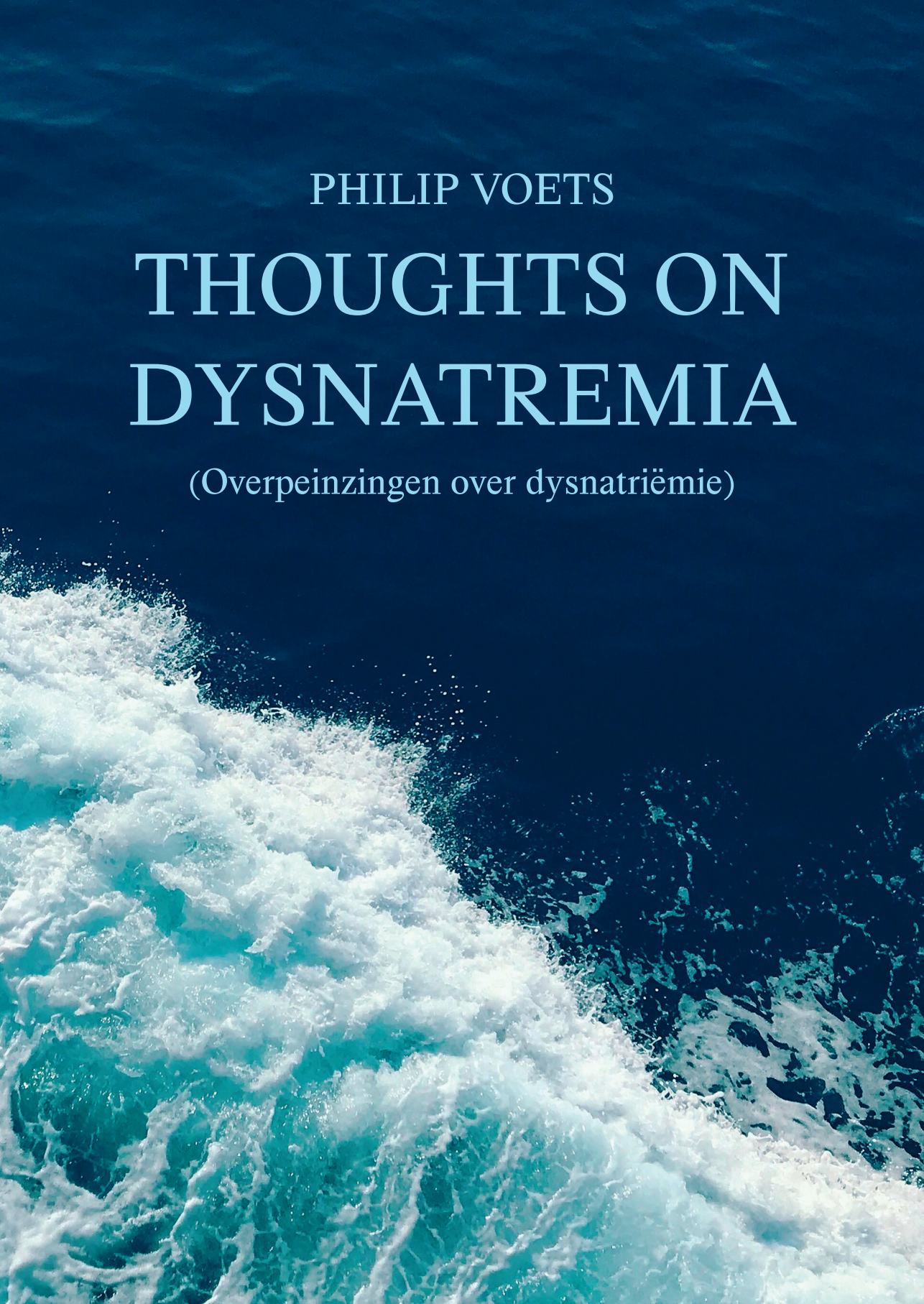
PHILIP VOETS

THOUGHTS ON DYSNATREMIA

(Overpeinzingen over dysnatriëmie)



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Philippus (Philip) Johannes Gerdiaan Maria Voets

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PROMOTOR:

Prof. dr. H.A.H. Kaasjager

COPROMOTOR:

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Aan mijn A(-)ukje en mijn zoon

Aan mijn ouders

TABLE OF CONTENTS

Chapter 1

General introduction

1. SODIUM

Sodium (Latin: *natrium*, symbol: Na) is the eleventh element in Mendelejev's periodic table of elements and belongs to the group of alkali metals. The name "natrium" is probably derived from the Egyptian valley Wadi el Natrun, which contains large sodium salt deposits.[1] Sodium has an electron configuration of $1s^2 2s^2 2p^6 3s^1$ or [Ne]$3s^1$, and therefore needs to lose only one electron from its 3s orbital in order to attain a more stable noble gas configuration with a full valence shell. Thus, almost all of the sodium exists as a cation with an oxidation state of 1+. The ionic assembly of the cation sodium and the anion chloride is often referred to simply as "salt". Sodium is the most important electrolyte (an ion dissolved in body water) in the extracellular fluid compartment in the human body, whereas it is a fairly minor electrolyte in the intracellular compartment (see Figure 1.1).[2] Its main biological functions are generating action potentials in several types of excitable cells, and osmoregulation.[2] The latter, and addressing difficulties encountered in the approach to its disorders, are the focus of this thesis.

2. WATER AND SODIUM BALANCE IN THE HUMAN BODY

Some authors have claimed that the salt composition of human plasma is a direct reflection of the salt composition of the primordial seas and oceans, the environment in which all life most likely began.[3] Although this hypothesis certainly is elegant, its scientific validity remains open for debate, especially because the salt content of these seas and oceans has changed dramatically over the eras and their original composition cannot be known for sure. Notwithstanding these evolutionary considerations, the plasma sodium concentration (reference range: 135 – 145 mmol/L, measured by ion-selective electrode or by flame photometry) is by far the most important determinant of the plasma tonicity, and therefore regulates osmotic movement of water between the fluid compartments in the human body (see Figures 1.1 and 1.2).[2] The eponymous Edelman equation describes the plasma sodium concentration as a function of total body exchangeable sodium and potassium ($Na_e^+ + K_e^+$)

and total body water (*TBW*), based on experimental work in 98 human patients in 1958:[4]

$$[Na^+]_p = \frac{1.11\left(Na_e{}^+ + K_e{}^+\right)}{TBW} - 25.6 \approx \frac{Na_e{}^+ + K_e{}^+}{TBW} \quad (1)$$

The equation on the right is known as the 'simplified' Edelman equation or Rose equation (which will be applied in some of the following chapters). The influence of the potassium mass balance on the plasma sodium concentration in the human body has been established conclusively by Edelman *et al.*, but is not conceptually self-evident. It could be explained by potassium-induced sodium shifts between the intracellular and extracellular compartments to maintain electroneutrality.[5] Indeed, Laragh *et al.* have shown experimentally that the plasma sodium concentration of hyponatremic patients can be increased by administering potassium. [6]

Sensu stricto, plasma tonicity is not synonymous with plasma osmolality (in mOsmol/kg) or plasma osmolarity (in mOsmol/L), since the latter two also incorporate osmotically inert solutes. These terms are often used interchangeably in clinical settings. Plasma tonicity should therefore be thought of as effective plasma osmolality, and its calculation –unlike that of plasma osmolality– does not include the plasma urea concentration, which has classically been considered an ineffective osmole. Urea can, however, be an effective osmole in urine when its concentration in electrolyte-poor urine is significantly higher than the interstitial urea concentration.[7] Plasma tonicity is calculated as follows (the factor 2 accounts for anions):

$$Plasma\ tonicity \approx 2([Na^+]_p + [K^+]_p) + [Glucose]_p \quad (2)$$

An elevated plasma sodium concentration (>145 mmol/L), also known as hypernatremia, will most often lead to plasma hypertonicity, whereas a decreased plasma sodium concentration (<135 mmol/L), also known as hyponatremia, will lead to plasma hypotonicity.[8] A clinically important

exception to this rule is normotonic or hypertonic hyponatremia. Here, the presence of excessive amounts of lipids (e.g., hypertriglyceridemia) or proteins (e.g., paraproteinemia) distorts measurement of the plasma sodium concentration by indirect ion-selective electrode assays.[8] Plasma hypertonicity will draw water out of the cells, whereas water will move into the cells as a result of plasma hypotonicity. An essential principle in osmoregulation – and vital for the understanding of its disorders– is that the plasma sodium concentration is primarily a reflection of the water homeostasis in the human body and only to a lesser extent of its total amount of sodium.[8][9] Increases in total body water dilute the plasma sodium concentration and lead to hypotonic hyponatremia. Conversely, losses of total body water concentrate the plasma sodium concentration and cause hypertonic hypernatremia. Significant changes in total body water usually result from a change in water intake or renal water clearance. Significant insensible water losses (e.g., perspiration) also occur, especially during disease.

The antidiuretic hormone (ADH) or arginine vasopressin (AVP) plays a pivotal role in renal water handling. This nonapeptide hormone is produced by the magnocellular neurosecretory cells in the hypothalamic supraoptic and paraventricular nuclei, and is released from the posterior pituitary gland in response to a range of stimuli. The primary stimulus is an increase in plasma osmolality (more precisely: *effective* plasma osmolality[10]), which osmotically deforms central osmoreceptors and activates stretch-inhibited cation channels (see Chapter 3 and Figure 1.3).[8][10] This results in thirst, water-seeking behaviour, and ADH release.[8] Other stimuli for ADH release are intravascular volume depletion (see Chapter 8), pain, and certain drugs. ADH stimulates the translocation of aquaporin-2 water channels in the collecting ducts by binding to the basolateral V_2 receptor on epithelial cells and activating G protein-coupled receptor signaling pathways (see Figure 1.4).[11] This promotes pure water reabsorption by the kidneys, granted that their medullary interstitial gradient allows osmotic water fluxes from the collecting duct lumen to the interstitium, where it is reabsorbed into the circulation via the vasa recta. This decreases plasma tonicity and shuts off central ADH release in a negative feedback loop.[11]

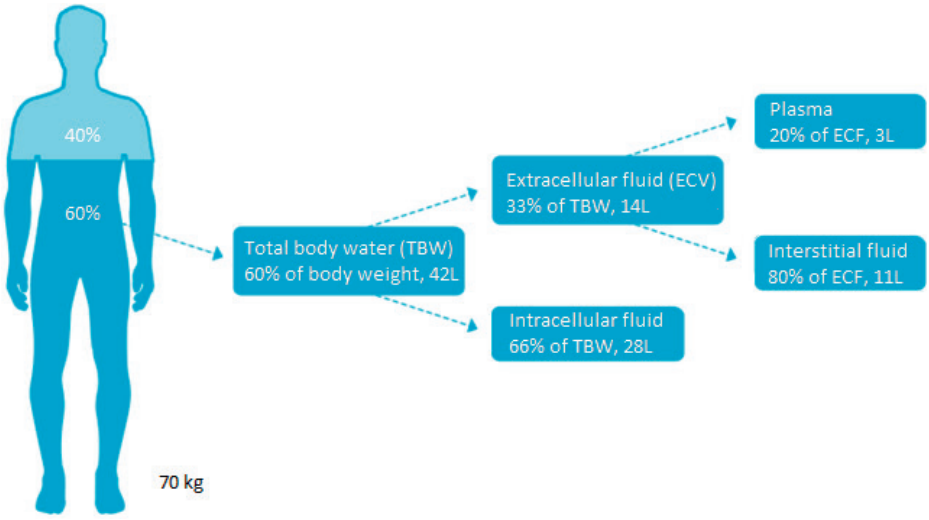

Figure 1.1: Schematic representation of the major fluid compartments in the human body for an average adult male with a body weight of 70 kilograms.

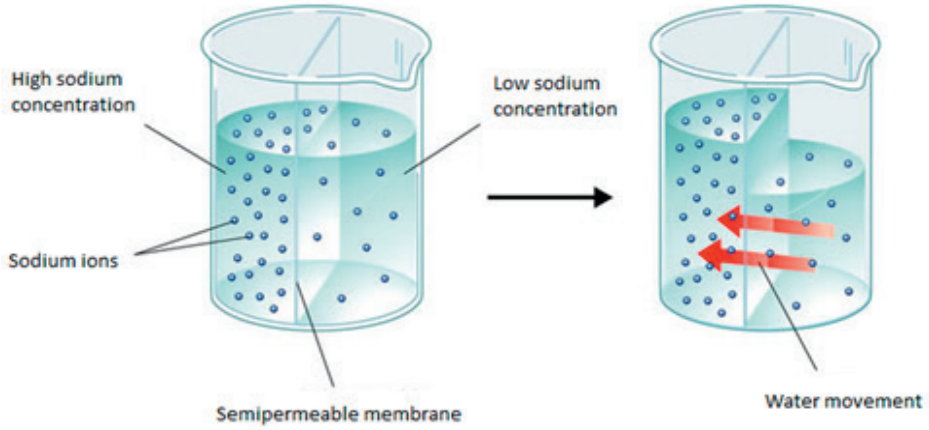

Figure 1.2: Representation of osmosis. As a result of a difference in tonicity between two compartments, separated by a semipermeable membrane, water moves from the compartment with a low tonicity to the compartment with a high tonicity until tonicity equalization has occurred between these compartments (adapted from: Biology 11 (online blog), consulted on: 13 June 2021).

