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REVIEW

Thiazide-induced hyponatraemia: distinguishing hypovolaemic and euvolaemic subtypes to guide management strategies

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Abstract

Hyponatraemia is the most prevalent electrolyte imbalance observed in acute clinical settings, occurring in up to 30% of inpatients. Thiazide-induced hyponatraemia (TIH) is common, accounting for approximately one quarter of hyponatraemia cases among hospitalised patients. TIH presentations may occur with either a diuretic-induced volume depletion and subsequent hypovolaemic hyponatraemia or with a syndrome of inappropriate antidiuresis (SIAD)-like presentation with euvolaemic hyponatraemia (which is more common). Hyponatraemia is associated with prolonged hospital length of stay and greater risk of readmission and, hence, a significant driver of additional inpatient healthcare costs. Similarly, TIH can lengthen hospital stay, underscoring the importance of early and accurate differentiation between its subtypes to guide management. Thiazides induce diuresis by inhibiting the sodium-chloride cotransporter in the distal convoluted tubule of the kidneys, thus leading to natriuresis, increased urinary chloride, aquaresis and mild volume depletion. However, thiazides can lead to a compensatory euvolaemic state through various mechanisms. Discriminating hypovolaemic from euvolaemic presentations can be challenging when using traditional approaches to assessing and managing hyponatraemia. Volume status assessment by physical examination can be unreliable, and since thiazides promote natriuresis, urine sodium levels provide limited diagnostic value. Thus, assessing serum (sodium, potassium, chloride) and urine (chloride, potassium) biochemistry in greater detail is useful for distinguishing between the two subtypes of TIH, which have different management strategies. We present a narrative review of TIH and propose a practical diagnostic approach to assist in clinical judgement for early and accurate determination of the subtypes, enabling prompt management.

Introduction

Hyponatraemia, defined as a serum sodium concentration ((Na+)) below 135 mmol/L, is the most prevalent electrolyte imbalance observed in clinical settings, occurring in up to 30% of hospitalised patients.[1] Thiazide and thiazide-like diuretics, including indapamide and hydrochlorothiazide, are commonly prescribed and are highly cost-effective antihypertensives.[2] Thiazide-induced hyponatraemia (TIH) is common, accounting for approximately one quarter of hyponatraemia cases among hospitalised patients.[3] Symptoms of TIH can range from asymptomatic, mild (nausea, headache and fatigue) to severe (confusion, seizure and coma).[4] Variation in hyponatraemic symptoms could be indicative of the degree of cerebral oedema and reflect the rapidity of onset.[5] Even in the absence of symptoms, hyponatraemia is associated with falls, attention deficits, osteoporosis with increased fracture risk and increased mortality.[6]

Hyponatraemia can be classified by a variety of categories: (i) time of onset (acute as <48 h onset, and chronic

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as >48 h onset), (ii) biochemical severity (mild (Na+) 130–135 mmol/L, moderate (Na+) 125–130 mmol/L and severe (Na+) <125 mmol/L), (iii) symptoms (symptomatic vs. asymptomatic), (iv) serum osmolality (hypotonic, isotonic and hypertonic) and (v) volume status (hypovolaemic, euvolaemic, hypervolaemic).[7] TIH clinical presentations are typically characterised by hypovolaemia or euvolaemia, which have different management strategies. Yet, the difference in hydration status for TIH presentations is not consistently or immediately recognised by inpatient general and specialist physicians. Furthermore, hyponatraemia is associated with a prolonged hospital length of stay (LOS) and a greater risk of readmissions, a significant driver of additional inpatient healthcare costs.[8] Hence, there are possible advantages in early, accurate determination of the TIH subtype to guide management.

We present a narrative review focused on TIH and propose a practical diagnostic algorithm to accurately subtype TIH, thereby guiding therapy. Broader aspects of hyponatraemia and its general management are beyond the scope of this review and will not be addressed.

