acute-onset imbalance in the tonicity of extracellular fluids during or after endurance exercise which results in a blood sodium concentration <135 mmol/L. Both excessive fluid intake and a concurrent decrease in urine formation contribute to this rapid-onset, predominantly dilutional, decrease in serum sodium, which can result in life-threatening pulmonary and cerebral oedema. Marathon runners with hypotonic encephalopathy related to EAH, including two cases with fatal cerebral oedema, demonstrated non-osmotic secretion of arginine vasopressin and fulfilled the essential diagnostic criteria for the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The pathophysiology of SIADH as the proximate cause of EAH accounts for otherwise puzzling clinical observations such as cases occurring after only moderate fluid intake or presenting hours after races. This formulation provides a framework for enhancing prevention by monitoring weight changes during races to detect positive fluid balance before the onset of mental status changes. Most importantly, SIADH supports a strategy for use of oral and intravenous hypertonic solutions, including 3% sodium chloride, for the emergent treatment of moderate and life-threatening symptoms of hypotonic encephalopathy, respectively.

Since the initial reports of exertional water intoxication in ultra-distance runners,^[1] exercise-associated hyponatraemia (EAH) has been demonstrated to be a complication in marathon runners that has led to several life-threatening and fatal cases of pulmonary and cerebral oedema.^[2,3] A recent evidence-based consensus statement concluded that both excessive fluid consumption and a decrease in urine formation contribute to this dilutional effect,^[4] although the relative roles of polydipsia and antidi-

uresis could not be delineated based upon evidence available at that time. A recent review of hyponatraemia therapy^[5] suggests strategies for prevention and treatment, including the use of oral and intravenous hypertonic solutions, such as 3% sodium chloride, to reverse the symptoms related to moderate and life-threatening hypotonic encephalopathy, respectively.

The underlying pathophysiology of exertional hypotonic encephalopathy was initially assessed in

Table 1. Differential diagnosis of hyponatraemia based upon urine chemistries. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) shows a less than maximally dilute urine with a high sodium concentration ($[Na^+]$) in contrast to primary polydipsia. Salt depletion leads to a concentrated urine with a low $[Na^+]$ due to activation of the renin-angiotensin-aldosterone pathway. The findings in marathon runners with hypotonic encephalopathy were consistent with SIADH (reproduced from Siegel,^[6] with permission from Elsevier)

Hypo-osmolar Hyponatraemia (<275 mOsm/kg H ₂ O)	Urine osmolality (390–1093 mOsm/kg H ₂ O)	Urine $[Na^+]$ (mmol/L)	AVP (0.5–12.3 pg/mL)
Dilutional (BUN <15 mg/dL)			
polydipsia	<100	<30	<0.5
SIADH	>100 ^a	>30	>0.5
Depletional (BUN >15 mg/dL)			
	>300	<20	>0.5

a Inappropriate urinary response to hypo-osmolality.

AVP = arginine vasopressin; **BUN** = blood urea nitrogen.

two previously healthy runners who experienced seizures during the 2002 Boston and Marine Corps Marathons, and who lost consciousness with a rapid progression to fatal cerebral oedema. Serum sodium concentration ($[Na^+]$) levels were <125 mmol/L, with urine chemistries showing a less than maximally dilute (>100 mOsm/kg H₂O) and urine $[Na^+]$ >20 mEq/L with measurable levels of arginine vasopressin (AVP). These findings were consistent with a decrease in urine formation induced by AVP as the proximate cause for EAH rather than polydipsia or salt depletion, where conditions would result in a maximally dilute urine and a urine $[Na^+]$ <20 mmol/L, respectively (table 1). The natriuretic effect seen in these cases is a well established finding in the syndrome of inappropriate antidiuretic hormone secretion (SIADH) due to the renal reabsorption of free water rather than representing salt loss, which would lower urine $[Na^+]$ due in part to activation of the renin-angiotensin-aldosterone system.

Subsequent studies in a larger group of marathon runners with symptomatic EAH also showed non-osmotic secretion of AVP, fulfilling the essential diagnostic criteria for SIADH.^[7,8] Measurable levels of AVP in the presence of serum hypo-osmolality are inappropriate and lead to progressive water retention even at values within the range of normal, as discussed by Verbalis.^[9] This non-osmotic stimulation of AVP secretion may be due in part to the release of interleukin-6 during exertional rhabdomyolysis.^[6] While avid fluid consumption is an established risk factor for EAH,^[2] this behaviour would not likely result in sufficient fluid retention to in-

duce symptomatic EAH without a concurrent decrease in urine production. Polydipsia might therefore be viewed as a precondition for EAH in these marathon runners, with SIADH as the proximate cause.

Beyond providing a unifying explanation for the pathophysiology of EAH, the SIADH hypothesis accounts for otherwise unexplained clinical features such as cases occurring after only moderate fluid intake or with a delayed onset after races in runners who continue to drink hypotonic fluids thinking they must be dehydrated. Observational reports that non-steroidal anti-inflammatory drugs are associated with an increase in risk for EAH is also consistent with SIADH as these agents pharmacologically enhance the renal effects of AVP.