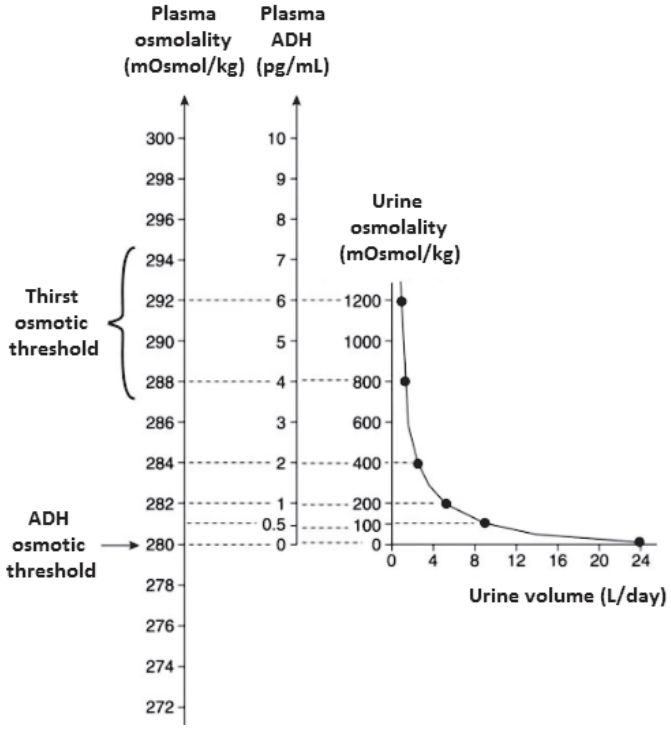

Figure 1.3: Graphic representation of the physiological relationship between the (effective) plasma osmolality, plasma antidiuretic hormone (ADH) concentration, urine osmolality, and daily urine production for an average, healthy adult. As plasma osmolality rises above a threshold of 280 mOsmol/kg, the osmotic stimulus will lead to thirst, and ADH secretion from the pituitary gland in an approximately linear fashion.[12]

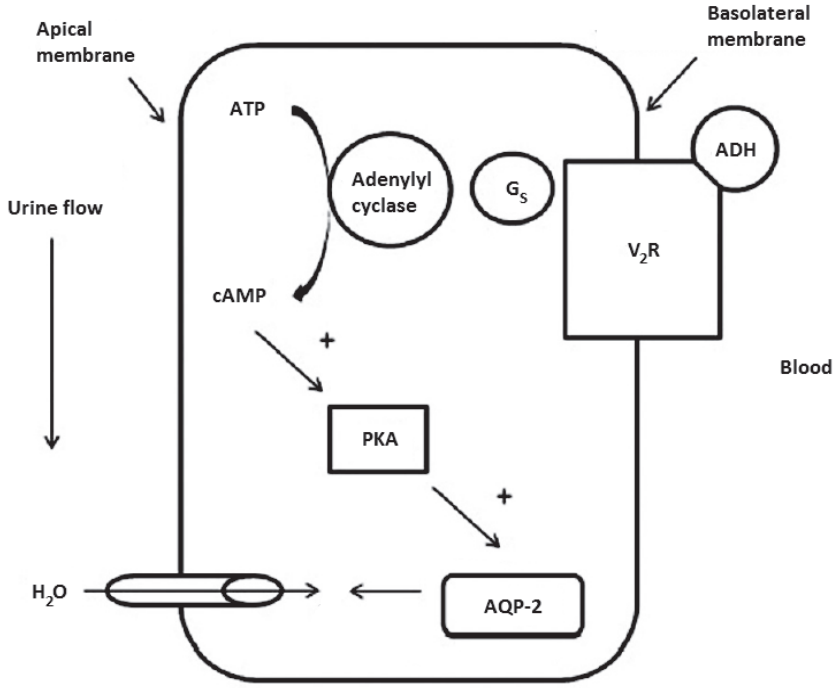

Figure 1.4: Schematic representation of renal water retention by the collecting duct epithelial cells. When antidiuretic hormone (ADH) binds to the basolateral vasopressin-2 receptor (V_2R), a G protein-coupled receptor, the enzymatic conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP) by adenylyl cyclase is stimulated. A rise in the intracellular cAMP concentration activates protein kinase A (PKA), which stimulates the translocation of aquaporin-2 water channels (AQP-2) from cytosolic vesicles to the apical cell membrane. This makes the apical membrane of the collecting duct epithelial cells permeable to water. The basolateral membrane is permeable to water due to the presence of constitutively expressed aquaporin-3 and aquaporin-4 water channels (not shown in the figure above). Water then passively flows through these collecting duct epithelial cells from the relatively hypotonic collecting duct lumen to the relatively hypertonic renal medullary interstitium, where it is transported back to the blood by the vasa recta.[11]

3. SOLUTE-FREE WATER CLEARANCE VERSUS ELECTROLYTE-FREE WATER CLEARANCE

In the previous section, it has been made clear that renal water handling plays a pivotal role in osmoregulation in the human body. A convenient physiological concept in this regard is 'free water clearance' (see Chapters 4 and 5). The terms 'free water' and 'pure water' refer to water in which other substances are absent. These substances can be either solutes in general (solute-free water clearance or SFWC) or –more specifically– electrolytes (electrolyte-free water clearance or EFWC). The main difference between SFWC and EFWC is the renal urea clearance.[13] Shimizu *et al.* have shown that EFWC should be considered the more accurate parameter with respect to regulation of the plasma sodium concentration.[13] Hypertonic hypernatremia due to osmotic urea diuresis is an excellent example of why the SFWC, which is negative in these patients due to the massive urinary urea excretion, should be considered misleading with regard to the plasma sodium concentration and plasma osmolality. The more accurate EFWC, which is positive in these patients due to their low concentration of electrolytes in their urine, easily explains the development of hypernatremia in this case.

The central idea behind EFWC is that a certain volume of urine produced per unit of time ($\dot{V}_u$) –when compared to plasma– can be thought of as a volume with an isotonic electrolyte concentration plus or minus a certain volume of electrolyte-free water. This is expressed as:

$$\dot{V}_u = C_{electrolytes} + EFWC = \dot{V}_u \frac{[E^+]_u}{[E^+]_p} + EFWC \approx \dot{V}_u \frac{[E^+]_u}{[Na^+]_p} + EFWC \tag{3}$$

Which can be rewritten as:

$$EFWC = \dot{V}_u - \dot{V}_u \frac{[E^+]_u}{[Na^+]_p} = \dot{V}_u \left(1 - \frac{[E^+]_u}{[Na^+]_p}\right) \tag{4}$$

When the electrolyte-free water clearance is neither positive nor negative ($EFWC = 0$), the urine is isotonic with regard to plasma, and electrolyte clearance ($C_{electrolytes}$) equals $\dot{V}_u$ (i.e., $[E^+]_u / [Na^+]_p = 1$). When urine is hypertonic as

compared to plasma, the free water clearance is negative (*EFWC*<0; i.e., free water is reabsorbed from urine), whereas the free water clearance is positive when urine is hypotonic as compared to plasma (*EFWC*>0; i.e., free water is excreted in urine).[13] The electrolyte-free water balance –the difference between electrolyte-free water intake and clearance– determines the plasma sodium concentration.

4. CLINICAL ASPECTS OF DYSNATREMIA: HYPONATREMIA AND HYPERNATREMIA

Dysnatremias –hyponatremia and hypernatremia, as defined in the previous section– are the most common electrolyte disorders in the general population, and are considered independent risk factors for mortality in hospitalized patients.[14][15] In our opinion and experience, however, their importance is often underestimated. This thesis aims to draw more attention to the clinical relevance of dysnatremia, and to provide clinical tools that will hopefully be of help to any physician who encounters these disorders. Pathophysiologically, dysnatremia symptoms are the result of the abnormal movement of water in the human body, and the presentations of hyponatremia and hypernatremia are very similar.[8] Hyponatremia moves water into the cells, whereas hypernatremia draws water out of the cells.[8][12] When analyzing dysnatremia, the central questions therefore are: "where does water go?" and "is this appropriate?".[8][12] For instance, hypotonic hyponatremia (i.e., a total body water excess) should ideally be accompanied by dilute urine as an appropriate response by the kidneys to excrete this superfluous water. The renal response in primary polydipsia (i.e., production of dilute urine) should thus be considered "appropriate", whereas the relatively concentrated urine in the syndrome of inappropriate ADH secretion (SIADH) should not, as the name of the syndrome already suggests. The brain is especially vulnerable to these osmotic water fluxes. The magnitude of change in plasma sodium concentration (mild versus severe), the rapidity of its onset (acute versus chronic), and patient factors (e.g., nutritional status, which reduces the ability of cells to adapt to a changing environment, or pre-existing neurological pathology, rendering the brain more prone to osmotic effects) all determine the clinical presentation of dysnatremia, which can range from asymptomatic, nausea, and confusion to coma, respiratory depression, and even death.[8] Dysnatremia can also have a warning function (e.g., paraneoplastic SIADH heralding small-cell lung cancer

in a smoking patient) or prognostic function (e.g., a patient with heart failure and otherwise unexplained hyponatremia has a significantly reduced median survival). [16][17]

5. THESIS OUTLINE

The previous sections contain a brief overview of the water and sodium homeostasis in the human body and its disorders, collectively known as dysnatremia. This thesis zooms in on several clinical aspects of dysnatremia, and the struggles for physicians they entail. In **Chapter 2**, we highlight frequently encountered pitfalls in the analysis and treatment of disorders of the water and sodium balance, and we reflect on the "image problem" that dysnatremia seems to have. In **Chapter 3**, we present a novel clinical nomogram with the parameters "urine osmolality" and "plasma osmolality" on the x-axis and y-axis, respectively, that facilitates the initial analysis of monofactorial disorders of the osmoregulation. **Chapter 4** focuses on the derivation of a governing dysnatremia equation, based on an electrolyte-free water balance, which integrates urine osmolality and urine tonicity. This equation describes the relationship between the (change in) plasma sodium concentration and the physiological variables that influence it. In **Chapter 5**, a modification of the abovementioned dysnatremia equation is presented, which can be used to calculate the expected change in plasma sodium concentration in SIADH patients in response to different types and volumes of crystalloid infusate. A retrospective validation of this model in SIADH patients and its comparison to the well-known Adrogue-Madias equation is discussed in **Chapter 6**. An alternative application of our equation in the prevention of osmotic demyelination syndrome is described in **Chapter 7**. In **Chapter 8**, the theoretical relationship between extracellular volume depletion and resultant hypotonic hyponatremia is discussed. **Chapter 9** focuses on the relationship between dysnatremia and coronavirus infectious disease 2019 (COVID-19), as compared to non-COVID-19 respiratory illness, in the form of a retrospective chart study. Lastly, in **Chapter 10** we summarize the research results of this thesis in both English and Dutch, and we reflect on some important remaining questions and future perspectives.

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Chapter 2

Pitfalls in the interpretation and management of dysnatremia: a matter of attitude?

Philip J.G.M. Voets
Barbara C. Van Münster
Katrien C. Castelijns
Nils P.J. Vogtländer
Karin A.H. Kaasjager

Submitted

ABSTRACT

Background: Disorders of the water and sodium balance in the human body have puzzled many physicians over the years and often remain elusive for those lacking experience in their interpretation and management. In our experience, consensus among physicians regarding the cause of dysnatremia in a specific patient and the appropriate treatment strategy is infrequently reached.

Methods and results: A hyponatremia patient case with a short structured interview was described and presented to medical specialists (n = 15; either internists of geriatrists), residents of Internal Medicine (n = 15), and medical students (n = 20) from the Gelre Hospital Apeldoorn and the University Medical Centre Utrecht. These participants were asked to write down the cause(s) of hyponatremia which they considered most plausible and the treatment which they deemed appropriate. They were also asked to comment on their attitude towards dysnatremia. Their anonymized responses were summarized and compared.

Discussion: Consensus among physicians with regard to both the cause and the management of the dysnatremia is only rarely reached. Several factors contribute to these discrepancies, which can broadly be summarized as overreliance on diagnostic and therapeutic algorithms, the multifactorial origin, cognitive bias, and lack of acquaintance with relevant physiological concepts.

Conclusion and recommendations: Despite its frequent occurrence, the clinical approach to dysnatremia seems to be inconsistent. The relatively negative attitude of many physicians towards dysnatremia might be a contributing factor. A “one size fits all” approach in the analysis and management of these disorders should be discouraged, especially in the light of the growing number of multimorbid patients.

1. INTRODUCTION

Dysnatremia –hyponatremia or hypernatremia– is frequently encountered in the clinical practice and often poses a diagnostic and therapeutic challenge for physicians. Although many dysnatremic patients remain asymptomatic (especially if the drop in plasma sodium concentration is mild and the onset is gradual), dysnatremia can cause debilitating symptoms, such as nausea, lethargy, and seizures, and has consistently been associated with a higher mortality in hospitalized patients.[1][2][3] A careful and critical analysis of the etiology of these electrolyte disorders is required for an effective treatment, whereas a treatment based on a misdiagnosis may not only delay the desired correction of the plasma sodium concentration, but may even deteriorate the existing dysnatremia.[4]

Disorders of the water and sodium balance in the human body have puzzled many physicians over the years and often remain elusive for those lacking experience in their interpretation and management, despite the wide range of diagnostic and therapeutic algorithms, flowcharts, and equations that has been developed in order to help evaluate and manage dysnatremia.[3][5] For many, it remains one of the least appealing subjects in medicine, and –in our collective experience– consensus among physicians regarding the cause of dysnatremia in a specific patient and the appropriate treatment strategy is rarely reached.[5][6][7] In this article, we demonstrate this by presenting the case of a dysnatremic patient to several physicians and medical students from our clinics (the Gelre Hospital Apeldoorn and the University Medical Centre Utrecht), asking them to produce a working diagnosis and a proposal for treatment, and summarizing the results. We investigate the general attitude of physicians and medical students towards dysnatremia, highlight pitfalls in the analysis and management, propose possible explanations for the encountered discrepancies, and warn against overreliance on protocols and algorithms.

