Chapter 10
Exercise-Associated Hyponatremia

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Introduction

Hyponatremia is the most common electrolyte disorder seen in nursing home and hospitalized patients [1]. However, in the past few decades it has also been described in athletes of both genders who participate in prolonged endurance events [2–5]. The term exercise-associated hyponatremia (EAH) has been used to describe hyponatremia developing in endurance athletes who participate in events lasting greater than four hours, and is clinically defined as a serum sodium concentration <135 mEq/L occurring up to 24 h after prolonged exertion [6]. Based on the symptoms associated with hyponatremia, an athlete with EAH can present in two forms: (1) athletes with isolated serum sodium levels <135 mmol/L who are either asymptomatic or have mild nonspecific symptoms such as nausea and (2) those presenting with confusion, seizures, and altered mental status, in association with serum sodium levels <135 mmol/L, who are considered to have exercise-associated hyponatremic encephalopathy (EAHE). EAHE is a potentially life-threatening condition. Although, EAH and especially EAHE are considered relatively rare occurrences in endurance athletes, it is becoming an increasingly more common

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finding in all ultra-endurance (>6 h) events worldwide, and is now well recognized as a cause of event-related fatality [6, 7]. Rapid diagnosis of EAH and the more severe form EAHE are critical to ensure good outcomes.

Much debate occurred in the late 1980s into the early 1990s regarding the possible etiology of EAH. Two camps emerged: one that supported overconsumption of water (dilutional hyponatremia) as the prime etiology [8] and the other supported excessive body sodium loss as the driving force [9]. Data are now most consistent with excess fluid consumption being the most important pathogenic feature with a smaller, variable component of solute loss [4–6].

EAH was first reported in the 1981 Comrades ultradistance marathon foot race between Pietermaritzburg and Durban, South Africa [8]. One case included a 46-year-old woman who developed EAH symptoms at approximately 70 km of the 90-km event [10]. After being driven to the medical tent at the finish line, she was administered 2 L of fluids for presumed dehydration. Since her symptoms continued to deteriorate she was transported in a vehicle back to Durban and while en route she suffered a grand mal seizure and lapsed into a coma. On admission to a hospital she was reported to have serum sodium of 115 mEq/L. She was diagnosed with EAHE with neurogenic (noncardiac) pulmonary edema secondary to overhydration of fluids.

In the following year, Frizzell et al. [11] described the development of EAH in a physician and medical student running in an ultramarathon in Chicago, USA, 1983. Both runners consumed over 20 L of fluid within 8–10 h and were diagnosed with EAH. Each patient was managed differently (3 % saline vs. 0.9 % saline) resulting in one being discharged within 8 h (3 % saline) and the other remaining semi-comatose for 36 h.

The emergence of EAH case presentations in the early to mid-1980s can be explained by the fact that endurance athletes were initially advised up to the late 1960s to avoid drinking fluids and consuming sodium during exercise since it was believed that it was not essential [12]. This paradigm shifted with the publication of an influential article by Wyndham and Strydom [13], which suggested that inadequate fluid consumption during marathon running was detrimental to performance. This in turn resulted in the development of hydration guidelines with the prevailing advice to have athletes consume the maximal amount of fluid that can be tolerated during exercise [5]. This dictum to consume as much fluids as tolerated during prolonged endurance events has likely influenced the greater emergence of EAH cases and deaths.

Since these case presentations by Noakes [8] and Frizzell [11], there have been many other EAH/EAHE published case presentations, prospective and retrospective research studies and review articles, two international EAH consensus reports, and other educational venues all in effort to educate clinical providers in both prehospital and in-hospital settings, and athletes and coaches about the causes, treatment, and prevention strategies for EAH/EAHE [4–7]. The objective of this chapter is to present the current consensus and findings for EAH/EAHE incidence rates, risk factors, pathophysiology, clinical management guidelines, and prevention strategies.

Epidemiology

The incidence of asymptomatic and symptomatic cases of EAH varies widely with regard to the geographical location of the event, type and duration of activity, gender, and ambient temperature during the event. Cases of "asymptomatic" hyponatremia are largely detected via convenient samples taken from consenting athletes participating in research screening protocols. Asymptomatic cases of EAH generally represent those which meet the biochemical diagnostic criteria for hyponatremia (blood sodium concentration <135 mmol/L) and are of unknown clinical significance. Obviously, the incidence of asymptomatic EAH is greater than the incidence of "symptomatic" EAH, which generally refers to a biochemical diagnosis of EAH combined with debilitating symptomatology, most often including significant mental status changes and perhaps pulmonary edema as well (EAHE).