The SIADH hypothesis suggests specific strategies for prevention of EAH. Because symptomatic cases are generally associated with positive fluid balance, monitoring changes in bodyweight during races provides an objective measure for early detection of fluid retention before progression to the 2–3% increase associated with the onset of mental status changes. As used successfully at ironman triathlon distances, this strategy is especially relevant for novice marathon runners, with finishing times >4 hours, in whom the subjective perception of thirst may be an inaccurate guide for adjusting fluid intake. Any weight gain indicates the need to limit additional intake of all hypotonic fluids, including sodium-enhanced sports drinks, which, like pure water, enhances the total fluid load under conditions of SIADH.

Point-of-care testing of serum $[Na^+]$ is the optimal strategy for diagnosing serum hypo- and hypernatremia for triage of cases to diametrically opposite treatments. While malaise and fatigue may occur in both EAH and dehydration, confusion and disorientation should raise the index of suspicion for EAH as a reliable early sign of the delirium associated with hypotonic encephalopathy. If otherwise unimpaired, such runners can be treated simply with fluid restriction until the onset of urination. Additionally, oral hypertonic solutions, such as concentrated bullion (3–4 cubes in 4oz of water) as used at several races, have been observed to promote a more rapid resolution of mental status changes. Improvement with such measures permits runners to be safely discharged from care with instructions to limit the intake of hypotonic fluids until urination resumes, as covered by Chorley.^[10]

Hallucinations, psychomotor agitation, seizures or coma require emergent treatment with intravenous hypertonic solutions, such as 3% sodium chloride, to reverse hypotonic encephalopathy.^[8] Full recovery was reported in a series of cases so treated,^[3] leading subsequently to a protocol for 3% sodium chloride in cases with a serum $[Na^+] < 125$ mmol/L used by emergency services at the San Diego Marathon.^[11] The Boston Athletic Association and Boston Emergency Medical and Fire Services jointly adopted a protocol for use of 3% sodium chloride after confirmation of the diagnosis of EAH by point-of-care testing, including initiation in the medical tent, based on the severity of neurological symptoms. While such measures may be initiated in the field by medical teams authorised to do so under specific protocols, expedited transfer to an intensive care unit should be arranged concurrently.

A consensus is emerging from the collective experience of several medical teams to initiate intravenous infusion of 3% sodium chloride at a rate of 1–2 mL/kg/hour in confirmed cases in runners who are unable to take oral hypertonic solutions. Seizures or unresponsiveness justify an initial bolus of 100mL of 3% saline over 10 minutes, followed by an infusion rate of 2–3 mL/kg/hour to establish an increase in the serum $[Na^+]$ of 4–5 mmol/L over the

first 1–2 hours in order to reverse the osmotic gradient and remove excess water from brain cells. Once clinical improvement is observed, the rate of infusion may be moderated to remain within the guidelines recommended for the safe correction of chronic hyponatraemia (maximum increase of 12 mmol/L over 24 hours).^[8] While use of 3% sodium chloride in cases of rapid-onset encephalopathy due to EAH may result in a more rapid initial increase in serum $[Na^+]$ than has been advised in chronic cases, osmotic demyelination syndrome has not been observed due to correction in rapid-onset cases before the adaptive response of brain cells to hypo-osmolality has taken place.^[5]

In addition to 3% sodium chloride, oxygen should be given to prevent or treat hypoxaemia, and loop diuretics administered for volume overload including pulmonary oedema. AVP receptor antagonists, including two oral agents (lixivaptan and tolvaptan) and an intravenous preparation (conivaptan), deserve study as adjunctive treatment, given their current approval for euvolemic and hypervolaemic hyponatraemia.^[12] Oral and intravenous hypertonic solutions would likely remain a mainstay of treatment to expedite reversal of encephalopathic symptoms due to cerebral oedema, while AVP receptor blockers would correct water intoxication by facilitating a sodium-sparing hypotonic diuresis.

Beyond considerations herein regarding SIADH as the proximate cause of dilutional hyponatraemia in marathon runners, further studies are needed to investigate alternative pathophysiological mechanisms during exercise of longer duration such as during ironman distance triathlons and ultramarathon races.

Cumulative salt losses with extra-cellular fluid volume depletion may result in symptomatic EAH under such circumstances. Salt losses as a cause of EAH may be supported in part by the findings of a concentrated urine with a low urine $[Na^+]$ (table I). Hypertonic sodium chloride infusion is the optimal initial treatment to reverse life-threatening hypotonic encephalopathy, even with a depletion aetiology, and has been shown to be effective for treating

seizures due to severe depletion hyponatraemia ($[Na^+] < 120$ mmol/L) during therapy with oral hypotonic solutions for dehydrating illness.^[13,14] Hypertonic sodium chloride may therefore be the preferred emergent therapy for exertional hypotonic encephalopathy independent of the underlying mechanism or the status of extra-cellular fluid volume. Medical support for endurance athletes from providers in the field to hospital-based specialists should take into account the recommendation that 3% saline is currently endorsed as the optimal treatment for exertional hypotonic encephalopathy.^[15]

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