2. METHODS AND RESULTS

The patient case with a short structured interview described below was presented to medical specialists (n = 20; either internists of geriatrists), residents of Internal Medicine (n = 15), and medical students (n = 20) from the Gelre Hospital Apeldoorn and the University Medical Centre Utrecht. These anonymous participants were asked to write down on paper the cause(s) of hyponatremia which they considered most plausible and the treatment which they deemed appropriate. They were also asked describe their attitude towards hyponatremia. We have deliberately interviewed only internists and geriatrists, rather than doctors from other specialties, because the latter will neither analyze nor treat electrolyte disorders and their views on hyponatremia were therefore considered less relevant. The results of our survey are shown in Tables 1 and 2 and Figure 1.

Patient case description

A 77-year old woman, with a documented history of hypertension, congestive heart failure, mild cognitive dysfunction, and recurrent depressive disorder, is admitted to the Internal Medicine ward with malaise, nausea, and lethargy. She uses paroxetine (20mg, once daily), metoprolol (25mg, twice daily), lisinopril (5mg, once daily), and until three days ago, she used chlortalidone (12.5mg, once daily). Her oral intake has been poor over the past few weeks. Her physical examination is unremarkable, and she does not appear to be dehydrated. Upon admittance, her plasma sodium concentration is 121 mmol/L and her plasma osmolarity is 253 mOsmol/L. Her urine osmolarity on admission is 457 mOsmol/L with a urine sodium concentration of 32 mmol/L. Both hypothyroidism and hypocortisolism are ruled out on clinical and biochemical grounds. Additional blood and urine tests show no abnormalities. The attending physician concludes that hypotonic hyponatremia is the cause of this patient's symptoms.

Q1: What causes this patient's hyponatremia?

Q2: What would be the appropriate course of action for this patient?

Q3: How would you describe your general attitude towards hyponatremia?

Table 1: Working diagnosis according to medical specialists, residents, and medical students (SIADH: 'syndrome of inappropriate antidiuretic hormone secretion')

	Diuretic use	*SIADH*	*Heart failure*	*Other*
Medical specialists (n = 15)	*11 (73%)*	*3 (20%)*	*1 (7%)*	*0 (0%)*
Residents (n = 15)	*10 (67%)*	*3 (20%)*	*0 (0%))*	*2 (13%)*
Medical students (n = 20)	*9 (45%)*	*3 (15%)*	*1 (5%)*	*7 (35%)*

Table 2: Appropriate treatment strategy according to medical specialists, residents, and medical students (more than one option allowed)

	Normal saline (0.9%)	*Hypertonic saline (3.0%)*	*Fluid restriction*	*Discontinue medication*	*Other*
Medical specialists (n = 15)	*7 (47%)*	*3 (20%)*	*2 (13%)*	*4 (27%)*	*4 (27%)*
Residents (n = 15)	*3 (20%)*	*10 (67%)*	*7 (47%)*	*6 (40%)*	*2 (13%)*
Medical students (n = 20)	*4 (20%)*	*10 (50%)*	*4 (20%)*	*7 (35%)*	*7 (35%)*

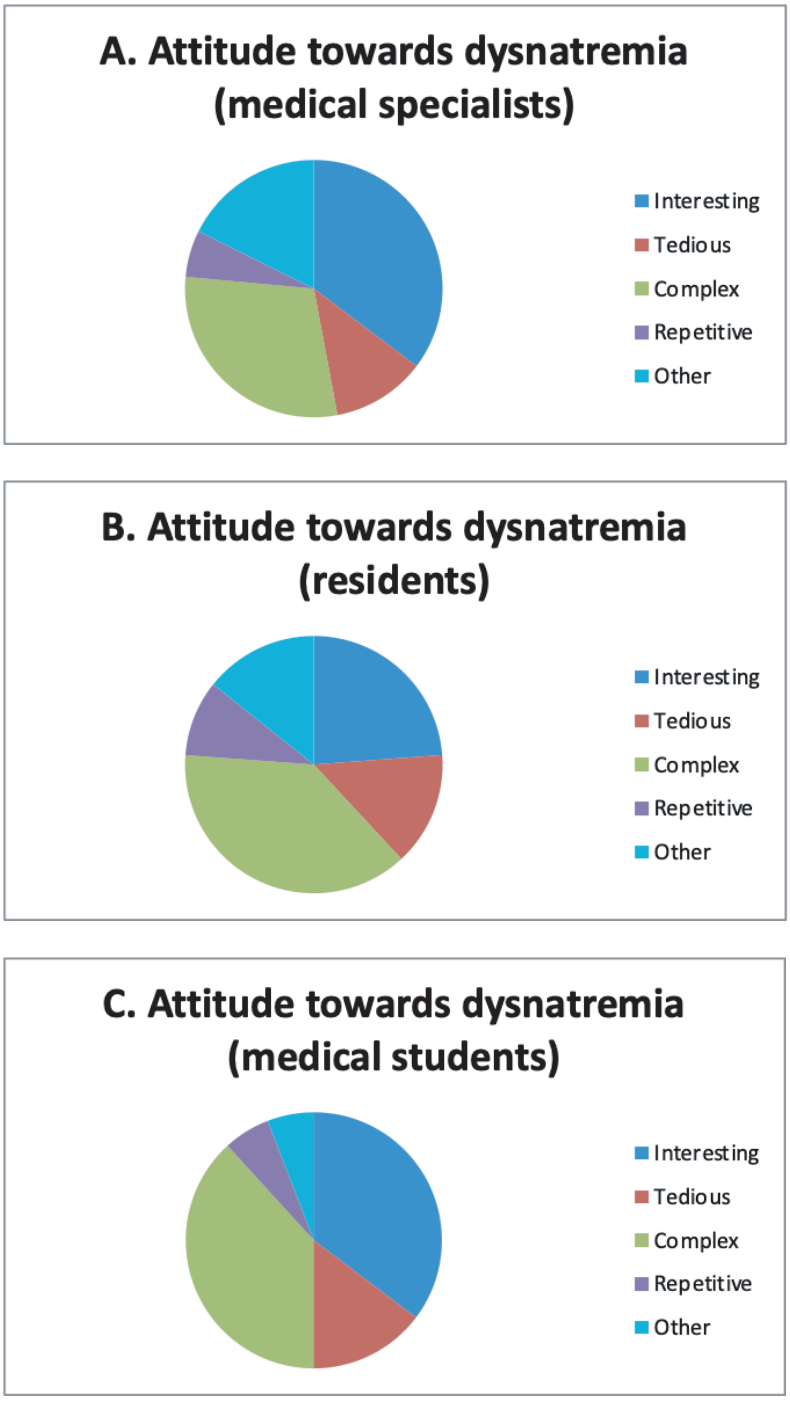

Figure 1: Results of survey regarding the attitude of medical specialists (A), residents (B), and medical students (C) towards dysnatremia (more than one option allowed).

3. DISCUSSION

In the previous section, we have described how doctors and future doctors evaluate a complex case of hyponatremia. Our results show that a consensus with regard to both the cause and the management of the hyponatremia is only rarely reached, which begs the question: how can this be explained? In our opinion and experience, several factors contribute to these discrepancies. Below, we highlight some of the common causes for misinterpretation or inadequate management of dysnatremia, which can broadly be summarized as –but are certainly not limited to– overreliance on diagnostic and therapeutic algorithms, cognitive bias, and lack of acquaintance with (or misinterpretation) of relevant physiological concepts.

The first reason for difficulties encountered during the analysis of dysnatremia is that many physicians – especially in those situations where on-the-spot analyses of blood and urinary test results may be required, such as in our experiment – tend to rely heavily on diagnostic algorithms.[5][8] However, the vast majority of these algorithms and guidelines can only be applied to monofactorial disorders of the plasma sodium concentration (i.e., a "pure" diabetes insipidus or a "pure" tea and toast syndrome).[8] This is unfortunate, as dysnatremia is a heterogeneous disorder and, as pointed out by Hoorn *et al.*, the "classical dysnatremic patient" does not exist.[9] Adding to the confusion, recommendations and cut-off values can vary significantly from one guideline to the next, especially if national and international guidelines are compared.[9] If multiple causes contribute to the development of dysnatremia, which is a common occurrence, many algorithms and flowcharts will yield unreliable results and can be misleading. This leads to an inappropriate treatment or even deterioration of the existing dysnatremia of multifactorial etiology.[4][10] A striking example of this is a patient with a chronic low dietary salt intake, whose hyponatremia is the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Although a physician evaluating this case would most likely expect concentrated urine and a significant natriuresis (>30 mmol/L) due to the SIADH, the urine sodium excretion will probably be reduced as a result of the chronic lack of salt intake, masking the underlying SIADH. If a diagnostic algorithm such as the Dutch Guideline (Acute Boekje) were to be followed in this particular case, this multifactorial hyponatremia could easily

be mistaken for hyponatremia due to a depletion of the effective circulating arterial volume, in which hypovolemia is a potent stimulus for antidiuretic hormone release.[8] This would be reflected by concentrated urine, whereas the simultaneous activation of the renin-angiotensin-aldosterone system would result in tubular sodium retention and therefore low natriuresis (<30 mmol/L). Administering isotonic saline, which would be an appropriate treatment strategy for many cases of intravascular volume depletion (e.g., due to diarrhea or vomiting), could exacerbate the misdiagnosed hyponatremia due to SIADH (especially if the urine osmolarity is higher than 530 mOsmol/L), which would most likely become apparent after administering saline infusate.[10][11] It should be noted that the same warning applies overreliance on equations and other tools that offer advice on how to correct the plasma sodium concentration. Although these models can be useful in managing hyponatremia, they can also yield unreliable results if applied to patients for whom these models have not been validated. A well-known example is the Adrogue-Madias equation, which aims to predict the change in plasma sodium concentration after administering intravenous fluids. Especially in patients with a relatively fixed urine osmolarity, such as in SIADH, this equation fails to accurately predict the effect of intravenous fluids on the plasma sodium concentration, because it does not take renal water- and salt-handling into account.[11]

Another common cause for misinterpretation of dysnatremia is the cognitive bias among many physicians, which can broadly be defined as an error in clinical reasoning or judgment that can negatively influence decision-making.[12] Notable examples of such cognitive bias during the analysis of hyponatremia are affinity bias (the tendency of a physician to be biased toward an explanation that he or she is familiar with), priming bias (the tendency of a physician to be biased toward an explanation suggested by a colleague or supervising physician), conformation bias (the tendency of a physician to interpret test results and other information in such a way that it confirms his or her hypothesis), and belief bias (the tendency of a physician to be biased toward an explanation based on his or her belief in its truth).[12] There can be a significant amount of overlap between these forms of cognitive bias. For instance, a Psychiatry resident who analyzes an in-patient with a large fluid intake and an increased urine production remembers the attending psychiatrist saying that "it's probably another case of primary polydipsia", which leads him to believe

that this patient is probably suffering from primary or psychogenic polydipsia (priming bias and belief bias). He also recalls that he has encountered multiple cases of primary polydipsia lately, which strengthens his belief in the truth of this diagnosis in his current patient (affinity bias and belief bias). He then goes on to ignore evidence pointing in another direction, such as hypernatremia (confirmation bias). Such errors in clinical reasoning can lead to the incorrect management of this hypernatremia and can even have potentially dangerous situations, such as a failure to diagnose diabetes insipidus and erroneously ordering a fluid restriction in this particular case. Clinical cognitive bias, while certainly not limited to or specific for the analysis of dysnatremia, does tend to occur more frequently when a doctor considers a patient case a "chore" rather than a "challenge". The results of our survey, as presented in the previous section, emphasize that many doctors simply do not consider dysnatremia an appealing subject. They often consider the analysis and management complex, troublesome or tedious, and feel that the clinical consequence of such a lengthy analysis is not always clear. Since the investigation of dysnatremia is often incomplete without the results of urine tests, discouraging delays in obtaining urine samples by the nursing staff and time-consuming urinalysis by laboratory technicians aggravate this negative attitude. Although admitting reluctance in medicine is considered taboo among physicians, we do believe that lack of affinity with dysnatremia can negatively affect a doctor's willingness to 'go the extra mile' for its analysis and management.