Epidemiology of Asymptomatic EAH

The highest reported incidence of "asymptomatic" hyponatremia has been noted in ultramarathon races covering 161 km (100 miles) in North America, where the incidence of EAH has ranged between 30 and 51 % [14–16]. Two of the 161-km footraces recording the highest number of hyponatremic finishers were conducted in peak temperatures of ~37 °C [14, 15], while the other 161-km race with a 44 % incidence of EAH was conducted in temperatures ranging between −8 and 4 °C [16]. Conversely, similar ultradistance marathon races have reported no cases of EAH at equally high ambient temperatures [17] or at greater racing distances (181 km) [18]. Thus, the seemingly logical presumption that the incidence of hyponatremia increases over distance and time and at higher ambient temperatures is difficult to support.

Other endurance events have variable reported levels of EAH. For example, the incidence of biochemical EAH in Ironman Triathlons has been reported to be as high as 18 % [19] to 25 % [20] while negligible in another [21]. Studies on endurance cyclists have yielded a range in incidence of EAH from no cases in a 720-km race completed in a mean time of 28.9 h [22] to 12 % in cyclists participating in a 109-km road race (mean racing time ~5 h) [23]. Seventeen percent of 36 swimmers participating in a 26.4-km swim (average finish time ~9 h) developed asymptomatic hyponatremia in a race where individual race crews provided food and fluid to each athlete throughout the swim [24]. At the standard marathon distance (42.2 km), 12–13 % of race finishers were diagnosed with asymptomatic EAH from the 2003 London [25] and 2002 Boston Marathons [26]. The range of reported incidences has been between zero [27] and 28 % [28] at the standard marathon distance.

Collectively, in the largest cohort analysis of 2,135 athletes participating in eight endurance events, the incidence of biochemical EAH was 6 % [10]. The ambient temperature range of reported cases varied between the extremes of −8 °C [16] and 37.6 °C [14]. With regard to gender, the majority of studies document a higher incidence of EAH in females versus males. For example, in the Boston Marathon study of 488 race finishers, 22 % of females and 8 % of males developed EAH [26]. In 330 New Zealand Ironman Triathletes, 45 % of female and 14 % of male race finishers were diagnosed with EAH [19]. Although the incidence of EAH is substantially higher in females, it is important to recognize that males are not "spared" from developing EAH.

Epidemiology of Symptomatic EAH (EAHE)

Cases of symptomatic EAH are generally reported as isolated cases presenting to medical facilities (medical tents at races and hospitals) for treatment related to a spectrum of symptoms ranging from feeling unwell to collapse with seizure activity. However, a few separate criteria have been utilized to evaluate the potential for clinical severity in the two largest cohorts analyzed to date. More specifically, in a large cohort analysis of 2,135 athletes, "clinically significant" hyponatremia was defined as a cutoff serum sodium concentration of <128.9 mmol/L [10]. According to this definition, the overall incidence was 1 % although it was unclear if the entire cluster of athletes reported significant symptoms [10]. Similarly, in 488 Boston Marathon finishers, 0.6 % developed "critical hyponatremia" represented by a serum sodium concentration below 120 mmol/L [26]. This small percentage of race finishers, however, did not appear symptomatic for EAH at the time of testing [26]. Other than these two reports, the reporting of symptomatic clusters of EAH detailed below represent small numbers of athletes seeking medical attention.

The majority of reported cases of symptomatic hyponatremia were in runners or in events where running was the last event (Ironman Triathlon). Nine confirmed deaths of public record have been directly attributed to complications associated with EAHE [25, 29–31]. The overall incidence of symptomatic EAH in all marathon participants is generally below 1 % [31, 32], but the percentage of EAH seen in all symptomatic athletes seeking medical care has been reported to be as high as 23 % in an Ironman Triathlon [19] and 38 % in runners participating in a marathon and ultramarathon in Asia [33]. The most alarming epidemiological trend is that symptomatic EAH is now being reported in shorter distance events such as a half marathon [34] and sprint distance triathlon taking 1 h and 33 min to complete [35].

