



ORIGINAL ARTICLE

A novel clinical nomogram for the evaluation of disorders of plasma osmolality

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ABSTRACT

Abstract. Disorders of water and sodium homeostasis in the human body—or dysnatraemias—are frequently encountered in clinical practice, but their analysis is often complex and their management is often troublesome. For many clinicians, it remains challenging to correctly interpret all relevant biochemical parameters involved in the analysis of dysnatraemia, especially when a rapid ‘bedside’ evaluation is required to initiate treatment. By mathematically deriving the relationship between plasma osmolality and urine osmolality under physiological circumstances, we were able to propose a novel and clinically useful nomogram for the rapid evaluation of disorders of plasma osmolality. We believe that the presented osmolality nomogram could be a transparent and clinically useful tool for the quick evaluation of disorders of the water and sodium balance in patients.

Keywords: clinical nomogram, plasma osmolality, urine osmolality

INTRODUCTION

Disorders of water and sodium homeostasis in the human body—or dysnatraemias—are frequently encountered in clinical practice, but their analysis is often complex and their management is often troublesome. The most notable example is hypotonic hyponatraemia, which has been consistently linked to increased morbidity and mortality in hospitalized patients [1, 2]. For many clinicians it remains challenging to correctly interpret all relevant biochemical parameters involved in the analysis of dysnatraemia, especially when a rapid ‘bedside’ evaluation is required to initiate treatment.

An important dogma in renal physiology states that the plasma sodium concentration in the human body, which strongly affects plasma osmolality, is regulated by balancing the retention and excretion of water rather than by retaining or excreting sodium itself [3–6]. This process is governed by

antidiuretic hormone (ADH), an oligopeptide hormone that is secreted by the posterior pituitary gland in response to an increase in plasma osmolality and which stimulates pure water retention by the kidneys through the translocation of aquaporin 2 water channels in the collecting ducts, reducing plasma hypertonicity [3–6]. Based on these well-known principles, we can mathematically derive the relationship between the measured plasma osmolality and urine osmolality under physiological circumstances. By plotting this relationship as a graph, we were able to propose a novel and clinically useful nomogram for the rapid evaluation of disorders of plasma osmolality—in some ways analogous to the Siggaard–Andersen nomogram for the interpretation of acid–base disturbances [7]. To the best of our knowledge, this has not been done before.

Below we present our mathematical derivation and extensively discuss our novel clinical nomogram for the interpretation of dysnatraemias.

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PHYSIOLOGICAL BASIS FOR CLINICAL NOMOGRAM

As plasma osmolality (O_p) rises above a threshold of 280 mOsmol/kg ($O_{p,threshold}$), the osmotic stimulus leads to the secretion of ADH or arginine vasopressin from the posterior lobe of the pituitary gland. In the absence of pathological ADH secretion [e.g. syndrome of inappropriate ADH (SIADH) secretion or hypovolaemic stimulus], the plasma ADH concentration ([ADH]) increases linearly with the increase in plasma osmolality [3–5]. Therefore

$$[ADH] = K(O_p - O_{p,threshold}) + [ADH]_{baseline} \quad (1)$$

where K and $[ADH]_{baseline}$ represent the slope of the ADH release per unit of increase in plasma osmolality (which equals ~ 0.5 pg.kg/mL/mOsm for the average healthy adult) and the baseline plasma ADH concentration, respectively [3–5].

Since osmolality-driven ADH release is much greater than the baseline ADH concentration (i.e. $[ADH] \gg [ADH]_{baseline}$), this means

$$[ADH] = K(O_p - O_{p,threshold}) \quad (2)$$

In the case of a normal ADH receptor sensitivity, an increase in the plasma ADH concentration stimulates the retention of pure water in the collecting ducts by increasing water permeability and therefore increases urine osmolality O_u . Since ADH is released almost instantly in response to a change in plasma osmolality, it is reasonable to assume that a steady-state urine osmolality is reached rapidly following a change in plasma ADH concentration [8, 9]. This relationship between urine osmolality and plasma ADH concentration can best be approached by a Michaelis-Menten-like or Hill-like concentration-effect curve (see Figure 1) [10–12]:

$$O_u = \frac{O_{u,max}[ADH]}{[ADH] + [ADH]_{50}} + O_{u,min} \quad (3)$$

Here $[ADH]_{50}$ represents the plasma ADH concentration at which O_u equals $\frac{1}{2}O_{u,max}$ (which is equivalent to ~ 2.0 pg/mL) [10, 11]. Maximum urine osmolality ($O_{u,max}$) is attained at plasma