The next pitfall –the focus of many physicians on so-called "sacred cows" in osmoregulation while analyzing hyponatremia– overlaps with that of cognitive bias. Some outdated concepts in water and salt physiology tend to remain stubbornly instilled in the clinician's mind, often due to a firm belief in the truth of concepts taught during their medical training or due to a lack of familiarity with novel scientific insights. A well-known example of a physiological concept that has recently garnered more attention, but has not yet found its way into most clinics, is that of electrolyte-free water clearance as opposed to the traditional model of solute-free water clearance.[10][13] The physiologically more accurate electrolyte-free water clearance focuses on the relative tonicity in the plasma and the urine rather than the relative osmolarity, and ignores the osmotically inert solutes, the most important example of which in urea.[10][13] The implications of adopting electrolyte-free water clearance in

the analysis and management of hyponatremia are significant. Suppose that the urine osmolarity of a hyponatremic patient is relatively high, but mostly as a result of inert solutes as opposed to electrolytes (an example of this would be a patient with a significant uremia whose renal function is rapidly recovering). This patient will have a negative solute-free water clearance due to massive renal urea excretion, but a positive electrolyte-free water clearance due to the low urine electrolyte concentration. The first implies that this patient's hyponatremia will most likely exacerbate, whereas the latter suggests that the free water excess is being excreted by the kidneys. However, many clinicians still rely on urine osmolarity rather than urine tonicity to guide intravenous fluid therapy. Another example is related to the detection of large subcutaneous sodium stores in humans in the 1950s.[14] An important consequence of this discovery is that the classical "two-compartment model" of osmoregulation –i.e., the intracellular fluid compartment versus the extracellular fluid compartment, with a strong focus on renal water and solute handling– is an oversimplification and that perhaps the skin interstitium should be considered a relevant third compartment.[14] Although the presence of subcutaneous sodium storage has been known for many years, this has in no way influenced been translated to patient care. Doctors seem to be hindered in their approach to dysnatremia by their reluctance to "kill their darlings" (i.e., the familiar concepts that they were taught in medical school) and adopt novel insights. It is plausible that our knowledge of water and sodium homeostasis in the human body is still incomplete, and that future discoveries could help us fine-tune our understanding of osmoregulation and its disorders, granted that the medical community keeps an open mind to them and is willing to translate them to patient care.

4. CONCLUSION AND RECOMMENDATIONS

Despite its frequent occurrence, the clinical approach to dysnatremia seems to be 'so many men, so many minds'. We have summarized some of the main factors that –in our opinion and in our experience– contribute to this lack of consensus and we hope that, by drawing attention to these potential pitfalls, we can help clinicians avoid them and facilitate the analysis of disorders of the water and sodium balance. Our article also demonstrates that the "one size fits all" approach to dysnatremia in many diagnostic and therapeutic flowcharts should be discouraged, especially in the light of the growing number of multimorbid patients, and that a solid, physiologically sound (and up-to-date), and patient-based analysis is required. We also conclude that osmoregulation and its disorders suffer from an 'image problem' among doctors. However, as the Dutch Tax and Revenue Administration tends to put it: "we can't make it more fun, but we can make it easier".

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Chapter 3

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

Philip J.G.M. Voets
Nils P.J. Vogtländer
Karin A.H. Kaasjager

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ABSTRACT

Disorders of the water and sodium homeostasis in the human body –or dysnatremias– are frequently encountered in the 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 dysnatremia, especially when a rapid "bed-side" 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.

1. LIST OF ABBREVIATIONS

ADH = Antidiuretic hormone
SIADH = Syndrome of inappropriate antidiuretic hormone secretion
K = Slope of the ADH release per unit of increase in plasma osmolality
O_p = Plasma osmolality
$O_{p,threshold}$ = Plasma osmolality above which osmolality-driven ADH release occurs
$O_{p,\ lower\ limit}$ = Plasma osmolality representing the lower limit of the nomogram curve
$O_{p,\ upper\ limit}$ = Plasma osmolality representing the upper limit of the nomogram curve
O_u = Urine osmolality
$O_{u,\ min}$ = Minimum urine osmolality
$O_{u,\ max}$ = Maximum urine osmolality
$[ADH]$ = Plasma antidiuretic hormone concentration
$[ADH]_{baseline}$ = Baseline plasma antidiuretic hormone concentration
$[ADH]_{50}$ = Plasma ADH concentration at which O_u equals $\frac{1}{2}O_{u,max}$

2. INTRODUCTION

Disorders of the water and sodium homeostasis in the human body –or dysnatremias– are frequently encountered in the clinical practice, but their analysis is often complex and their management is often troublesome. The most notable example is hypotonic hyponatremia, 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 dysnatremia, especially when a rapid "bed-side" 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 the plasma osmolality, is regulated by balancing retention and excretion of water, rather than by retaining or excreting sodium itself.[3][4][5][6] This process is governed by antidiuretic hormone (ADH), an oligopeptide hormone that is secreted by the posterior pituitary gland in response to a rise 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][4][5][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 dysnatremias.

3. PHYSIOLOGICAL BASIS FOR CLINICAL NOMOGRAM

As plasma osmolality (O_p) rises above a threshold of 280 mOsmol/kg ($O_{p,threshold}$), the effective osmotic stimulus will lead to the secretion of antidiuretic hormone (ADH) or arginine vasopressin. In the absence of pathological ADH secretion (e.g., syndrome of inappropriate ADH secretion or hypovolemic stimulus), the plasma ADH concentration ($[ADH]$) increases linearly with the rise is plasma osmolality.[3][4][5] Therefore:

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

In which K and $[ADH]_{baseline}$ represent the slope of the ADH release per unit of increase in plasma osmolality (which equals approximately 0,5 pg·kg·mL^{-1}·mOsm^{-1} for the average healthy adult) and the baseline plasma ADH concentration, respectively.[3][4][5]

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

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

In the case of a normal ADH receptor sensitivity, a rise 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:[10][11][12]

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

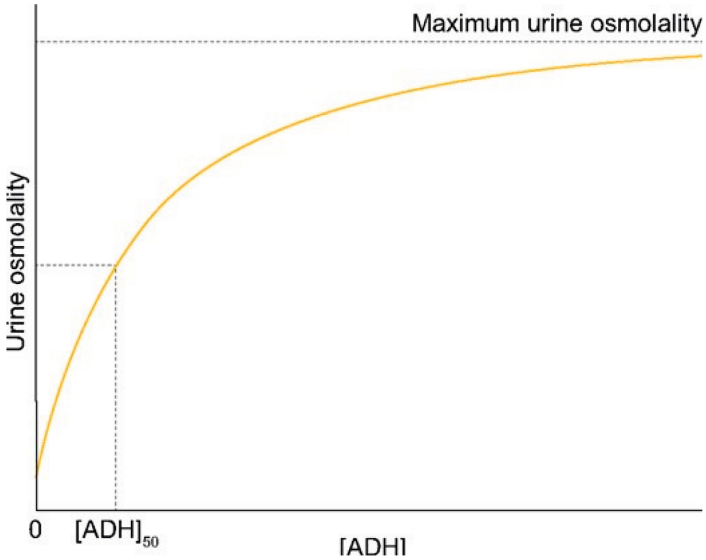

Figure 1: Graphic representation of the Michaelis-Menten-like relationship between the plasma ADH concentration ([ADH]) and urine osmolality. Note that this curve cuts the y-axis at y > 0, because urine cannot consist of pure water.

Here $[ADH]_{50}$ represents the plasma ADH concentration at which O_u equals $\frac{1}{2} O_{u,max}$ (which is equivalent to approximately 2,0 pg·mL^{-1}).[10][11]

Maximum urine osmolality ($O_{u,max}$) is attained at plasma ADH concentrations higher than 5,0 pg·mL^{-1}, reflecting maximal receptor occupancy by ADH).[10][11][12] Rearranging Equation (3) produces:

$$(O_u - O_{u,min})([ADH] + [ADH]_{50}) = O_{u,max}[ADH] \tag{4.1}$$

$$(O_u - O_{u,min})[ADH] + (O_u - O_{u,min})[ADH]_{50} = O_{u,max}[ADH] \tag{4.2}$$

$$[ADH] = [ADH]_{50}\left(\frac{O_u - O_{u,min}}{O_{u,max} + O_{u,min} - O_u}\right) \tag{4.3}$$

Combining the Equations (2) and (4.3) yields:

$$K\left(O_p - O_{p,threshold}\right) = [ADH]_{50}\left(\frac{O_u - O_{u,min}}{O_{u,max} + O_{u,min} - O_u}\right) \tag{5.1}$$

$$O_p - O_{p,threshold} = \frac{[ADH]_{50}}{K}\left(\frac{O_u - O_{u,min}}{O_{u,max} + O_{u,min} - O_u}\right) \tag{5.2}$$

In which:

$$\frac{[ADH]_{50}}{K} \approx \frac{2{,}0}{0{,}5} \approx 4 \tag{6}$$

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

$$O_p = 4\left(\frac{O_u - 50}{1250 - O_u}\right) + 280 = \frac{4O_u - 200}{1250 - O_u} + 280 \tag{7}$$

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:

$$O_{p,lower\ limit} = 3\left(\frac{O_u - 50}{1250 - O_u}\right) + 275 = \frac{3O_u - 150}{1250 - O_u} + 275 \tag{8.1}$$

$$O_{p,upper\ limit} = 5\left(\frac{O_u - 50}{1250 - O_u}\right) + 285 = \frac{5O_u - 250}{1250 - O_u} + 285 \tag{8.2}$$

In which $[ADH]_{50}/K = 3$ 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 the Equations (7), (8.1), and (8.2) produces the following nomogram (see Figure 2), which will be further elucidated below:

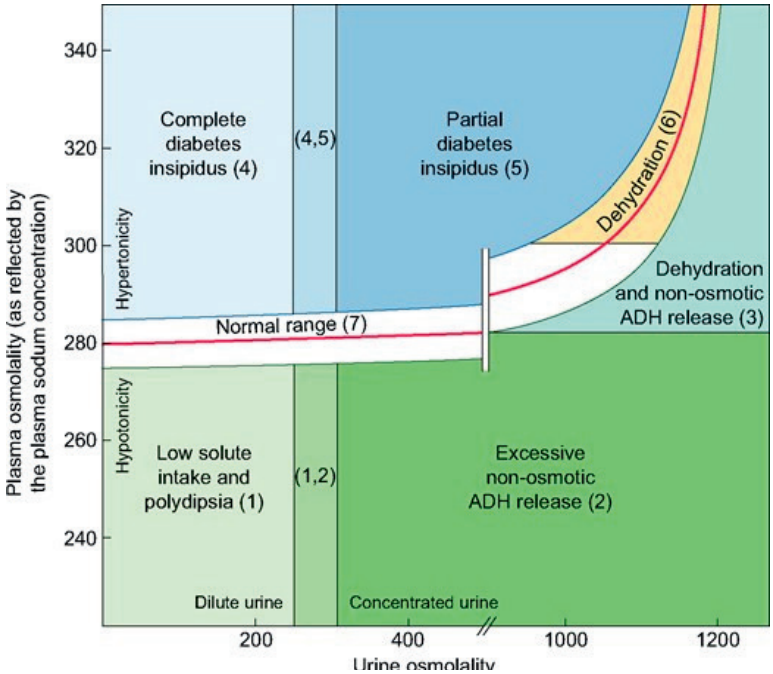

Figure 2: Osmolality nomogram depicting the physiological relationship between the measured plasma osmolality (y-axis, in mOsmol/kg) and urine osmolality (x-axis, in mOsmol/kg) under the assumption of osmolality-driven ADH release (gray-shaded areas). This nomogram is only valid on the conditions that 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 non-effective solute or an effective non-electrolyte solute is significantly elevated). The numbered areas can be interpreted as follows, in which the colour gradients represent the transitions between overlapping areas:

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

4. DISCUSSION

In the previous section we have 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 a rise 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 (7) can be plotted graphically with a certain error band (Equation (8.1) and (8.2)), 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 dysnatremia 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 hypovolemic ADH release (when intravascular volume depletion exceeds approximately 5%) and the syndrome of inappropriate ADH secretion (SIADH), and complete and partial diabetes insipidus (areas 4 and 5, respectively).[13][14] SIADH and hypovolemia-mediated ADH release can often be distinguished by the degree of natriuresis, which is generally >30 mmol/L in SIADH, reflecting euvolemia, and <20 mmol/L in hypovolemia as a result of activation of the rennin-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 the ADH release, as the plasma ADH concentration already is negligible under these circumstances.[3][4][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 gray). This reflects the renal ability to effectively retain or excrete water in order to maintain homeostasis.[3][4][5] Only when the steep (right-sided) part of the shoulder of the curve 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 approximately equals 1200 mOsmol/kg –although some variability between persons exists.[3][4][5] By definition, dehydration occurs when the plasma osmolality rises above 300 mOsmol/kg (area 6, shaded in dark gray), 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.

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 eight liters of urine per day), polydipsia, and hypertonic hypernatremia. 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 rise in the 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 hyponatremia. His plasma sodium concentration is 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 liters of beer per day without eating properly. A diagnosis of potomania or 'beer-drinker's hyponatremia', 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, a 82-year old woman, was admitted to the Pulmonology ward with a pneumonia. Her blood tests also showed a hypotonic hyponatremia 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 a 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 a mild and asymptomtic hypotonic hyponatremia 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.

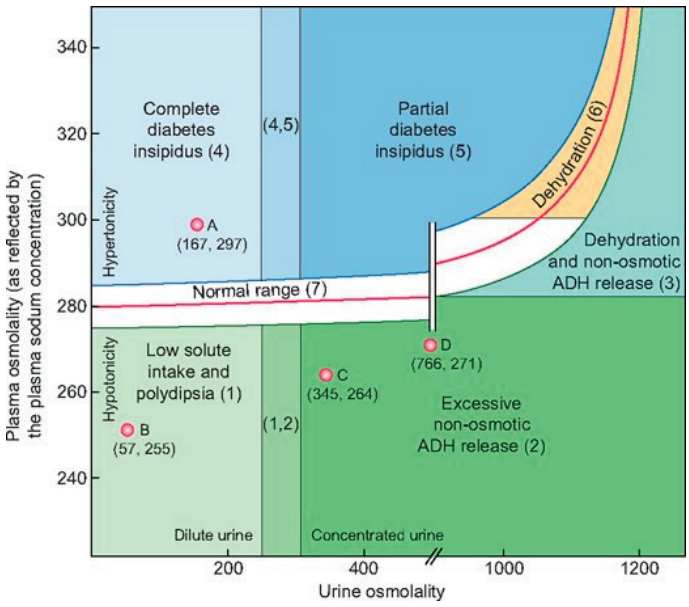

Figure 3: Patients A, B, C, and D are represented by the red dots (x-coordinate: urine osmolality; y-coordinate: plasma osmolality) and their corresponding letters in the osmolality nomogram.