Also at the turn of the second millennium, symptomatic cases of hyponatremia were being reported with increased frequency in both hikers and military personnel. The reported incidence of hyponatremia in Grand Canyon hikers seeking medical care from exercise-associated collapse or exhaustion from May 31, 1993 through September 31, 1993 was 16 % with an estimated incidence rate between 0.02 and 0.4 per 1,000 persons [36, 37]. In the United States Military, between 1989 and

1999 there were 190 hospitalized cases of hyponatremia [38]. Data from the Defense Medical Surveillance system, however, estimated an incidence rate between 0.01 and 0.03 per 1,000 person years across all military populations from 1997 to 2005 [37]. There have been four reported deaths from hyponatremia in the military [39, 40]. Thus, although less strenuous than running, even very modest hiking and marching activities in young and healthy individuals [41] have led to documented morbidity and mortality from EAHE.

More unusual presentations associated with more modest exercise levels have been reported in: a football player presenting to the trainer's room with cramps and receiving 8 L of hypotonic fluid [42] and a 48-year-old male lawn bowler, heterozygous for the Delta F508 cystic fibrosis mutation, bowling in 42 °C heat [43]. Cases of symptomatic EAH have also been induced in two separate laboratory studies involving low intensity exercise conducted in high (>30 °C) ambient conditions [44, 45]. Deaths from hyponatremia have also been reported in the lay press in a 25-year-old male police officer participating in a 12-mile bicycle training ride [46], a 17-year-old male football player after a summer practice [47], and in a case of fraternity hazing involving a 21-year-old male pledge performing calisthenics in a cold cellar [48]. Many more of these unfortunate events have likely occurred and either have not been recognized or reported on.

In summary, the incidence of asymptomatic hyponatremia ranges from 0 to 51 % while cases of symptomatic hyponatremia are much lower (<0.5 % of all standard marathon runners). However, at least nine deaths from EAHE have been reported in the literature, five females and four males. The incidence of asymptomatic cases of EAH which eventually progress to life-threatening EAHE is currently unknown and requires further investigation.

Risk Factors for EAH

Case series of athletes who have developed EAH reveal that the development of EAH is associated with identifiable risk factors, some of which may be modifiable. The major risk factor for EAH is a high rate and total amount of fluid intake during and immediately after exercise [11, 21, 26, 31, 32, 49]. For example, in the Boston Marathon, the development of EAH was independently associated with weight gain during the race (which could only occur from fluid intake) and the amount of weight gained correlated with the severity of hyponatremia (17 % of runners who gained at least 2.0 kg developed hyponatremia) [26]. In a large review of 2,135 athletes participating in endurance races, the authors estimated that athletes who gained more than 4 % body weight during exercise had an 85 % probability of developing hyponatremia [10]. Of note, not all athletes who develop EAH gain weight during exercise suggesting that while excessive consumption of fluids is a clear risk for the development of EAH, it is not absolutely required [14, 15]. However, severe hyponatremia is rare in athletes who lose weight during the event [31]. It is also important to note that consumption of sports beverages, which typically contain

carbohydrates and electrolytes, do not provide protection against the development of EAH [26, 31]. This is due to the fact that these drinks are hypotonic to plasma and that the typical sodium plus potassium content is approximately 20–30 meq/L.

Other risk factors for the development of EAH include: longer race times, female gender, slower training pace, and a low body mass index [21, 26, 31, 32, 49]. While some studies have implicated the use of nonsteroidal antiinflammatory agents (NSAIDS) as a risk factor for EAH [50], others have not [26]. Conceptually, NSAIDS could increase the risk for EAH due to their ability to increase the activity of arginine vasopressin (AVP) by removing the inhibitory effect of prostaglandins. The role of other medications that can lead to non-osmotic secretion of AVP such as selective serotonin release inhibitors has not been studied in this group.

Pathogenesis of EAH

The two major pathogenic mechanisms that account for the development of EAH are: (1) increased fluid intake and (2) impaired urinary water excretion due largely to persistent secretion of AVP [4, 5].

As noted above, increased fluid intake appears to be the primary risk factor for the development of EAH. This is reflected in the weight gain seen in the majority of athletes who become hyponatremic. However, a source of "endogenous" water that may contribute to the increase in extracellular water in athletes who develop EAH is derived from the breakdown of glycogen during exercise [51]. Water is found in a complex with glycogen in the liver and muscle, and as glycogen is metabolized, water is released without a concomitant weight gain. How much this mechanism contributes to the risk of EAH without weight gain is not known.