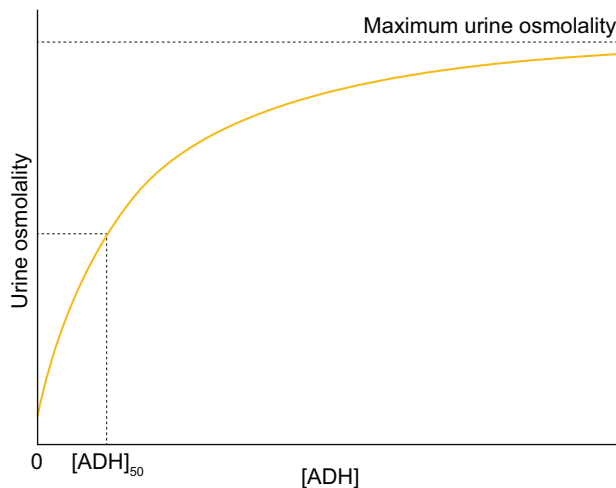


FIGURE 1: Graphic representation of the Michaelis-Menten-like relationship between the plasma ADH concentration ([ADH]) and urine osmolality. Note that this curve cuts the y-axis at $y > 0$, because urine cannot consist of pure water.

ADH concentrations > 5.0 pg/mL, reflecting maximal receptor occupancy by ADH [10–12]. Rearranging Equation (3) produces

$$(O_u - O_{u,min})([ADH] + [ADH]_{50}) = O_{u,max}[ADH] \quad (4)$$

$$(O_u - O_{u,min})[ADH] + (O_u - O_{u,min})[ADH]_{50} = O_{u,max}[ADH] \quad (5)$$

$$[ADH] = [ADH]_{50} \left(\frac{O_u - O_{u,min}}{O_{u,max} + O_{u,min} - O_u} \right) \quad (6)$$

Combining Equations (2) and (6) yields

$$K(O_p - O_{p,threshold}) = [ADH]_{50} \left(\frac{O_u - O_{u,min}}{O_{u,max} + O_{u,min} - O_u} \right) \quad (7)$$

$$O_p - O_{p,threshold} = \frac{[ADH]_{50}}{K} \left(\frac{O_u - O_{u,min}}{O_{u,max} + O_{u,min} - O_u} \right) \quad (8)$$

where

$$\frac{[ADH]_{50}}{K} \approx \frac{2,0}{0,5} \approx 4 \quad (9)$$

Assuming physiological reference values for $O_{u,min}$, $O_{u,max}$ and $O_{p,threshold}$ for the average healthy adult, this means [3, 4]

$$O_p = 4 \left(\frac{O_u - 50}{1250 - O_u} \right) + 280 = \frac{4O_u - 200}{1250 - O_u} + 280 \quad (10)$$

In order to allow for a certain degree of interindividual variation in both the osmostat sensitivity and the ADH receptor sensitivity in a pragmatic manner, the error band around the derived curve is defined by the following equations, representing the green (lower limit) curve and blue (upper limit) curve in the presented nomogram, respectively:

$$O_{p,lower\ limit} = 3 \left(\frac{O_u - 50}{1250 - O_u} \right) + 275 = \frac{3O_u - 150}{1250 - O_u} + 275 \quad (11)$$

$$O_{p,upper\ limit} = 5 \left(\frac{O_u - 50}{1250 - O_u} \right) + 285 = \frac{5O_u - 250}{1250 - O_u} + 285 \quad (12)$$

where $[ADH]_{50}/K = 3$ and $[ADH]_{50}/K = 5$, respectively, and $O_{p,threshold} = 275$ mOsmol/kg and $O_{p,threshold} = 285$ mOsmol/kg, respectively. In our opinion, this degree of variation between these curves seems physiologically plausible and therefore a reasonable assumption. Plotting the curves of Equations (10), (11) and (12) produces the following nomogram (see Figure 2), which will be further elucidated below:

1. plasma hypotonicity with dilute/intermediate urine, suggesting polydipsia or ‘tea and toast’ syndrome;
2. plasma hypotonicity with intermediate/concentrated urine, suggesting inappropriate ADH release;
3. plasma hypertonicity with urine concentrated beyond the prediction by the curve, suggesting dehydration with non-osmolality-driven (e.g. hypovolaemia-driven) ADH release on top of osmolality-driven ADH release;
4. plasma hypertonicity with dilute/intermediate urine, suggesting complete diabetes insipidus;
5. Plasma hypertonicity with inadequately concentrated urine, suggesting partial diabetes insipidus;

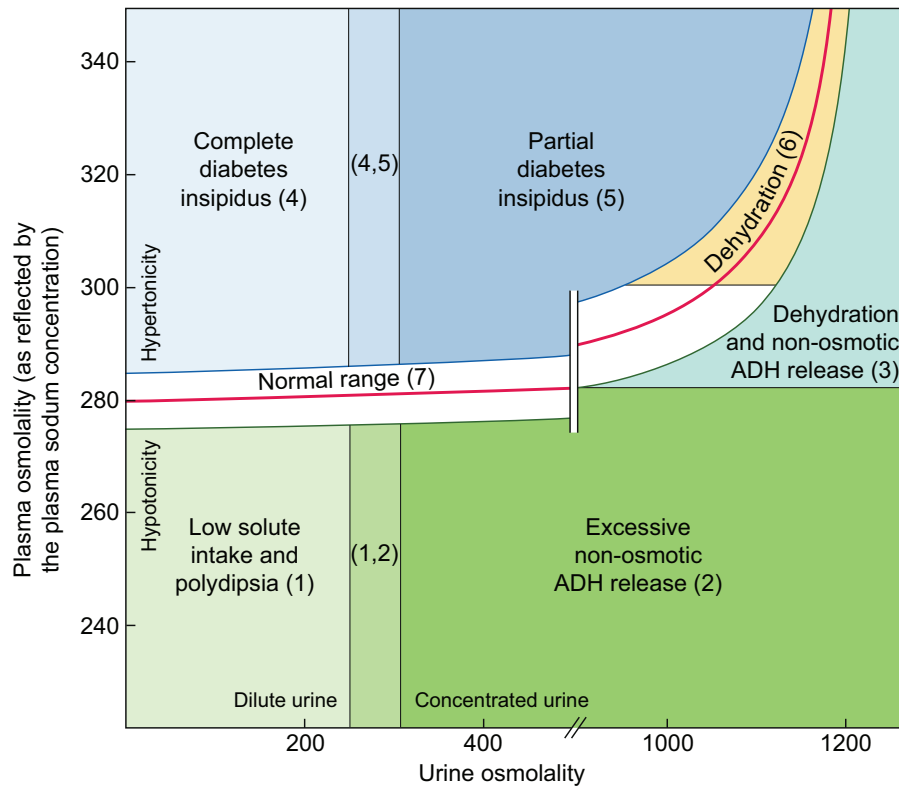


FIGURE 2: Osmolality nomogram depicting the physiological relationship between the measured plasma osmolality (y-axis, in mOsmol/kg) and urine osmolality (x-axis, in mOsmol/kg) under the assumption of osmolality-driven ADH release (grey-shaded areas). This nomogram is only valid on the conditions that the renal ability to concentrate urine is intact and that plasma osmolality is reflected by the plasma sodium concentration (which is not true if the plasma concentration of an effective non-electrolyte solute is significantly elevated). The the colour gradients represent the transitions between overlapping areas.

6. plasma hypertonicity with adequately concentrated urine (area shaded dark gray), suggesting pure dehydration (defined as plasma tonicity >300 mOsmol/kg) and
7. plasma normotonicity with a variable degree of urine concentration (area shaded light gray), corresponding to the normal or physiological range of plasma osmolality.