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 approximately 1200 mOsmol/kg in the average healthy adult under 60 years old, but is reduced with roughly 20% in persons aged 60 to 80 years.[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 the plasma osmolality. Whenever a clinician suspects multiple concurrent causes underlying a patient's dysnatremia, 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 "bed-side" 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 analyzing dysnatremia; a thorough assessment of the relevant patient characteristics remains imperative for every clinical examination.

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Chapter 4

Understanding dysnatremia

Philip J.G.M. Voets
Nils P.J. Vogtländer
Karin A.H. Kaasjager

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ABSTRACT

Background: Dysnatremia –either hyponatremia or hypernatremia– is frequently encountered in the clinical practice and often poses a diagnostic and therapeutic challenge for physicians. Despite their frequent occurrence, disorders of the water and sodium balance in the human body have puzzled many physicians over the years and often remain elusive for those lacking experience in their interpretation and management.

Methods: In this article, we derive a transparent governing equation that can be used by clinicians to describe how a change in relevant physiological parameters will affect the plasma sodium concentration. As opposed to many existing models, our model takes both input and output into account, and integrates osmolarity and tonicity.

Conclusion: Our governing equation should be considered a means for clinicians to get a better qualitative understanding of the relationship between the plasma sodium concentration and the variables that influence it for a wide range of scenarios.

LIST OF ABBREVIATIONS

ADH = Antidiuretic hormone
SIADH = Syndrome of inappropriate antidiuretic hormone secretion
$[Na^+]_p$ = Plasma sodium concentration
$\Delta[Na^+]_p$ = Change in plasma sodium concentration
$Na_e^+ + K_e^+$ = Total body exchangeable sodium and potassium
$\Delta T_{p,u}$ = Plasma tonicity minus urine tonicity
$\Delta T_{p,i}$ = Plasma tonicity minus input tonicity
$[E^+]_i$ = Cation concentration of input
$[E^+]_u$ = Cation concentration of urine
O_u = Urine osmolarity
V_u = Urine output flow rate
V_i = Input flow rate
EFW = Electrolyte-free total body water
EFWI = Electrolyte-free total body water input
EFWC = Electrolyte-free total body water clearance
TBW = Total body water (0.6 times body weight for men, 0.5 times body weight for women)
ΔTBW = Change in electrolyte-free total body water
N= Obligatory osmole excretion

1. INTRODUCTION

Dysnatremia –either hyponatremia or hypernatremia– is frequently encountered in the clinical practice and often poses a diagnostic and therapeutic challenge for physicians.[1][2] Although many dysnatremic patients remain asymptomatic (especially if a change in the plasma sodium concentration is mild and the onset is gradual), dysnatremia can cause debilitating symptoms, such as nausea, lethargy, and seizures, and has consistently been associated with a higher mortality in hospitalized patients.[1][2] However, despite their frequent occurrence, disorders of the water and sodium balance in the human body have puzzled many physicians over the years and often remain elusive for those lacking experience in their interpretation and management.[1]

In this article, we propose a transparent governing equation (Equation (11)) that provides insight into how a change in relevant physiological parameters affects the plasma sodium concentration. Our model takes both input and output into account, and integrates osmolarity and tonicity.[3][4][5] It is important to note that it is not the aim of this equation to calculate changes in the plasma sodium concentration exactly, and it does not remove the need for frequent plasma sodium measurements while treating dysnatremia. Rather, the derived equation should be considered a useful means for clinicians to get a better qualitative understanding of the relationship between the plasma sodium concentration and the physiological variables that influence it. Therefore, an experimental validation of our model falls beyond the scope of this article.

Below, the mathematical derivation of Equation (11) will be discussed stepwise.

2. MATHEMATICAL DERIVATION

The plasma sodium concentration ($[Na^+]_p$) can be fairly accurately described by the simplified Edelman equation as a function of the total body exchangeable sodium and potassium ($Na_e^+ + K_e^+$) and the total body water (TBW):[6][7]

$$[Na^+]_p = \frac{Na_e^+ + K_e^+}{TBW} \tag{1}$$

It has been shown experimentally that the use of Equation (1) sometimes leads to a slight –but clinically allowable– overestimation of the plasma sodium concentration.[7] For the purpose of deriving our qualitative model, this small deviation from the original, but mathematically more intricate, Edelman equation was deemed acceptable.

A change in plasma sodium concentration is determined by the change in electrolyte-free total body water (ΔTBW), assuming that the total amount of exchangeable sodium and potassium does not change:[6][7][8]

$$\Delta[Na^+]_p = \frac{Na_e^+ + K_e^+}{TBW + \Delta TBW} - \frac{Na_e^+ + K_e^+}{TBW} \tag{2}$$

We have previously shown that –under the reasonable condition that $TBW >> \Delta TBW$ holds true– the equation above can be algebraically reduced to:[8]

$$\Delta[Na^+]_p = -[Na^+]_p \frac{\Delta TBW}{TBW} \tag{3}$$

The net change in electrolyte-free total body water can be described as the difference between the electrolyte-free total body water input ($EFWI$), both oral and parenteral, and the electrolyte-free total body clearance ($EFWC$):[9][10][11]

$$\Delta TBW = EFWI - EFWC \tag{4}$$

In contrast to the traditional concept of solute-free water, electrolyte-free water ignores osmotically inert solutes, such as urea. Equation (4) should be

considered invalid in the case of significant volume redistributions between the intracellular and extracellular compartment, which primarily occurs in plasma hypertonicity and severe dehydration. In this derivation, the insensible body water losses (such as through perspiration) in the period between plasma sodium concentration measurements are considered negligible.

The equation for electrolyte-free total body water input and the electrolyte-free total body clearance are as follows:[8][9][11]

$$EFWI = V_i\left(1 - \frac{[E^+]_i}{[Na^+]_p}\right) \tag{5.1}$$

$$EFWC = V_u\left(1 - \frac{[E^+]_u}{[Na^+]_p}\right) \tag{5.2}$$

In which V_i and V_u represent the input flow rate and urine output flow rate, respectively. With regard to the mathematical transparency of our model, effective non-electrolyte solutes (e.g., glucose and mannitol) are not incorporated in the equations above and their effect on tonicity is assumed to be small compared to the effect of electrolytes. Clearly, This assumption is not valid for hypertonic hyponatremia. Substitution of these equations in Equation (4) produces:[8]

$$\Delta TBW = V_i\left(1 - \frac{[E^+]_i}{[Na^+]_p}\right) - V_u\left(1 - \frac{[E^+]_u}{[Na^+]_p}\right) \tag{6}$$

Therefore:

$$\Delta[Na^+]_p = -\frac{[Na^+]_p}{TBW}\left(V_i\left(1 - \frac{[E^+]_i}{[Na^+]_p}\right) - V_u\left(1 - \frac{[E^+]_u}{[Na^+]_p}\right)\right) \tag{7.1}$$

$$\Delta[Na^+]_p = \frac{V_u\left([Na^+]_p - [E^+]_u\right) - V_i\left([Na^+]_p - [E^+]_i\right)}{TBW} \tag{7.2}$$

The numerator and denominator in Equation (7.2) are multiplied by 2, which produces:

$$\Delta [Na^+]_p = \frac{2V_u([Na^+]_p - [E^+]_u) - 2V_i([Na^+]_p - [E^+]_i)}{2TBW} \quad (8)$$

The terms $2([Na^+]_p - [E^+]_u)$ and $2([Na^+]_p - [E^+]_i)$ –in which the factor 2 accounts for the anions– can broadly be redefined as the difference in tonicity between the plasma and urine ($\Delta T_{p,u}$) and the difference in tonicity between plasma and input ($\Delta T_{p,i}$), respectively:

$$\Delta T_{p,u} = 2([Na^+]_p - [E^+]_u) \quad (9.1)$$

$$\Delta T_{p,i} = 2([Na^+]_p - [E^+]_i) \quad (9.2)$$

The Equations (9.1) and (9.2) can be substituted in Equation (8), which produces:

$$\Delta [Na^+]_p = \frac{\Delta T_{p,u} V_u - \Delta T_{p,i} V_i}{2TBW} \quad (10)$$

Because two times the total body water approximately equals body weight (W), and because the obligatory urine production is determined by the ratio of osmoles that need to be excreted (N) to osmole excretion per liter of urine (i.e., the urine osmolarity or O_u), Equation (10) can be rewritten to:[12][13]

$$\Delta [Na^+]_p = \frac{\Delta T_{p,u} N / O_u - \Delta T_{p,i} V_i}{W} \quad (11)$$

Although the simultaneous use of urine osmolarity and tonicity in the equation above may seem inconsistent at first, it is important to note that, while the electrolyte-free water balance ultimately determines the change in the plasma sodium concentration, the urine flow rate itself –which sets a limit on the amount of electrolyte-free water loss– is determined by the rate of solute excretion (which includes inert solutes, such as urea).[13]

3. DISCUSSION

In the previous section, a governing dysnatremia equation has been derived that describes the effect of a change in any of the physiological parameters on the change in the plasma sodium concentration. Our model can be applied to a wide range of clinical dysnatremia scenarios, several of which will be discussed below.

It is well-known that the osmole intake of a person strongly influences his or her water and sodium balance.[12][13] Therefore, changes in osmole intake frequently cause, or predispose for, dysnatremia. Equation (11) clearly demonstrated that a significant decrease in osmole intake -which is reflected by a decreased value for N, as fewer osmoles need to be excreted- predisposes for drop in plasma sodium concentration.[12][13][14][15] Among clinicians, this is also known as 'tea and toast syndrome', and it is often encountered in the elderly and the malnourished.[13][14] As a compensatory mechanism, the kidneys will optimize their renal water excretion by minimizing the osmole excretion per liter of urine, which is reflected by a decrease in O_u, correcting the aforementioned ratio N/O_u.[12][13][14][15] Because the urine cannot be composed of pure water, but must contain a minimum amount of osmoles (approximately 50 mOsmol/L), this compensatory mechanism will eventually fail when the urine cannot be diluted any further while a patient continues to ingest a significant volume of hypotonic fluids, such as beer or even pure water.[13] The inability of the human body to get rid of the introduced water load due to a lack of osmoles that can be excreted in order to produce urine, leads to a water excess and hypotonic hyponatremia.[13][14]]15] Administering normal saline to these patients will increase their plasma sodium concentration much more than would be expected from the simple redistribution of the introduced infusate.[3][4][5] Our model shows that both the reintroduction of solutes -reflected by an increased value for N- which greatly enhances urinary water excretion in these patients, and the relative hypertonicity of normal saline compared to their hypotonic hyponatremic plasma (and thus a negative value for $\Delta T_{p,i}$) contribute to this increase in their plasma sodium concentration. Analogously, as the osmole input and therefore the value for N strongly increases (e.g., in parenterally fed patients), hyperalimentation hypernatremia can develop due to an increase in urinary water loss.[15]

With regard to differences in input and output tonicity, it stands to reason that the plasma sodium concentration will drop as the value for $\Delta T_{p,u}$ becomes smaller, and the value for $\Delta T_{p,i}$ becomes larger. This reflects a situation in which the urine becomes hypertonic, whereas the input consists of more hypotonic fluids. An example of the latter is primary polydipsia, which would result in an increased value for both V_i (due to the large volume of ingested fluids) and $\Delta T_{p,i}$ (due to the low electrolyte concentration in the ingested fluids and thus the low value for $[E^+]_i$, resulting in an increase in the value for $2([Na^+]_p - [E^+]_i)$).[13][14][15] Conversely, any increase in $\Delta T_{p,u}$ (i.e., by reducing the urinary electrolyte excretion, which lowers $[E^+]_u$ and thus increases the value for $2([Na^+]_p - [E^+]_u)$) and/or decrease in $\Delta T_{p,i}$ will predispose for a rise in the plasma sodium concentration.[14]

In the clinical practice, hypotonic hyponatremia is often the result of excessive production of antidiuretic hormone (ADH), which stimulates pure water retention in the collecting ducts.[16][17] Under physiological conditions, the plasma osmolarity determines the degree of ADH release from the pituitary gland. However, in the case of intravascular volume depletion (which often occurs as a result of the chronic use of diuretics, diarrhea, vomiting, adrenal insufficiency or forward failure due to cardiac pathology), a hypovolemic stimulus can override coexisting osmotic stimuli and trigger the release of ADH.[17][18] In Equation (11), this increases the value for O_u. The effect of hypovolemia on $\Delta T_{p,u}$ is more difficult to predict, as this parameter is strongly influenced by the degree of natriuresis and the urine flow rate, and therefore depends on the specific cause of hypovolemia.[13] Regardless of the underlying cause, removing the hypovolemic stimulus for ADH release by treating the underlying pathology and/or by initiating intravenous fluid therapy promotes renal water excretion, reduces O_u, and often corrects the hypotonic hyponatremia.[17][18] Another frequently encountered example of excessive ADH release is the syndrome of inappropriate antidiuretic hormone secretion (SIADH), which is frequently caused by lung disease, medication, malignancy or disorders of the central nervous system.[16][17] According to a classical clinical dogma, normal saline should be avoided in SIADH patients with a high urine osmolarity, as the kidneys were believed to simply excrete the introduced electrolytes, while retaining the introduced water. However, Equation (11) shows that SIADH patients can be effectively treated with normal saline, even in the setting

of a relatively high urine osmolarity as long as the urine tonicity remains sufficiently low (i.e., the value for $\Delta T_{p,u}$ remains relatively high).[8][16][18] This corresponds with clinical observations by -among others- Shimizu *et al.*, Hoorn *et al.* and Zietse *et al.*.[10][18][19] Administering normal saline to SIADH patients with a high urine tonicity due to significant natriuresis (which is further amplified by administering saline infusate) and therefore a negative value for $\Delta T_{p,u}$ (i.e., $[E^+]_u > [Na^+]_p$) will most likely exacerbate their initial hypotonic hyponatremia, whereas SIADH patients with a relatively low urine tonicity and therefore a positive value for $\Delta T_{p,u}$ may benefit from saline infusion, regardless of their urine osmolarity.[8][15][16][17] In diabetes insipidus, which is in many ways the opposite of SIADH, massive urinary water loss dilutes urinary electrolytes and increases the value for $\Delta T_{p,u}$, which results in hypernatremia.[15][16][17] By drinking sufficient amounts of electrolyte-free water (with a high value for V_i and $[E^+]_i = 0$), and by taking diuretics such as amiloride (which reduce the value for $\Delta T_{p,u}$), the plasma sodium concentration can be decreased effectively.[17]