Individuals with normal renal function, ingesting a regular diet, can excrete between 500 and 1,000 ml/h of water [52]. With the additional, non-renal losses of water due to sweat and insensible fluid losses, athletes should be able to consume as much as 1,000–1,500 ml/h before developing water retention and hyponatremia. Thus, while fluid ingestion is necessary to develop EAH, it is likely not sufficient except in those circumstances where water intake is very excessive (>1,500 ml/h).

Failure to suppress AVP can markedly reduce the ability of the kidneys to excrete a water load. For instance, in normal circumstances, ingestion of water should suppress AVP leading to production of dilute, high volume urine (urine osmolality as low as 50 mOsm/kg and a volume of 500–1,000 ml/h). If AVP is not suppressed appropriately with water loading, then the ability to produce dilute urine is markedly impaired (for instance, low level persistence of AVP can result in a fixed urine osmolality of 150 mOsm/kg and a decrease in the rate of water excretion by two-thirds as compared to a urine osmolality of 50 mOsm/kg). In fact, the available data support the concept that many athletes who develop EAH have submaximal suppression of AVP and an inappropriately high urine osmolality [30]. This is similar to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). There are a number of non-osmotic stimuli that lead to secretion of

AVP that may be operable in endurance athletes: intense exercise itself; nausea and/or vomiting; hypoglycemia; and nonspecific stresses such as pain and emotion [23, 53, 54]. Not all AVP release in athletes may be inappropriate as excessive sweat sodium losses may induce volume depletion and appropriate secretion of AVP. This appropriate AVP secretion may be important in those athletes who develop EAH along with net weight loss.

While the combination of excessive water intake along with inappropriate AVP secretion will clearly lead to hyponatremia, other factors may be operable in endurance athletes. Suggesting that other factors may be operative, was the important finding that in the review of 2,135 athletes, 70 % of the athletes who gained weight during the event maintained normal serum sodium levels [10]. What explains this finding as well as the fact that some athletes may lose weight and become hyponatremic?

In a study of endurance athletes running for a mean of 6 h and ad libitum fluid intake, it was noted that despite a mean 3.8 kg mass loss, serum sodium was maintained at normal levels [55]. While, not surprisingly, AVP levels were elevated, so were the levels of brain natriuretic peptide (NT-BNP) despite the loss in plasma volume [55]. The elevations in BNP may lead to excessive losses of urine sodium and raise the risk of hyponatremia. Further studies are needed in order to determine how much urine solute loss may contribute to the development of EAH.

A possible mechanism for maintenance of a normal serum sodium level despite weight gain is the release of sodium from internal stores [10]. Up to 25 % of body sodium is bound in bone (to negatively charged proteoglycan matrix) and though not osmotically active is potentially recruitable into an osmotically active form [56, 57]. Thus, this pool could minimize the fall in serum sodium induced by overhydration. This may explain the following findings, which were reported in 18 athletes who were hospitalized for EAH [10]. Sodium and water balance were estimated at the time of admission and measured during recovery. At the time of admission, the predicted serum sodium based upon electrolyte and water balance estimates was higher than the actual concentration in 14 of the 18 athletes. This suggested exchange of sodium from an osmotically active to an inactive state and worsening of the hyponatremia. Interestingly, during recovery, 8 of the athletes showed evidence of osmotic activation of sodium (the increase in serum sodium was greater than could be explained by simple balance of sodium and water intake and output). On the other hand, 10 of the athletes showed evidence of osmotic inactivation of sodium (the increase in sodium was less than could be explained by simple balance of sodium and water intake and output).

There are other factors likely operative in endurance athletes that affect the serum sodium. However, their impact on the development of EAH is speculative [4, 5]. These include: (1) the absorption of water retained in the gastrointestinal tract at the end of the race which will lower the serum sodium; (2) the breakdown of glycogen into smaller, more osmotically active molecules, such as lactate, during exercise which will initially increase cellular osmolality and shift water into cells leading to a rise in serum sodium, and then reverse within 5 min after the cessation of exercise and lower the serum sodium [58, 59], and (3) changes in potassium