Pathophysiology of TIH

Thiazides induce diuresis by inhibiting the sodium-chloride cotransporter (NCC) in the distal convoluted tubule (DCT) of the kidneys, leading to natriuresis, increased urinary chloride, aquaresis and mild volume depletion (Fig. 1).[9] Decreased sodium reabsorption also results in increased urinary potassium excretion.[9] In the initial response to the diuresis, increased thirst and excess free water consumption result in a dilutional hyponatraemia in an overall hypovolaemic state. However, thiazides can lead to exaggerated impaired maximal free-water excretion, counteracting the tendency to hypovolaemia, resulting in a compensatory euvolaemic state in the majority of TIH cases.[10] Studies in the

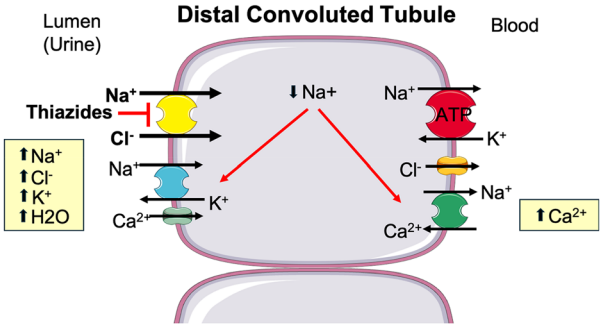

Figure 1 Mechanism of thiazide diuretic action in the distal convoluted tubule of the nephron.

mechanism of thiazides for hypertension have shown a reduction in the extracellular fluid and plasma volume, which returns to normal 4–6 weeks after initiation.[11]

The proposed pathophysiology for euvolaemic hyponatraemia includes (i) reduced distal delivery of filtrate due to reduced glomerular filtration rate from the initial volume depletion and enhanced proximal tubule reabsorption, (ii) inhibition of NCC impairing maximal dilution, (iii) hypovolaemia resulting in a baroreceptor-mediated release of arginine vasopressin (AVP) (also known as antidiuretic hormone), (iv) increased collecting duct water permeability via AVP-independent mechanisms involving luminal prostaglandin and direct effects of thiazide and (v) reduced urea solute load (Fig. 2).[12] Furthermore, thiazides may directly increase prostaglandin E2 (PGE2) synthesis. PGE2 reaching the lumen is able to stimulate PGE2 receptor subtype 4 (EP4), causing insertion of aquaporin 2 (AQP2) in the absence of AVP, and directly reduce urine dilution, causing osmotic water reabsorption.[12]

Thus, TIH can present as either a hypovolaemic state or a euvolaemic state, similar to the presentations described for the classical syndrome of inappropriate antidiuresis (SIAD) relative to the duration of treatment and active pathophysiology.

Clinical features

TIH often occurs in elderly multimorbid individuals, in particular females. This may be due to age-related impairment in free water excretion, hypokalaemia, low body weight and high fluid intake.[4] TIH typically occurs within 2 weeks, although it can develop later (months or years) after commencement.[10] Dose dependency of hyponatraemia has not been uniformly described. Concomitant use of non-steroidal anti-inflammatory drugs can increase the risk of TIH due to decreased free water clearance through prostaglandin inhibition.[4] Antidepressants such as selective serotonin reuptake inhibitors and anticonvulsants may be associated with inappropriate AVP secretion predisposing to TIH.[13]

Differentiation of hypovolaemic versus euvolaemic presentations of TIH

Accurate differentiation between hypovolaemic and euvolaemic subtypes of TIH is important, as it enables timely initiation of appropriate therapy and thereby may aid time to resolution. Detailed physical examination to assess the fluid status, such as haemodynamic measure, jugular venous pressure and the presence of peripheral oedema, is assistive. However, it can be challenging to