As described above, Equation (11) can be used to describe the plasma sodium response –and the renal compensatory response– for a wide range of scenarios. The magnitude of the aforementioned changes in the plasma sodium concentration will, in part, depend on the initial amount of total body water.[17][20] The total body water is proportional to body mass (represented by the term W); i.e., the larger the body weight, the smaller the impact of a parameter change on the plasma sodium concentration, and vice versa.[17][20] Our mathematical model can also be applied to interpret complex cases of multifactorial dysnatremia, in which multiple factors simultaneously –but not necessarily synergistically– contribute to an observed change in the plasma sodium concentration. However, Equation (11) should not be applied to cases of hypertonic hyponatremia (such as overt hyperglycemia), as the effect of effective non-electrolyte solutes on the input and output tonicity balance is considered relatively insignificant. These solutes are thus ignored in the presented tonicity balance, as we feel that incorporating these solutes in the Equations (5.1) and (5.2) would greatly diminish the mathematical transparency and clinical utility of our final equation.[21]

As a concluding remark, it stands to reason that patient characteristics should be considered in the analysis of every disorder of the water and sodium balance

and that frequent measurements of the plasma sodium concentration remain imperative. We would like to emphasize again that the presented model is a transparent tool for the analysis of dysnatremia, which is not intended for exact calculations.

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Chapter 5

A quantitative approach to intravenous fluid therapy in the syndrome of inappropriate antidiuretic hormone secretion

Philip J.G.M. Voets
Nils P.J. Vogtländer

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ABSTRACT

Background: Over the years, a wide range of interesting mathematical models has been derived to predict the effect of intravenous fluid therapy on the plasma sodium concentration (most notably the Adrogue-Madias equation), but unfortunately, these models cannot be applied to patients with disorders characterized by aberrant antidiuretic hormone (ADH) release, such as the syndrome of inappropriate ADH secretion (SIADH). The use of intravenous fluids in these patients should prompt caution, as the inability of the kidneys to properly dilute the urine can easily result in deterioration of hyponatremia.

Methods: In this report, a transparent and clinically applicable equation is derived that can be used to calculate the estimated effect of different types and volumes of crystalloid infusate on the plasma sodium concentration in SIADH patients. As a "proof of concept", we discuss five SIADH patient cases from our clinic. Alternatively, our mathematical model can be used to determine the infusate volume that is required to produce a certain desired change in the plasma sodium concentration in SIADH patients.

Conclusion: The presented model facilitates rational intravenous fluid therapy in SIADH patients, and provides a valuable addition to existing prediction models.

LIST OF ABBREVIATIONS

ADH = Antidiuretic hormone
SIADH = Syndrome of inappropriate antidiuretic hormone secretion
$Na_e^+ + K_e^+$ = Total body exchangeable sodium and potassium
$[Na^+]_{p,1}$ = Plasma sodium concentration before intravenous fluid
$[Na^+]_{p,2}$ = Plasma sodium concentration after intravenous fluid
O_p = Plasma osmolarity before intravenous fluid
$\Delta[Na^+]_{p,m}$ = Measured change in plasma sodium concentration
$\Delta[Na^+]_{p,p}$ = Predicted change in plasma sodium concentration
$\Delta[Na^+]_{p,d}$ = Desired change in plasma sodium concentration
O_u = Urine osmolarity
T_u = Urine tonicity
$T_{u,max}$ = Theoretical maximum urine tonicity
V_u = Urine volume
$[Na^+]_u$ = Urinary sodium concentration
O_i = Infusate osmolarity
T_i = Infusate tonicity
V_i = Infusate volume
$EFWI$ = Electrolyte-free total body water intake
$EFWC$ = Electrolyte-free total body water clearance
$[E^+]_i$ = Cation concentration of the administered crystalloid infusate
$[E^+]_u$ = Cation concentration of urine
TBW = Total body water (0.6 times body weight for men, 0.5 times body weight for women)
ΔTBW = Change in total body water

1. INTRODUCTION

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is characterized by aberrant, feedback-independent secretion of antidiuretic hormone (ADH) by the posterior pituitary gland. ADH stimulates the insertion of aquaporin-2 channels in the apical membrane of collecting duct epithelial cells, which results in the renal retention of pure water.[1] Because of the tonic ADH secretion in SIADH, it is characterized by a relatively fixed level of urine concentration, which is reflected by a relatively fixed urine osmolarity, and often by hypotonic hyponatremia.[2][3] The improvident administration of intravenous fluids in SIADH patients frequently exacerbates hyponatremia. As SIADH is a common finding in hospitalized patients, a quantitative insight into the effects of administering intravenous fluids in this disorder is essential for every clinician.

Over the years, a wide range of interesting mathematical models has been derived to predict the effect of intravenous fluid therapy on the plasma sodium concentration (most notably the Adrogue-Madias equation), but unfortunately, the vast majority of these models cannot be applied to a patient with a disorder of abnormal renal water-handling.[4] Another model, proposed by Nguyen and Kurtz, could theoretically be used to calculate the required amount of intravenous fluid volume in patients with SIADH, but its daunting mathematical complexity discourages its application in the clinical practice.[5] In this report, a novel and comprehensible – and therefore clinically more appealing – model is proposed, that provides a quantitative insight on the effects of fluid replacement therapy on the plasma sodium concentration in patients with SIADH.

A stepwise derivation is presented below.

2. MATHEMATICAL DERIVATION

The plasma sodium concentration ($[Na^+]_p$) can be accurately described by the simplified Edelman equation as a function of the total body exchangeable sodium and potassium ($Na_e^+ + K_e^+$) and the total body water (TBW):[6][7]

$$[Na^+]_p = \frac{Na_e^+ + K_e^+}{TBW} \tag{1}$$

A change in plasma sodium concentration is determined by the change in electrolyte-free total body water, assuming that the total amount of exchangeable sodium and potassium does not change:

$$\Delta\,[Na^+]_p = [Na^+]_{p,2} - [Na^+]_{p,1} = \frac{Na_e^+ + K_e^+}{TBW + \Delta TBW} - \frac{Na_e^+ + K_e^+}{TBW} \tag{2}$$

In which $[Na^+]_{p,1}$ and $[Na^+]_{p,2}$ represent the plasma sodium concentrations before and after the change in total body water, respectively. Algebraic rearrangement of the expression above produces:

$$\Delta\,[Na^+]_p = \frac{TBW\left(Na_e^+ + K_e^+\right)}{TBW(TBW + \Delta TBW)} - \frac{(TBW + \Delta TBW)\left(Na_e^+ + K_e^+\right)}{TBW(TBW + \Delta TBW)}$$

$$= -\frac{\Delta TBW\left(Na_e^+ + K_e^+\right)}{TBW(TBW + \Delta TBW)} \tag{3.1}$$

$$\Delta\,[Na^+]_p = -\frac{\Delta TBW\left(Na_e^+ + K_e^+\right)}{TBW(TBW + \Delta TBW)} = -\frac{\Delta TBW[Na^+]_p}{TBW + \Delta TBW} \tag{3.2}$$

Because $TBW >> \Delta TBW$ holds true, the equation above can be reduced to:

$$\Delta\,[Na^+]_p = -[Na^+]_p \frac{\Delta TBW}{TBW} \tag{4}$$

When administering an intravenous crystalloid fluid volume, the net change in electrolyte-free total body water can be described as the difference between the electrolyte-free total body water intake ($EFWI$) and the electrolyte-free total body clearance ($EFWC$):[8]

$$\Delta TBW = EFWI - EFWC \tag{5}$$

For the purpose of this model, the insensible body water losses (such as through perspiration and evaporative water loss from the respiratory tract) in the period between plasma sodium concentration measurements are considered negligible. However, if such losses are significant and known, they can easily be taken into account by adding a factor $-\Delta TBW_{loss}$ to the right-hand side of Equation (5).

As opposed to the traditional concept of solute-free water intake and clearance, the physiologically more accurate electrolyte-free water intake and clearance focus on relative tonicity rather than relative osmolarity, and ignore osmotically inert solutes (such as urea). Electrolyte-free total body water intake and the electrolyte-free total body clearance can be calculated as follows:[8][9]

$$EFWI = V_i \left(1 - \frac{[E^+]_i}{[Na^+]_p}\right) \tag{6.2}$$

$$EFWC = V_u \left(1 - \frac{[E^+]_u}{[Na^+]_p}\right) \tag{6.2}$$

Here, V_i, V_u, $[E^+]_i$, and $[E^+]_u$ represent the infusate volume, the urine volume, the cation concentration of the administered crystalloid infusate, and the cation concentration of urine, respectively (in which: $[E^+]_i = [Na^+ + K^+]_i$ and $[E^+]_u = [Na^+ + K^+]_u$).

Musch et al. have extensively investigated which urinary parameter best describes renal electrolyte-free water-handling in SIADH patients and most accurately predicts their plasma sodium response to saline infusion.[10] It was concluded that the theoretical maximum value for the urine cation concentration ($[E^+]_{u,max} = [Na^+ + K^+]_{u,max}$, which was defined by the authors as the theoretical steady-state of the urine cation concentration after several hours of saline infusion), and not the initial urine cation concentration ($[E^+]_u$), has the best predictive value for this response ($r = -0.81$, $p < 0.001$ versus $r = -0.51$, $p < 0.05$).[10] This implies that the theoretical maximum urine tonicity ($T_{u,max}$) most accurately predicts the change in plasma sodium concentration due to saline infusion in SIADH patients.

Therefore, Equation (6.2) has to be modified as follows:

$$EFWC = V_u\left(1 - \frac{[E^+]_{u,max}}{[Na^+]_p}\right) \tag{7}$$

Assuming that renal salt-handling is intact in SIADH, the kidneys will excrete the introduced electrolytes (the factor 2 to account for urine anions cancels out on both sides of Equation (8.1)):[11]

$$V_i[E^+]_i = V_u[E^+]_{u,max} \tag{8.1}$$

$$V_u = \frac{V_i[E^+]_i}{[E^+]_{u,max}} \tag{8.2}$$

Combining the Equations (5), (6.1), (6.2), (7) and (8.2) produces:

$$\Delta TBW = V_i\left(1 - \frac{[E^+]_i}{[Na^+]_p}\right) - \frac{V_i[E^+]_i}{[E^+]_{u,max}}\left(1 - \frac{[E^+]_{u,max}}{[Na^+]_p}\right) \tag{9.1}$$

$$\Delta TBW = V_i - V_i\frac{[E^+]_i}{[Na^+]_p} - V_i\frac{[E^+]_i}{[E^+]_{u,max}} + V_i\frac{[E^+]_i}{[Na^+]_p} = V_i\left(1 - \frac{[E^+]_i}{[E^+]_{u,max}}\right) \tag{9.2}$$

Combining this result with Equation (4) results in:

$$\Delta[Na^+]_p = -\frac{[Na^+]_pV_i}{TBW}\left(1 - \frac{[E^+]_i}{[E^+]_{u,max}}\right) = \frac{[Na^+]_pV_i}{TBW}\left(\frac{[E^+]_i}{[E^+]_{u,max}} - 1\right) \tag{10}$$

Infusate tonicity (T_i) and urine tonicity (T_u) are determined by the osmotically active cations and anions in the infusate and urine, respectively. Therefore, in terms of tonicity, Equation (10) can be rewritten as follows:

$$\Delta[Na^+]_p = \frac{[Na^+]_pV_i}{TBW}\left(\frac{2[E^+]_i}{2[E^+]_{u,max}} - 1\right) = \frac{[Na^+]_pV_i}{TBW}\left(\frac{T_i}{T_{u,max}} - 1\right) \tag{11}$$

The tonicity of a crystalloid intravenous fluid (which only consists of equal concentrations of cations and anions) is constant and equals twice its cation concentration. It is therefore equal to its osmolarity (O_i):

$$T_i = [E^+]_i + [E^-]_i = 2[E^+]_i = O_i \tag{12}$$

Whereas urine osmolarity remains relatively fixed in SIADH, urine tonicity will change during the infusion of saline due to the renal excretion of the infused electrolytes until a steady-state tonicity $T_{u,max}$ is reached, which cannot be measured prior to infusate administration. However, $T_{u,max}$ can be fairly reliably estimated as a percentage of the initial urine osmolarity (i.e., before infusate administration).[9][10] Both Shimizu et al. and Musch et al. have experimentally established that –for any given urine osmolarity– the $T_{u,max}$ of SIADH patients constitutes approximately 60% of the initial urine osmolarity under normal dietary conditions; they concluded that $2[Na^+ + K^+]_{u,max}/O_u$ equals 59.7 ± 1.7%, and that $[Na^+ + K^+]_{u,max}/O_u$ equals 33.0 ± 10.0%, respectively.[9][10] The remaining 40% consists of osmotically inert solutes, such as urea.[9][10] Therefore:

$$T_{u,max} = [E^+]_{u,max} + [E^-]_{u,max} = 2[E^+]_{u,max} \approx 0.6O_u \tag{13}$$

Because the urine osmolarity in SIADH is relatively fixed for a given patient, so is the corresponding maximum urine tonicity.[2][3] The expression above is in line with the clinical observations by –among others– Hoorn et al., Zietse et al. and Shimizu et al. that isotonic saline can be an effective treatment for SIADH if, and only if, the initial urine osmolarity is lower than 530 mOsmol/L.[9][12][13] The osmolarity of normal saline (308 mOsmol/L) equals approximately 60% of 530 mOsmol/L. In other words, saline infusion will raise the plasma sodium concentration in SIADH as long as its tonicity is higher than the maximum urine tonicity for a given urine osmolarity.