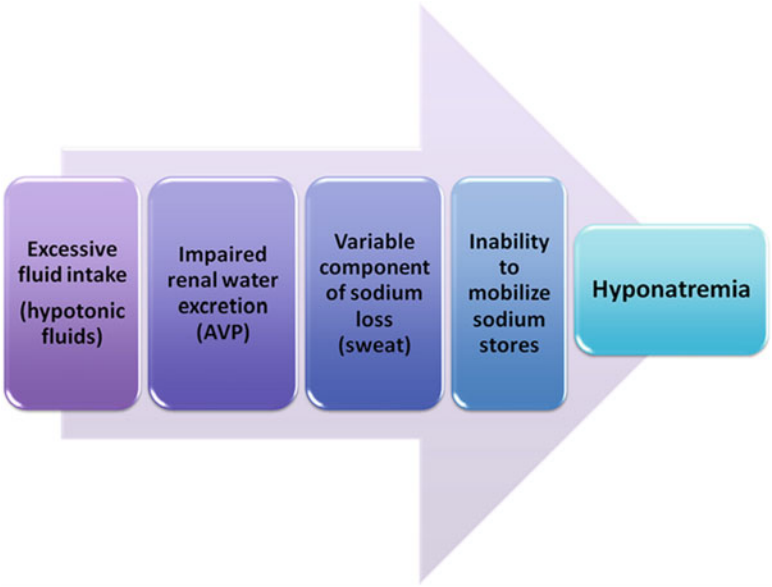

Fig. 10.1 Major pathogenic features that ultimately lead to exercise-associated hyponatremia

balance that serve as effective osmoles and affect the serum sodium such that hypokalemia will lead to hyponatremia.

The issue of whether sweat sodium loss contributes to the development of EAH remains controversial. There is a highly variable degree of sodium loss from sweat (ranging from 15 to 65 meq/L) and as compared to the general population endurance athletes generally have lower sweat sodium levels [60, 61]. The direct effect of losing hypotonic sweat would be to raise the serum sodium. However, sweat loss could contribute to the development of hyponatremia if the degree of fluid loss were sufficient to produce significant volume depletion and provide a stimulus to AVP release and thereby, impair urine excretion of water. In this case, there would also have to be ingestion of hypotonic fluids. This scenario may explain the finding of EAH developing in some athletes with net weight loss [14, 15]. However, sweat solute loss is likely only a minor contributing factor, as one study documented that the mean sodium deficit of athletes with EAH was only 104 meq [10]. This observation is consistent with another report in which the plasma volume was maintained in 181 triathletes despite a mean mass loss of 4.9 kg during the race [62].

Thus, the pathogenesis of EAH is complex (Fig. 10.1) with the two main factors being the excessive ingestion of water and inappropriate secretion of AVP. There are likely numerous variations on this theme, which reflect variable contributions from other mechanisms such as sweat sodium loss, osmotic inactivation of sodium, and variable potassium losses.

Treatment of Exercise-Associated Hyponatremia

Historical Perspective

Early clues to the appropriate management of EAH came with the previously referenced paper published by Frizzell and co-workers describing two participants of the 1983 American Medical Joggers Association 50-mile and 100-km ultramarathons [11]. At the time of the event, race guidelines advised runners to drink 300–350 ml per aid station which amounted to 15–18 L in the 50-mile event and 18–22 L in the 100-km event. The second place finisher of the 100-km event was a 24-year-old medical student who was reported to have become "stuporous and disoriented" within 5 min of finishing. He was found to have a serum sodium concentration of 123 mmol/L. After treatment with intravenous (IV) normal saline, he developed seizures and was semicomatose for 36 h. Fortunately, he ultimately recovered and was discharged in satisfactory condition on the fifth hospital day. In contrast, a 45-year-old physician who became "disoriented and confused" about 30 min after finishing the 50-mile event, and with a serum sodium of 118 mmol/L, was treated with IV 3 % hypertonic saline. He was fully alert in 3 h and was discharged after 8 h. Fluid intake was estimated at 20 L and 24 L for the 100-km and 50-mile runners, respectively. The authors cautioned about excessive fluid intake, commented that the postexercise onset of EAH symptoms might be due to accelerated gastric emptying with cessation of exercise, and noted the apparent benefit of hypertonic saline over normal saline in the treatment of EAH.

Since the report of these two cases, other case reports have provided additional support for the efficacy of IV hypertonic saline over normal saline in the treatment of EAH [29, 30, 32]. Furthermore, clinical trials during the 2009 and 2010 161-km Western States Endurance Run demonstrated that 100 ml of IV 3 % hypertonic saline in neurologically asymptomatic finishers with EAH resulted in a 2–4 mmol/L increase in serum sodium concentration within 60 min [63].

Additional work has focused on the potential of treating EAH with oral hypertonic saline. Siegel and colleagues describe treatment of three runners from the 2008 Boston Marathon with "mental status changes" and serum sodium concentrations of 128–133 mmol/L [64]. Each was tolerant of oral intake and was provided oral 9 % saline from concentrated broth (4 bouillon cubes in ~120 ml water). Each had rapid symptomatic recovery, and serum sodium concentrations reached normal levels within approximately 15–25 min.