DISCUSSION

In the previous section we mathematically derived the physiological relationship between the measured plasma osmolality and urine osmolality. This derivation rests on two main pillars, namely the (approximately) linear increase of ADH release in response to an increase in plasma osmolality above the physiological threshold of 280 mOsmol/kg, and the Michaelis-Menten-like or Hill-like concentration-effect kinetics of ADH-mediated renal water retention [3, 4, 10, 11]. The resulting Equation (10) can be plotted graphically with a certain error band [Equations (11) and (12)], accounting for interindividual variation in both the osmostat sensitivity and the ADH receptor sensitivity [8, 9]. This results in our nomogram (Figure 2), which can be used by clinicians for a dysnatraemia evaluation at a glance. This being said, including the relevant patient characteristics in the analysis remains imperative, as evidenced below.

Because the derived curve represents the physiological relationship between plasma osmolality and urine osmolality, resulting from an 'appropriate' osmolality-driven ADH release from the posterior pituitary gland, many points outside this curve represent disorders that are characterized by a

pathological release of ADH or a pathological response to ADH. The most important examples of these are non-osmolality-driven ADH release (Areas 2 and 3), such as hypovolaemic ADH release (when intravascular volume depletion exceeds $\sim 5\%$) and SIADH secretion, and complete and partial diabetes insipidus (Areas 4 and 5, respectively) [13, 14]. SIADH and hypovolaemia-mediated ADH release can often be distinguished by the degree of natriuresis, which is generally >30 mmol/L in SIADH, reflecting euvolaemia and <20 mmol/L in hypovolaemia as a result of activation of the renin-angiotensin-aldosterone system [13, 14]. As mentioned before, osmolality-driven ADH release starts when plasma osmolality rises above 280 mOsmol/kg and the plasma ADH concentration is almost immeasurably low at plasma osmolality values well below 280 mOsmol/kg. As a result of this, the human body is unable to respond to hypotonicity of the plasma by altering ADH release, as the plasma ADH concentration already is negligible under these circumstances [3-5]. Therefore disorders such as polydipsia and 'tea and toast' syndrome are also located outside of the physiological curve in the presented nomogram (Area 1), although these conditions are not the result of an aberrant ADH release or response [13, 15]. The urine osmolality in these disorders is low, as the kidneys will optimize their free water clearance by excreting as much water per osmole in the urine as possible [13, 15, 16].

It can easily be seen in the presented nomogram is that plasma osmolality remains relatively constant for a wide range of urine osmolality values in the absence of an underlying disorder (Area 7, shaded in light grey). This reflects the renal ability

to effectively retain or excrete water in order to maintain homeostasis [3–5]. Only when the steep (right-sided) part of the shoulder of the curve is reached does it become increasingly difficult—and eventually impossible—for the kidneys to maintain the desired plasma osmolality, as the urine cannot become more concentrated than the physiological upper limit for urine osmolality ($O_{u,max}$), which equals ~1200 mOsmol/kg—although some variability between persons exists [3–5]. By definition, dehydration occurs when the plasma osmolality increases to >300 mOsmol/kg (Area 6, shaded in dark grey), despite an adequate attempt by the kidneys to conserve water by maximally concentrating the urine they produce [17].

The application of our nomogram can be demonstrated by the following four patient cases from our clinic (see Figure 3).

Patient A, a 66-year-old male who had recently undergone radiation therapy and neurosurgery for a glioblastoma was admitted to the Internal Medicine ward with polyuria (up to 8 L of urine per day), polydipsia and hypertonic hypernatraemia. His plasma sodium concentration was 151 mmol/L with a plasma osmolality of 297 mOsmol/kg and a urine osmolality of 167 mOsmol/kg. Desmopressin was administered, and based on the significant increase in urine osmolality, a diagnosis of central diabetes insipidus was made (Area 4 in our nomogram).

Patient B, a 31-year-old Russian male with a documented medical history of schizophrenia and alcohol abuse presented to our Emergency Department with nausea, lethargy and hypotonic hyponatraemia. His plasma sodium concentration was 125 mmol/L with a plasma osmolality of 255 mOsmol/kg and a urine osmolality of 57 mOsmol/kg. On further inquiry, this patient admitted to drinking several litres of beer per day without eating properly. A diagnosis of potomania or ‘beer-drinker’s hyponatraemia’, in essence a combination of ‘tea and toast’ syndrome and primary polydipsia, was made (Area 1 in our nomogram). He quickly improved with an adequate diet.