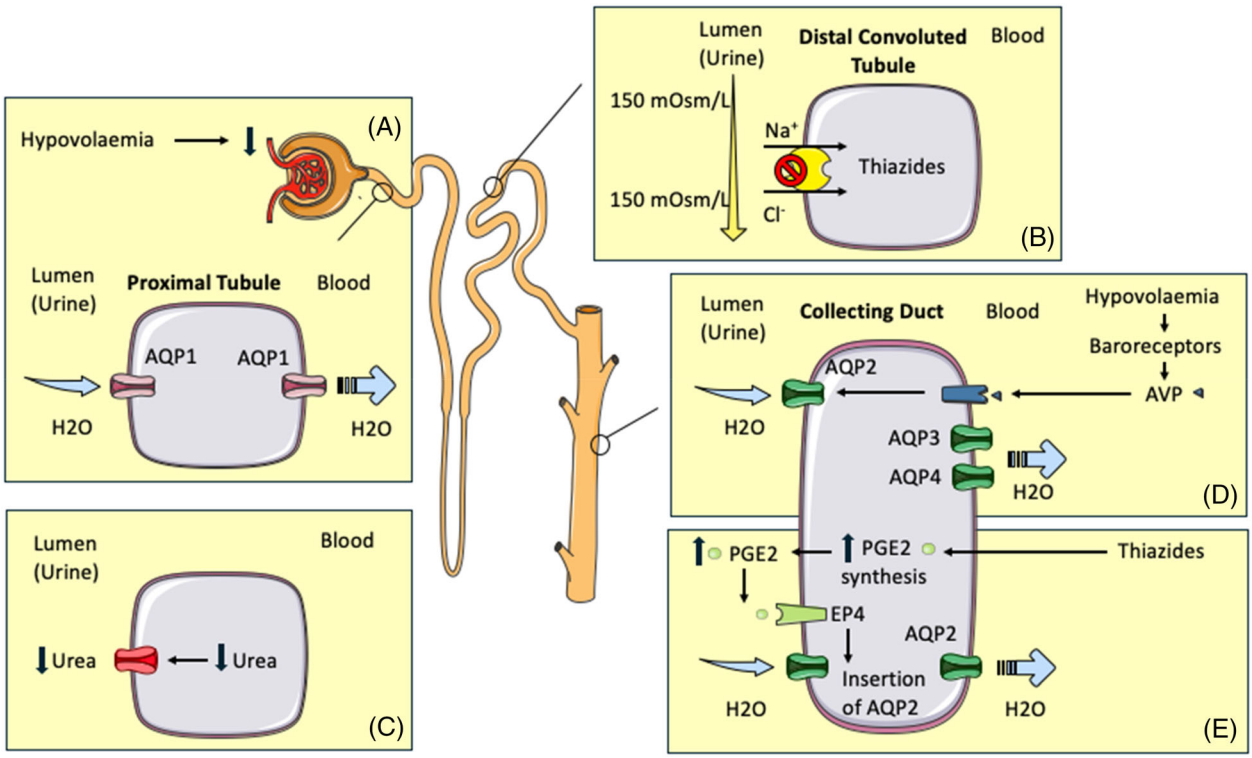

Figure 2 Hypothesised pathophysiology of impaired maximal free-water excretion in thiazide use. (A) Reduced distal delivery of filtrate due to reduced glomerular filtration rate from the volume depletion and enhanced proximal tubule reabsorption. (B) Inhibition of NCC impairing maximal dilution. (C) Reduced urea solute load. (D) Hypovolaemia resulting in a baroreceptor-mediated release of AVP. (E) Increased collecting duct water permeability via AVP-independent mechanisms involving luminal prostaglandin and direct effects of thiazide. AQP, aquaporin; AVP, arginine vasopressin; DCT, distal convoluted tubule; EP4, PGE2 receptor subtypes 4; GFR, glomerular filtration rate; H_2O, water; NCC, sodium chloride cotransporter; PGE2, prostaglandin E2.

clinically differentiate mild hypovolaemia from euvolaemia. Serum and urine biochemistry are useful for discernment of fluid status. Serum urea and uric acid levels are high (or high normal) in hypovolaemic states but typically lower in euvolaemic states or SIAD.[14] In a diuretic-naïve setting, urine sodium is a helpful tool to help differentiate hypovolaemic hyponatraemia (urine sodium <20 mmol/L) from SIAD (urine sodium >40 mmol/L).[14] However, urine sodium is elevated with thiazide diuretics, even in hypovolaemic states. Also, urine osmolality is elevated in TIH, typically exceeding serum osmolality[10]; however, it does not aid in the differentiation of the volume status.

Urine potassium and chloride levels have been proposed as useful tools in distinguishing between the two subtypes of TIH. A post hoc analysis of a prospective study involving hospitalised patients with severe TIH suggested that the simplified apparent strong ion difference in serum electrolytes (sodium + potassium − chloride) >42 mmol/L may help identify those with hypovolaemic TIH with a positive predictive value (PPV) of 79.1%.[15] In contrast, a value of <39 mmol/L excluded hypovolaemic TIH with a negative predictive value (NPV) of 76.5%.[15] For intermediate values (39–42 mmol/L), urine chloride and potassium score (urine chloride − potassium) and the fractional excretion of uric acid (FEUA) can serve as secondary markers to

Table 1 Serum and urine biochemistry to differentiate hypovolaemic versus euvolaemic subtypes of TIH[15]