At the 2009 and 2010 Western States Endurance Run, a comparison between 100 ml of 3 % hypertonic saline given orally vs. IV among neurologically asymptomatic finishers with EAH was performed. In the larger trial, there was a significant and comparable increase in serum sodium concentration of 2 mmol/L in both groups over the 60-min treatment period. A significant body mass loss due to diuresis was also evident from the treatment received by both groups. Therefore, at least among those with mild EAH who can tolerate oral intake, hypertonic saline taken orally appears to be a viable treatment option.

Making the Diagnosis

A requisite for correctly diagnosing EAH is that it must be routinely considered in the differential diagnosis of an individual presenting for medical attention during or shortly after exercise. In fact, EAH can easily be mistaken for dehydration if the diagnosis is not considered. Differentiation between dehydration and EAH is critical as provision of isotonic or hypotonic fluids is appropriate for the dehydrated athlete [65], whereas such treatment could be disastrous for an athlete with EAH.

The second international exercise-associated hyponatremia consensus development conference concluded that "medical directors should ensure the availability of on-site serum sodium concentration analysis [6]." When EAH is routinely considered in the differential diagnosis of a collapsed runner and point-of-care serum sodium concentration analysis is available, the field diagnosis of EAH becomes straightforward. However, the reality is that on-site analysis of serum sodium concentration is not widely available. Even relatively large and established organized endurance and ultra-endurance events often have no capacity for on-site blood analysis. For perspective, of the 556 ultramarathon competitions in North America in 2010 that had at least 20 finishers, the median event size was only 56 runners. Given the small size of so many of these competitions, few events can legitimately provide little more than "first aid/first responder" medical capabilities, and many of them have no medical coverage at all.

Other limitations to the viability of point-of-care blood analysis at endurance events include the high cost of the analyzer and the expense associated with operation. Furthermore, even when point-of-care blood analysis is available, it can be technically difficult for events that traverse remote areas to assure such testing is available at all sites where it might be needed. Temperature sensitivity of the analyzers can be another issue that interferes with on-site analysis [14, 15, 66].

The development of salivary osmolality [67] or tear osmolarity [56] analyzers have resulted in some attention for possible use in defining hydration status, but are not viable diagnostic tools for EAH. Ideally, an inexpensive portable serum sodium analyzer that requires only a drop of blood and is operational across a wide temperature range will eventually become available. Until then, the availability of on-site determination of serum sodium concentration is too high of a standard to be expected of most organized endurance and ultra-endurance events. As such, the consideration of alternative diagnostic means has been explored. Unfortunately, the possible signs and symptoms that have been reported to be present with EAH are quite similar to those present with heat illness or dehydration (Table 10.1). Even oliguria, which would be typical of the dehydrated state, is also commonly seen with EAH when AVP secretion is part of the pathophysiological mechanism leading to a highly concentrated, low volume urine output.

In some environments, those developing EAH have been shown to be more likely to lose less weight or to gain weight during the exercise compared with those not developing EAH [10]. Among 2,135 observations, Noakes et al. demonstrated an indirect relationship between post-event serum sodium concentration and weight

Table 10.1 Signs and symptoms of EAH and heat illness or dehydration

	EAH	Heat Illness or Dehydration
General		
Fatigue/weakness	Possible	Possible
Increased thirst	Possible	Likely
Temperature		
Normal	Possible	Possible
Elevated	Possible	Possible
Cardiovascular		
Tachycardia	Possible	Likely
Orthostasis	Possible	Likely
Gastrointestinal		
Nausea/vomiting	Possible	Possible
Neurological		
Headache/dizziness	Possible	Possible
Blurred vision	Possible	Possible
Confusion/disorientation	Possible	Possible
Obtundation	Possible	Possible
Seizure	Possible	Not likely
Coma	Possible	Possible
Respiratory		
Distress	Possible	Not present
Urine Output		
Oliguria	Possible	Likely
Diuresis	Possible	Not present

change such that those who gained weight or lost the least amount of weight generally had lower serum sodium concentrations than those who lost more weight [10]. In fact, of those with EAH, only 25 % had lost more than 3 % body weight, and among those with "clinically significant" EAH (serum sodium concentration <129 mmol/L), none had lost more than 3 % body weight. As such, within that population, it was unlikely for an athlete to have clinically significant EAH with a weight loss of 3 % or more.