Patient C, an 82-year-old woman, was admitted to the Pulmonology ward with pneumonia. Her blood tests also showed a hypotonic hyponatraemia with a plasma sodium concentration of 122 mmol/L, a plasma osmolality of 264 mOsmol/kg and a urine osmolality of 345 mOsmol/kg. A diagnosis of SIADH as a result of pneumonia was made (Area 2 in our

nomogram). Her plasma sodium concentration responded well to moderate fluid restriction, after which she was discharged.

Patient D, a 79-year-old male was admitted to the Psychiatry ward with complaints of dysphoria for which he was treated with citalopram, a selective serotonin reuptake inhibitor. A routine blood test revealed mild and asymptomatic hypotonic hyponatraemia with a plasma sodium concentration of 129 mmol/L, a plasma osmolality of 271 mOsmol/kg and a urine osmolality of 766 mOsmol/kg. A diagnosis of SIADH as a result of chronic citalopram use was made (Area 2 in our nomogram). The citalopram was discontinued.

It should be noted that the presented physiological curve in our nomogram applies to the average healthy adult. The renal ability to concentrate the urine diminishes with age and with chronic kidney disease [18, 19]. As mentioned before, the maximum urine osmolality equals ~1200 mOsmol/kg in the average healthy adult <60 years of age but is reduced by ~20% in persons 60–80 years of age [3, 4, 18]. A left shift of the curve will occur in these elderly patients because their maximum urine osmolality is often reached at values somewhere between 700 and 900 mOsmol/kg and they are unable to concentrate their urine any further in order to retain pure water [18]. Chronic kidney disease might also limit the renal ability to concentrate urine, possibly due to a disrupted microanatomy of the inner medulla [19]. Another limitation of our clinical nomogram is that it is primarily intended for monofactorial disorders of plasma osmolality. Whenever a clinician suspects multiple concurrent causes underlying a patient’s dysnatraemia, caution is warranted when relying on this nomogram. An exception to this limitation is dehydration with concurrent non-osmolality-driven ADH release on top of regular osmolality-driven ADH release, which is represented by Area 3 in Figure 2. The fact that plasma hypertonicity occurs in the context of excessive ADH release suggests coexisting dehydration, in which intravascular volume depletion is the most likely stimulus for ADH release [13]. Lastly, as mentioned in the legend of Figure 2, our nomogram is only valid on the condition that plasma osmolality is reflected by the plasma sodium concentration, which is not true if the plasma concentrations of effective non-electrolyte solutes (such as glucose or mannitol) are strongly elevated.

In conclusion, we strongly believe that the presented osmolality nomogram could be a transparent and clinically useful tool for the quick ‘bedside’ evaluation of disorders of the water and sodium balance in patients. However, we would like to emphasize that our nomogram should be considered an aid in analysing dysnatraemia; a thorough assessment of the relevant patient characteristics remains imperative for every clinical examination.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ETHICAL APPROVAL

The authors declare to have no conflicts regarding ethical approval.

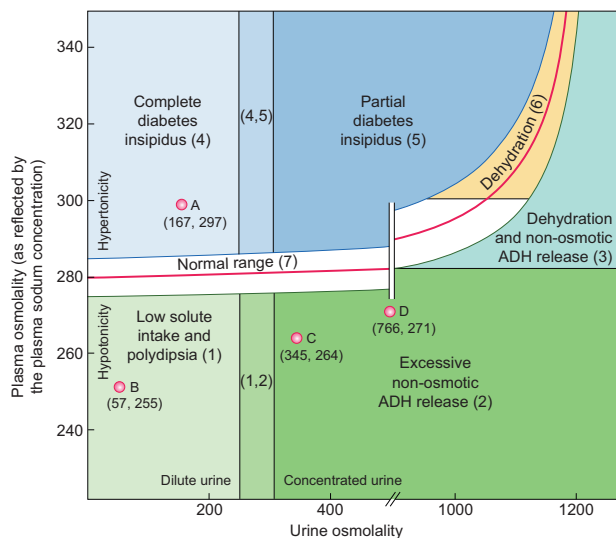


FIGURE 3: Patients A, B, C and D are represented by the red dots (x-coordinate: urine osmolality; y-coordinate: plasma osmolality) and their corresponding letters in the osmolality nomogram.

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