Serum and urine biochemistry	Hypovolaemic subtype	Euvolaemic/SIAD-mimic subtype
Serum sodium + potassium − chloride	>42 mmol/L (PPV 79.1%)	<39 mmol/L (NPV 76.5%)
Urine chloride − potassium	<15 mmol/L (PPV 100%, NPV 83.3%)	
Fractional uric acid excretion†	<12% (PPV 85.7%, NPV 64.3%)	
Serum bicarbonate	>28 mmol/L (PPV 72.7%, NPV 31.5%)	

†In those with intermediate serum sodium + potassium − chloride value (39–42 mmol/L).NPV, negative predictive value; PPV, positive predictive value; SIAD, syndrome of inappropriate diuresis; TIH, thiazide-induced hyponatraemia.

clarify the diagnosis.[15] Low urine chloride, which indicates hypovolaemia,[16] triggers renin release and intercalated cell activation, further depleting urine potassium in patients using thiazides.[17] Urine chloride and potassium score of <15 mmol/L had a PPV of 100% and a NPV of 83.3%.[15] In hypovolaemic states, low effective circulating volume leads to increased reabsorption of uric acid in the renal proximal tubules, resulting in a low FEUA.[18] A

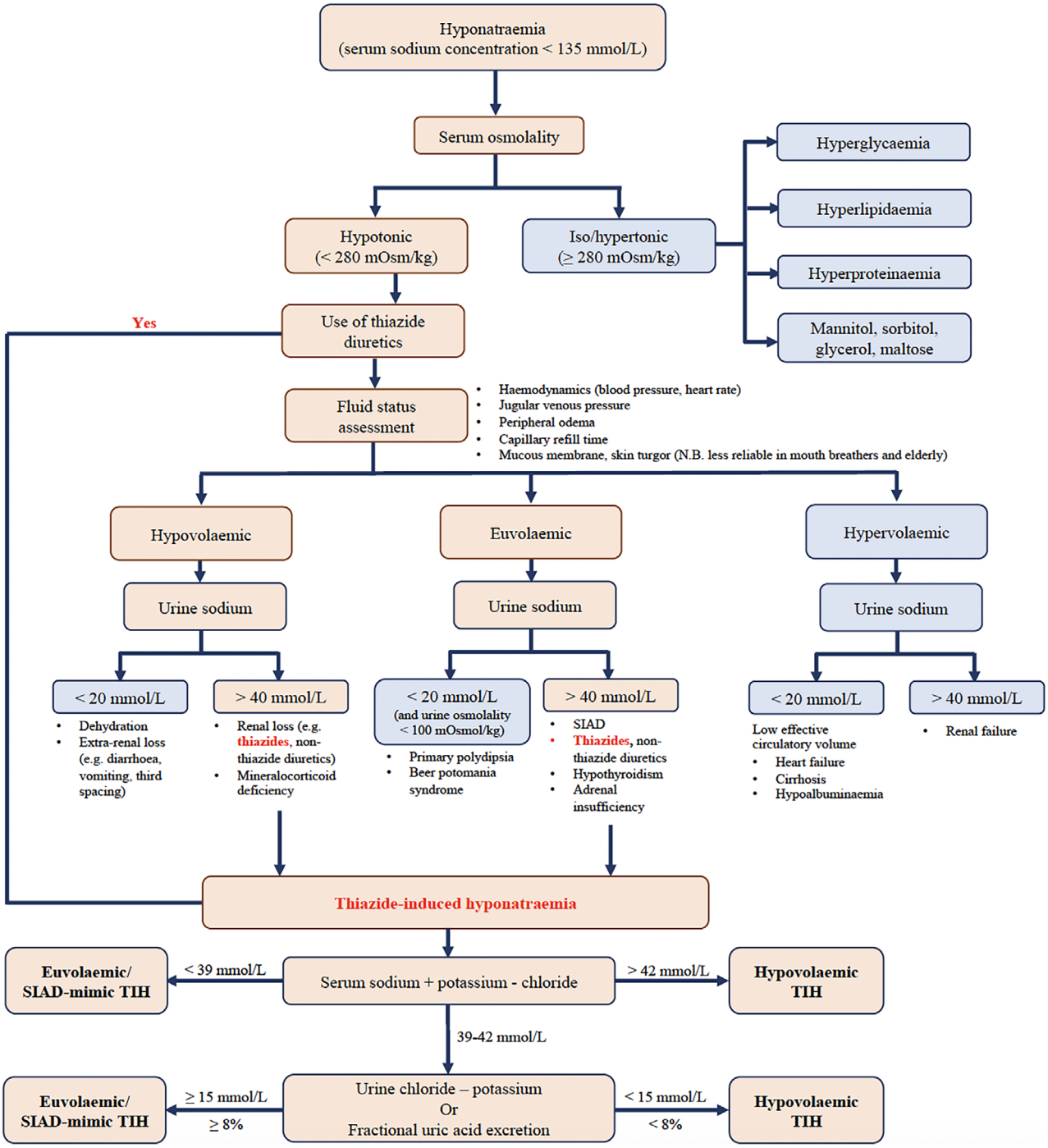

Figure 3 The proposed practical algorithmic approach to evaluating TIH with serum and urine biochemistry to differentiate euvolaemic and hypovolaemic subtypes of TIH. SIAD, syndrome of inappropriate antidiuresis; TIH; thiazide-induced hyponatraemia. Adapted from UpToDate,[20] Cumming *et al.*[21] and Potasso *et al.*[15]

FEUA of <12% had a PPV of 85.7% and an NPV of 64.3% in identifying patients with hypovolaemic TIH (Table 1).[15] Similarly, a FEUA cut-off of >12% has been suggested for diagnosing euvolaemic/SIAD hyponatraemia.[19] These serum and urine biochemical tests can assist in clinical judgement, which can lead to early accurate determination of the TIH subtypes to guide prompt management. We propose a practical algorithm to assist evaluating TIH (Fig. 3).

Management of TIH

In individuals with severe symptoms of hyponatraemia, such as seizures or reduced consciousness, hypertonic saline (sodium chloride 3% 100 mL up to 3 doses) is indicated to increase the serum sodium concentration by 4–6 mmol/L to reduce the intracranial pressure.[5] Subsequently, whether fluid restriction versus volume replacement with 0.9% NaCl is required depends on the subtype. In euvolaemic TIH, fluid restriction is recommended. In contrast, for hypovolaemic TIH, which is not improving with thiazide cessation alone, intravenous fluid replacement (e.g. sodium chloride 0.9%) is recommended. Overt hypovolaemia accompanied by hypotension and elevated urea should be managed with intravenous fluid replacement prior to obtaining detailed urine biochemistry results, in order to prioritise haemodynamic stabilisation. Evaluation of the response to fluid therapy is important to guide further fluid prescription, including its administration rates. The thiazide should be ceased and such adverse drug reactions documented to avoid future prescription. The rate of correction should be limited to 8–10 mmol/L per 24 h, as per guidelines and expert recommendations.[22,23]