Interestingly, some recent observations at four 161-km ultramarathon runs in northern California have been considerably different. From 430 observations, a direct relationship between post-event serum sodium concentration and weight change was seen such that those who lost weight were more likely to have lower serum sodium concentrations than those gaining weight during the event [15, 66]. It was also found that of those with EAH, 40 % had lost more than 3 % body weight, and when just considering those with "clinically significant" EAH, 31 % had lost more than 3 % body weight with some losing more than 5–8 %. The explanation for the different findings between this study and that of Noakes and colleagues is not clear but may be due to the events in this cohort generally being longer in duration and likely under higher ambient temperatures. Nonetheless, in this environment, weight loss or gain has not proven to be helpful in making the diagnosis of EAH. This unfortunately means that the only reliable method of diagnosing EAH at present is through measurement of serum sodium concentration.

Field Treatment Guidelines

Perhaps the most important element in the treatment of EAH is to avoid exacerbating the condition with improper treatment. Pushing isotonic or hypotonic fluids, whether orally or intravenously, is contraindicated in EAH. It is also important to understand that serum sodium concentration does not necessarily correspond with the magnitude of symptoms. The necessary level of care and urgency in treatment is based upon symptoms.

Cases of mild EAH without neurological symptoms are likely to go unrecognized unless in a situation where post-event serum sodium concentration is being measured for another purpose. Those individuals with hyponatremia who are neurologically stable are best advised to limit fluid intake and consume salty snacks or a small volume of hypertonic fluid until the onset of urination. They should be observed for at least 60 min during the initial post-exercise period since water remaining in the gastrointestinal tract can be quickly absorbed at the cessation of exercise and result in rapid development of symptoms from EAH. They should also be advised to urgently seek medical attention if signs or symptoms of EAH develop.

Individuals with EAH who have neurological symptoms, regardless of the actual serum sodium concentration, should be treated emergently with hypertonic saline. When able to tolerate oral intake, a hypertonic solution of concentrated broth would be an appropriate initial treatment. If the individual is unable to tolerate oral intake, or when there is no improvement or symptoms worsen with oral hypertonic saline, the recommended treatment is a 100 ml bolus of 3 % hypertonic saline infused through a peripheral vein in <60 s [6, 7]. This can be repeated two additional times at 10 min intervals if not clinically improved. Experience has proven this treatment to be without untoward symptoms at the infusion site (no burning, phlebitis or residual discomfort). Supplemental oxygen, if available, should be provided to treat hypoxemia. The intent of the field management is to stabilize the subject until their care can be transferred to a definitive care medical facility. When transferring care, it is most important to relay the diagnosis of EAH and to caution the transport team about potential dangers of aggressive IV hydration with isotonic or hypotonic fluids.

The sodium load from each 100 ml bolus of 3 % hypertonic saline (51 mmol) is expected to increase serum sodium concentration by 1–2 mmol/L. There is evidence that such treatment also acts to expand the plasma volume which removes the volume-receptor stimulus for AVP secretion [63]. A reduction in AVP secretion should then cause an aquaresis which will result in an additional increase in serum sodium concentration. This increase in serum sodium concentration shifts the osmotic gradient and reverses neurological symptoms. Neurological improvement often occurs within minutes with minimal increase in serum sodium [64]. Furthermore, unlike the situation with rapid correction of chronic hyponatremia, there appears to be no risk of osmotic demyelination or central pontine myelinolysis with rapid reversal of EAH.

When the capacity for on-site serum sodium measurement is not available, the decision-making process becomes more challenging. Suspicion of EAH necessitates fluid restriction. Certainly in environments where the incidence of EAH is recognized to be high, such as certain ultramarathon runs where the incidence of EAH has been found to be as high as 30–51 % [14, 63, 66], one should resist treating athletes with IV normal saline without certainty that they do not have EAH. However, fluid restriction is contraindicated in the case of dehydration and rhabdomyolysis with impending acute kidney injury [65]. Thus, the lack of diagnostic capacity in the field creates a treatment dilemma. In the event of neurological deterioration without access to rapid determination of serum sodium concentration, the use of IV hypertonic saline, if available, is a consideration but, at present, cannot be recommended as being without potential risk. In some regard, one could make the argument that when point-of-care serum sodium concentration cannot be determined, it might be best to completely avoid the availability of IV supplies. Under such situations, an appropriate emergency transport system must be in place.