Substitution of the results from Equations (12) and (13) in Equation (11) produces the following relationship:

$$\Delta[Na^+]_p = \frac{[Na^+]_p V_i}{TBW}\left(\frac{T_i}{T_{u,max}} - 1\right) = \frac{[Na^+]_p V_i}{TBW}\left(\frac{O_i}{0.6O_u} - 1\right) \tag{14.1}$$

$$\Delta[Na^+]_p = \frac{[Na^+]_p V_i}{TBW}\left(1.7\frac{O_i}{O_u} - 1\right) \tag{14.2}$$

In line with the Adrogue-Madias equation, Equation (14.2) can be further simplified for an infusate volume of one liter (i.e., $V_i = 1$):

$$\Delta[Na^+]_p = \frac{[Na^+]_p}{TBW}\left(1.7\frac{O_i}{O_u} - 1\right) \tag{15}$$

Alternatively, Equation (14.2) can easily be rewritten algebraically in order to determine the infusate volume that is required to cause a certain desired change in the plasma sodium concentration ($\Delta[Na^+]_{p,d}$) in SIADH patients:

$$V_i = \frac{\Delta[Na^+]_{p,d} O_u TBW}{[Na^+]_p(1.7O_i - O_u)} \tag{16}$$

3. DISCUSSION AND CONCLUSION

In the previous section, a novel and straightforward equation has been derived that can be useful to estimate the effect of intravenous fluid therapy on the plasma sodium concentration in SIADH patients. As mentioned, the use of intravenous fluids in this patient category should prompt caution, as the inability of the kidneys to properly dilute the urine can easily result in deterioration of hyponatremia.[2][3] Previously described mathematical prediction models, such as the well-known Adrogue-Madias equation, only look at input, whereas output is neglected.[14][15][16] Therefore, they cannot be applied to patients with abnormal renal water-handling.[14][15][16] Owing to its mathematical transparency, the presented equation provides "bed-side" guidance on fluid replacement therapy in patients with disorders of autonomous vasopressin secretion.

In order to validate our model, we have collected five patient examples from our clinic (Table 1). In all of these patients the diagnosis of SIADH was made, based on elevated urinary sodium excretion (>30 mmol/L), and elevated urine osmolarity – indicating (inappropriate) ADH-mediated free water retention. These patients did not use diuretics, and both hypothyroidism and adrenal insufficiency (or other forms of renal salt-wasting) were ruled out on clinical and biochemical grounds, as these conditions would have perturbed the diagnosis of SIADH. One of these case examples will be discussed in more detail below in order to demonstrate how the calculation of the expected change in plasma sodium concentration is performed.

Patient A is a 59-year old male with a documented case of bipolar disorder, who was admitted to the surgery ward because of an incisional hernia. The patient has a body weight of 77 kilograms, which corresponds to an estimated total body water of 46 liters. The surgeon consults the internist because the plasma sodium concentration of this patient has dropped after the administration of normal saline. Upon admittance, his plasma sodium concentration is 129 mmol/L and his plasma osmolarity is 269 mOsmol/L. His urine osmolarity on admission is 890 mOsmol/L with a urine sodium concentration of 77 mmol/L. The patient does not use diuretics and both hypothyroidism and hypocortisolism are ruled out on clinical and biochemical grounds. Therefore, the diagnosis of hypotonic hyponatremia due to SIADH is made, most likely as a result of his long-term use

of quetiapine. At the moment of consultation, the patient had already received one liter of normal saline. The effect of administering one liter of normal saline (with an uncorrected osmolarity of approximately 308 mOsmol/L) on his plasma sodium concentration can easily be predicted by inserting the above-mentioned values in Equation (14.2):

$$\Delta[Na^+]_p = \frac{[Na^+]_p V_i}{TBW}\left(1.7\frac{O_i}{O_u} - 1\right) = \frac{129 \cdot 1.0}{46}\left(\frac{1.7 \cdot 308}{890} - 1\right) = -1.15 \quad (17)$$

This calculation shows that the expected change in his plasma sodium concentration, according to our mathematical model, is –1.15 mmol/L, which means that administering normal saline should exacerbate his pre-existing condition.

On the other hand, according to the Adrogue-Madias equation the expected change in plasma sodium concentration would be:[4]

$$\Delta[Na^+]_p = \frac{[Na^+ + K^+]_i - [Na^+]_p}{TBW + 1} = \frac{154 - 129}{46 + 1} = 0.53 \quad (17)$$

Which means that the Adrogue-Madias equation predicts that the plasma sodium concentration will increase with 0.53 mmol/L, rather than decrease.

The evening after administration of the normal saline, blood is drawn again. His new plasma sodium concentration turns out to be 128 mmol/L. This measured change in plasma sodium concentration of –1 mmol/L corresponds to the change that was predicted by our equation. Because the Adrogue-Madias equation only focuses on the administered infusate and does not take renal water- and salt-handling into account, it will incorrectly predict the change in plasma sodium concentration in disorders characterized by tonic ADH secretion, such as SIADH.

As can be seen in Table 1, the presented equations accurately predict the measured change in plasma sodium concentration in these five SIADH patients for different types and different volumes of saline infusion. A second measurement of plasma sodium concentration was performed several hours

after the intravenous fluid volume had been completely administered in order to allow renal handling of the infusate. The included patient cases have been selected retrospectively from various wards, as we consider it unethical to deliberately administer a type of infusate that would likely exacerbate their conditions according to our model.

The derived mathematical model primarily rests on the notion that the change in electrolyte-free total body water –and therefore the change in plasma sodium concentration– results from the imbalance between the electrolyte-free total body water intake and the electrolyte-free total body clearance.[2][3][8][9] Because of the approximately fixed and feedback-independent urine tonicity in SIADH, the ratio of infusate tonicity to maximum urine tonicity defines whether a certain infusate volume represents a net electrolyte-free body water load or a net electrolyte-free body water loss, which intuitively stands to reason. Indeed, in the previously discussed case of normal saline infusion in a patient with SIADH – who produces very concentrated urine – it can easily be seen that $T_i/T_{u,max} < 1$, which means that this type of infusate will aggravate the pre-existing hypotonic hyponatremia (as was the case in the aforementioned example). Even in SIADH – which is classically characterized by tonic ADH secretion – the secretion of ADH will most likely fluctuate to some extent and the urine osmolarity will not remain entirely constant. However, it can reasonably be assumed that the renal handling of electrolyte-free water in SIADH will not fluctuate to a clinically significant degree during the relatively short period of time between plasma sodium measurements, in which the kidneys process the administered infusate.[2][3] Therefore, if the time between the measurement of urinary indices and the administration of an infusate is relatively short, the urine osmolarity and therefore the theoretical maximum urine tonicity will be considered approximately fixed during the hours following infusion in this model.

As mentioned before, the presented equation should only be used to calculate infusate-induced changes in plasma sodium concentration in disorders characterized by *tonic* ADH secretion (most notably SIADH, but it could theoretically also be applied to the reset osmostat syndrome, to diabetes insipidus, and to those receiving vasopressin as a part of a treatment for circulatory shock). The proposed model is not suited to be applied to patients

with a disorder of aberrant ADH secretion in which hypovolemia is the primary stimulus for ADH release (e.g., intravascular volume depletion due to diuretic use, adrenal insufficiency, extra-renal volume loss, heart failure with forward failure, and cirrhosis), since administering intravenous fluid will correct hypovolemia and remove the ADH secretion stimulus.[12] In this case, the urine osmolarity – and therefore $T_{u,max}$ – can no longer be assumed to be fixed following infusion. Furthermore, in patients with significant extra-renal water loss (e.g., considerable perspiration) or significant water gain (e.g., psychogenic polydipsia), the total body water balance as described in Equation (5) will be inaccurate.

In conclusion, the presented model is a useful and transparent clinical tool to predict the effect of fluid replacement therapy in patients with SIADH (and potentially in patients with other disorders of tonic ADH secretion). The equations can be used as a means for clinicians to get a quantitative 'order-of-magnitude' understanding of how intravenous crystalloid fluids will influence the plasma sodium concentration in these patients, in which both input and output are considered.

Table 1: Plasma sodium concentration response to infusate in five SIADH patients

Patient	A	B	C	D	E
Sex, age	M, 59 y.o.	M, 79 y.o.	F, 82 y.o.	M, 59 y.o.	F, 85 y.o.
$[Na^+]_{p,1}$	129 mM	133 mM	128 mM	106 mM	122 mM
$[Na^+]_{p,2}$	128 mM	131 mM	128 mM	107 mM	124 mM
O_s	269 mOsM	271 mOsM	263 mOsM	216 mOsM	264 mOsM
$\Delta[Na^+]_{p,m}$	-1 mM	-2 mM	0 mM	+1 mM	+2 mM
$\Delta[Na^+]_{p,p}$	-1.15 mM	-1.97 mM	+0.40 mM	+0.88 mM	+2.10 mM
O_u	890 mOsM	766 mOsM	496 mOsM	336 mOsM	345 mOsM
$[Na^+]_u$	77 mM	143 mM	127 mM	33 mM	90 mM
Infusate	0.9%-NaCl	0.9%-NaCl	0.9%-NaCl	2.5%-NaCl	2.5%-NaCl
O_i	308 mOsM	308 mOsM	308 mOsM	856 mOsM	856 mOsM
V_i	1.0L	1.5L	1.5L	0.15L	0.15L
TBW	46L	32L	27L	60L	28L
Primary diagnosis	Incisional hernia	Mediastinitis	Sjögren's syndrome	Lingering pneumonia	Viral RTI
Secondary diagnosis	SIADH, drug-induced	SIADH, drug-induced	SIADH	SIADH	SIADH, drug-induced

$[Na^+]_{p,1}$ = Plasma sodium concentration before intravenous fluid
$[Na^+]_{p,2}$ = Plasma sodium concentration after intravenous fluid
O_p = Plasma osmolarity before intravenous fluid
$\Delta[Na^+]_{p,m}$ = Measured change in plasma sodium concentration
$\Delta[Na^+]_{p,p}$ = Predicted change in plasma sodium concentration
O_u = Urine osmolarity
$[Na^+]_u$ = Urinary sodium concentration
O_i = Infusate osmolarity
V_i = Infusate volume
TBW = Total body water (0.6 times body weight for men, 0.5 times body weight for women)

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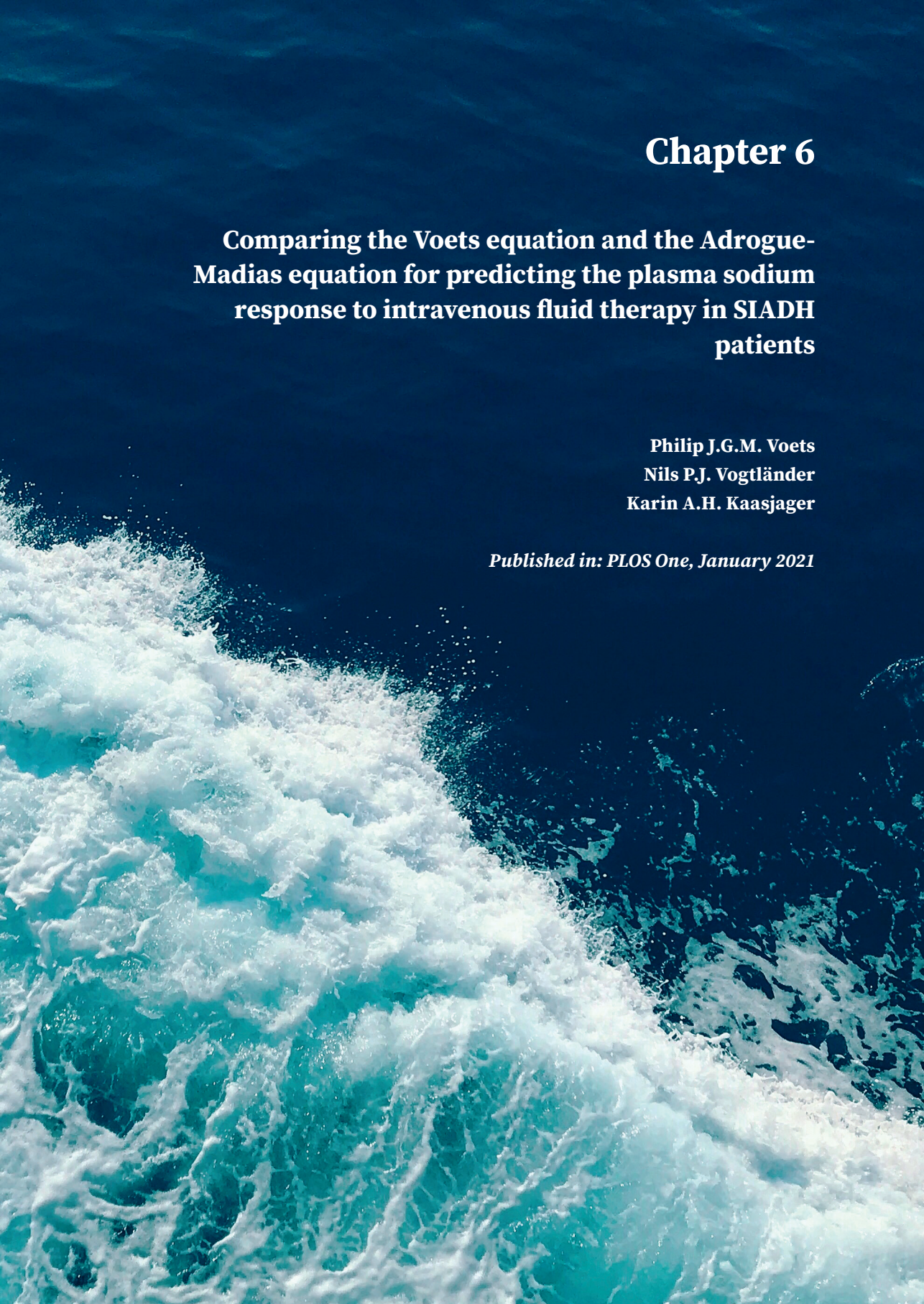