In TIH, as relative hypovolaemia is resolved after initiating fluid resuscitation, it can remove the drive for AVP secretion, triggering an aquaresis, which may lead to rapid over-correction of hyponatraemia. Monitoring the urine output to detect polyuria is crucial for detecting the potential for overcorrection. High-dependency or intensive care settings are recommended for severe cases of hyponatraemia to enable intensive clinical and biochemical monitoring for timely treatment intervention to minimise the risk of osmotic demyelination syndrome from overcorrection.

Limitations

In some instances, multiple causes of hyponatraemia may be apparent, making it more challenging to differentiate the underlying mechanism and management. For instance, a patient may present with hyponatraemia in the setting of both pneumonia, which can cause SIAD, and concomitant use of a thiazide drug. Urine biochemistry may be repeated after the diuretic washout to further delineate the underlying predominant aetiology. Importantly, treatment responses to fluid restriction or fluid resuscitation can aid in understanding the underlying predominant aetiology. It is also important to appreciate that TIH presentations may occur on a continuum whereby hypovolaemic states might evolve into euvolaemic states or vice versa.

Conclusion

TIH is a common cause of hospital presentations for hyponatraemia and a relatively common adverse drug reaction. TIH presentations are typically characterised by euvolaemia; however, hypovolaemic presentations should be considered. Discriminating hypovolaemic from euvolaemic presentations can be challenging for physicians. Assessing serum (sodium, potassium, chloride) and urine (chloride, potassium) biochemistry in detail to distinguish TIH presentations can guide therapy. Regardless of the underlying presentations, thiazide should be withheld and, in severe cases, ceased. Euvolaemic TIH presentations require fluid restriction, while hypovolaemic TIH not responsive to thiazide cessation requires volume resuscitation. The proposed algorithm may assist in clinical judgement for early and accurate determination of the subtypes, enabling prompt management and reduced hospital LOS. Larger prospective studies are warranted to evaluate the utility of serum and urine biochemistry in differentiating TIH states and their management.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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