Additional considerations for endurance and ultra-endurance events that will not have on-site capabilities to measure serum sodium concentration include education of event participants about prevention of EAH and medical personnel about treatment guidelines for EAH. The unnecessary use of IV fluid replacement will also reduce the risk of exacerbating EAH. The assurance that an emergency transport system is in place becomes critical, and local emergency department physicians and transport personnel should also be educated about EAH.

Prevention

Prevention of exercise-associated hyponatremia is largely—if not exclusively—dependent on optimal fluid and sodium intake guidelines and drinking habits during exercise. Acknowledging the wide range of ambient temperature fluctuations during an athletic event, athlete size and experience level, exercise intensity and duration as well as individual stress levels, creation of a safe “one size fits all” range of pre-calculated fluid intake recommendations is an impossible task. Thus, more individualized strategies are necessary to accommodate all athletes participating in a wide variety of athletic endeavors.

In athletic events and exercise lasting less than 18 h, the predominant pathophysiological mechanism in the development of EAH is overconsumption of hypotonic fluids beyond the capacity to excrete any fluid excess [6]. There are two individualized strategies to prevent the overconsumption of fluid during exercise. The first strategy is to use body weight changes during exercise as a guide to estimate the amount of fluid lost during exercise, and rehydrate accordingly. This strategy is favorable to athletes desiring a more structured “pre-competition” hydration plan. However, this option of maintaining body weight during exercise should always be subservient to bodily cues suggestive of overhydration (bloating, gastrointestinal distress) [68]. Replacement of 100 % of body weight losses during

endurance races appear to result in overhydration due to the combination of substrate losses combined with the liberation of glycogen-bound water during exercise [10, 69]. Furthermore, although weight gain has been shown to be a reliable predictor of dilutional hyponatremia in athletic events lasting <18 h [10, 26], in athletic events lasting over 20 h, the reliance on body weight to predict hyponatremia is abolished or even inverted [15, 66]. Thus, estimations of body weight losses should be used as a guide rather than a rule, especially during uncontrolled settings (endurances races) where the potential for non-osmotic stimuli to AVP secretion (and water retention) are higher than in training.

The second, preferred, hydration strategy to prevent EAH is to drink according to the dictates of thirst [6]. Since the body strives to maintain plasma osmolality—not body weight—at rest and during exercise, drinking to thirst protects against dilutional hyponatremia without performance or health decrements [69]. Decreasing the number of fluid stations along a race course (optimal distance every 20 km in a cycle race and every 2.5 km in a marathon run) [70] and appropriate educational strategies designed to reverse inappropriate "drink as much as possible" beliefs and drinking behaviors [71] have also been shown to be effective in preventing the development of EAH.

Sodium supplementation during exercise has not been shown to be effective in the prevention of EAH during endurance exercise lasting <18 h. Sodium supplementation in athletes who lost >2 % body weight during an Ironman Triathlon did not affect serum sodium concentration [72, 73]. However, for athletes who hydrate to replace ≥100 % of body weight losses during exercise, sodium supplementation appears to attenuate the decline in serum sodium concentration but does not prevent the occurrence of hyponatremia if fluid intake exceeds fluid losses [68, 74]. It is important to note that most commercially available sports drinks are hypotonic to plasma, typically containing only 10–18 mmol/L of sodium, and do not offer a significant amount of supplemental sodium.

In summary, drinking according to the dictates of thirst before, during, and after exercise appears to be the primary strategy in preventing exercise-associated hyponatremia. Sodium supplementation may attenuate the decline in serum sodium concentration when fluid intake matches or exceeds body weight losses, but cannot prevent hyponatremia when sustained fluid intake exceeds fluid losses.

Summary

EAH is a potentially devastating condition that can complicate participation in endurance events. In recent years, a greater understanding of the risk factors and pathogenesis of EAH has led to a consensus recommendation regarding its treatment [6]. However, recognition of EAH and EAHE remains challenging and first responding medical personnel still require education in this regard. Ideally, on-site blood sodium measurement would be available at endurance events, but this is not practical. Thus, a high-index of suspicion is required in order to diagnose EAH.

Clearly, prevention is the key factor in protecting athletes and others from EAH. Unfortunately, there is no "one size fits all" recipe for fluid and salt consumption during endurance events, although drinking to thirst and avoiding water intakes $>$1,500 ml/h are prudent and reasonable recommendations. Education continues to be needed to ensure that athletes understand the risk of overdrinking and the consequences of EAH.

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