Chapter 6

Comparing the Voets equation and the Adrogue-Madias equation for predicting the plasma sodium response to intravenous fluid therapy in SIADH patients

Philip J.G.M. Voets
Nils P.J. Vogtländer
Karin A.H. Kaasjager

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ABSTRACT

Background: The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is one of the most common causes of hypotonic hyponatremia. In our previous work, we have derived a novel model (Voets equation) that can be used by clinicians to predict the effect of crystalloid intravenous fluid therapy on the plasma sodium concentration in SIADH.

Methods: In this retrospective chart review, the predictive accuracy of the Voets equation and the Adrogue-Madias equation for the plasma sodium response to crystalloid infusate was compared for fifteen plasma sodium response measurements ($n = 15$) in twelve SIADH patients. The medical records of these patients were accessed anonymously and none of the authors were their treating physicians. The Pearson correlation coefficient r and corresponding p-value were calculated for the predictions by the Voets model compared to the measured plasma sodium response and for the predictions by the Adrogue-Madias model compared to the measured plasma sodium response.

Results and conclusion: The presented results show that the Voets model ($r = 0.94$, $p < 0.001$) predicted the aforementioned plasma sodium response significantly more accurately than the Adrogue-Madias model ($r = 0.49$, $p = 0.07$) in SIADH patients and could therefore be a clinically useful addition to the existing prediction models.

1. INTRODUCTION

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is one of the most common causes of hypotonic hyponatremia, which is defined as a plasma sodium concentration below 135 mmol/L in the context of plasma hypotonicity.[1][2][3][4] This condition is characterized by the feedback-independent –and often tonic– release of antidiuretic hormone (ADH) or arginine vasopressin.[1][2][4] Because the ADH release in SIADH patients is not governed by physiological osmotic stimuli, their renal ability to excrete water is greatly diminished –which is reflected by concentrated urine with a relatively elevated and fixed urine osmolality– whereas their renal ability to excrete sodium remains fairly unaffected.[1][2][4] As a result, it has classically been accepted by clinicians that administering normal saline infusate to a SIADH patient will exacerbate hypotonic hyponatremia and should thus be considered an inappropriate treatment strategy for these patients.[1][2][3] Some authors have even suggested that the exacerbation of hypotonic hyponatremia in response to administered normal saline should be considered a confirmation of SIADH.[3]

In our previous work, we have expounded on this clinical dogma and we have presented a theoretical foundation for the opposing observations by –among others– Shimizu *et al.*, Hoorn *et al.* and Zietse *et al.* that normal saline can in fact be effective in treating SIADH-induced hypotonic hyponatremia, as long as the urine is not concentrated beyond approximately 530 mOsmol/L.[4][5][6][7][8] Based on the electrolyte-free water balance of intravenous fluid input versus urine output, we have previously derived a novel model –hereafter referred to as the Voets equation for clarity– that can be used to predict the effect of various volumes of crystalloid infusate with various tonicities on the plasma sodium concentration in SIADH, taking into account patient characteristics, such as the total body water, the urine osmolality, and the initial plasma sodium concentration.[4] Using a retrospective chart review, we have experimentally validated our previously presented mathematical model in SIADH patients by comparing the plasma sodium response to crystalloid intravenous fluid therapy of varying volumes and tonicities as predicted by our model to the measured plasma sodium change. Furthermore, we have compared these predictions of our model to the plasma sodium change predictions by the widely used Adrogue-Madias equation.[2][9]

Below, we present and discuss the results of this retrospective validation study.

2. METHODS AND RESULTS

Fifteen measurements of the plasma sodium response to saline infusate (n = 15) in twelve different SIADH patients from our clinic were documented. Their plasma sodium concentration before and after administering the saline infusate ($[Na^+]_{p,1}$ and $[Na^+]_{p,2}$, respectively) was recorded from their patient files. The aforementioned patients were included retrospectively, as we strongly felt that it would be unethical to deliberately administer a treatment which might potentially exacerbate a pre-existing hyponatremia. The medical records of these patients were accessed anonymously and none of the authors were their treating physicians.

The measured difference in plasma sodium concentration ($\Delta[Na^+]_p$) was compared to the change in the plasma sodium concentration predicted by the Voets equation and the Adrogue-Madias equation and the Pearson correlation coefficient r was calculated for both prediction models. Our calculations showed that in order to detect an estimated and rather conservative correlation of r = 0.70, using a two-sided test, a 5% significance level (a = 0.05), and a statistical power of 80% (β= 0.20), the required sample size would be approximately thirteen (n = 13). Patient characteristics are summarized in Table 1. If multiple volumes of saline infusate had been administered to the same SIADH patient (which was the case in three patients), the results are presented as separate measurements and thus as separate patients in Table 2. The average time between the first and second measurement of the plasma sodium concentration was approximately six hours. If plasma sodium measurements are performed too soon after each other, the kidneys will not have had sufficient time able to process the introduced saline. The diagnosis of SIADH was made based largely on the original Bartter-Schwartz criteria (i.e., hypotonic hyponatremia, urine that is not maximally diluted (higher than 100 mOsmol/L), clinical euvolemia, no hypothyroidism or adrenal insufficiency, and no diuretic use reported by the patients).[1] In order to further establish SIADH as the most likely cause of hypotonic hyponatremia, only patients with a urine osmolality higher than their plasma osmolality were included, as we felt that this was a strong argument in favor of significant inappropriate ADH release. If possible, a

causative underlying condition for the SIADH was identified. The administered saline volumes ranged from 0.10 liters to 1.5 liters and tonicities ranged from 308 mmol/L (0.9%-NaCl) to 856 mmol/L (2.5%-NaCl). Below, the Voets equation is presented as Equation (1):

$$\Delta[Na^+]_p = \frac{[Na^+]_p V_i}{TBW}\left(1.7\frac{O_i}{O_u} - 1\right) \quad (1)$$

In order to correct for varying infusate volumes, the Adrogue-Madias equation was algebraically modified, as the original equation can only be used for 1.0 liter of administered infusate (see Appendix).[2] Hereafter, Equation (2) will be referred to as the (modified) Adrogue-Madias equation:

$$\Delta[Na^+]_p = \frac{V_i\left([Na^+]_i - [Na^+]_p\right)}{TBW + V_i} \quad (2)$$

The Pearson correlation coefficient r ($r = 0.94$ for the predictions by the Voets model compared to the measured plasma sodium response versus $r = 0.49$ for the predictions by the Adrogue-Madias model compared to the measured plasma sodium response) and the corresponding p-values ($p < 0.001$ for Voets model versus $p = 0.07$ for Adrogue-Madias model) were calculated and the correlation scatter plots were presented (see Figure 1).[10]

Informed consent and ethical approval were not applicable for retrospective chart review; the medical records of these patients were accessed anonymously and none of the authors were their treating physicians.

3. DISCUSSION

In the previous section we have compared the predictive accuracy of the Voets equation and the Adrogue-Madias equation for the plasma sodium response to crystalloid infusate for fifteen plasma sodium response measurements in SIADH patients from our clinic.[2][4][9] The presented results show that the Voets model ($r = 0.94$, $p < 0.001$) predicted this plasma sodium response significantly more accurately than the Adrogue-Madias model ($r = 0.49$, $p = 0.07$) in SIADH patients. When comparing our model to the one presented by Adrogue-Madias, a rather intuitive Bayesian principle seems to apply, in which predictions tend to become more accurate as more information is included in the model. This was especially true when a decrease in the plasma sodium concentration occurred in response to intravenous fluid therapy, whereas both equations were relatively comparable in predictive accuracy for increases in the plasma sodium concentrations. This discrepancy can be explained by the fact that the Voets model takes both infusate input and urine output into account and therefore provides a more accurate overall prediction of the plasma sodium response, as opposed to the Adrogue-Madias equation which solely considers redistribution of the introduced infusate.[2][4][9] The more concentrated the urine of these SIADH patients (which generally reflects a stronger release of ADH) and thus the lower their electrolyte-free water excretion, the stronger the effect of output –rather than input– on their overall electrolyte-free water balance and therefore on their net plasma sodium response to intravenous fluid therapy.[4][5][8] In our opinion, including the urine output parameter in our equation considerably increases its predictive accuracy, but does not significantly add to its complexity and therefore does not limit its clinical applicability.[4] Although we feel that the assumption of relatively fixed urine osmolality in SIADH (classically considered a hallmark of this condition) is reasonable for the purpose of deriving our prediction model, this is not always true, as more than one ADH release pattern has been described in SIADH.[1] It also stands to reason that the stimulus or agent which provokes aberrant ADH release can be removed, in which case SIADH ceases to exist and our model can no longer be reliably used.

The limitations of the Adrogue-Madias equation, which we have also discussed in this article, and comparable prediction models have previously been noted by

several authors.[11][12][13] At the same time, these authors also express the strong desire among physicians for a clinical equation that can accurately predict the plasma sodium response to intravenous fluid therapy.[11][12][13] The daunting mathematical complexity of some existing models is another factor that can limit their clinical utility.[13][14] Since the Voets equation is primarily intended for a quick 'bed-side evaluation' of the effect of intravenous fluid therapy on the plasma sodium concentration in SIADH patients, mathematical transparency should be considered a *condicio sine qua non*. Furthermore, our model can be used to predict the plasma sodium response to varying volumes and tonicities of crystalloid infusate, rather than the standard 1.0 liter of crystalloid infusate in the original Adrogue-Madias equation.[2][9] For the purpose of our model, other sources of fluid input and/or output, such as insensible water losses or diarrhea, were not taken into account.[4] If such fluid gains or losses are significant, this should be considered a potential source of error.

The most important limitation of our equation is that it can only be reliably applied to SIADH patients.[4] Although we strongly suspect that our model could also be applied to patients with other types of feedback-independent ADH release (such as diabetes insipidus or reset osmostat syndrome) and to patients receiving continuous administration of vasopressin analogues (most notably, Intensive Care patients with circulatory shock or patients with severe hyponatremia who are treated with a so-called "desmopressin (DDAVP) clamp strategy" to prevent rapid auto-correction of the plasma sodium concentration), these have not been included in our analysis.[4][15] The reason for this limitation is that our model assumes that the urine osmolality in SIADH patients, which we have used as a measure for the theoretical maximum urine tonicity in our previous work, does not change to a relevant extent between the two measurements of the plasma sodium concentration.[4][5][16] This is a reasonable assumption in the case of relatively tonic, feedback-independent ADH release, but not for many other causes of dysnatremia. When applying our model to guide intravenous fluid therapy in hypotonic hyponatremia, the clinician should verify that SIADH is the most likely causative disorder. Furthermore, our equation has not been validated in patients receiving non-crystalloid intravenous fluids (e.g., intravenous sugar solutions).[4] However, since it seems highly unlikely that a patient suffering from hypotonic hyponatremia would receive non-crystalloid infusate, this does not seem to be a clinically

important limitation. Due to the retrospective nature of this validation study, our model was tested in a relatively small group of SIADH patients. Further (prospective) validation of our prediction model in a larger group of SIADH patients remains desirable. Ideally, such a validation study should also aim to expand the application of our model to other disorders that are characterized by feedback-independent ADH release, but this falls beyond the scope of this article.

In conclusion, we believe that the Voets equation is a mathematically transparent clinical tool to accurately guide intravenous fluid therapy in patients suffering from SIADH, which remains one of the most common causes of hypotonic hyponatremia. This being said, no mathematical model is incontrovertible. Frequent measurements of the plasma sodium concentration and astute clinical reasoning by the attending physician remain imperative.

APPENDIX

In order to correct for varying infusate volumes, the Adrogue-Madias equation was algebraically modified, as the original equation (Equation 3.1) can only be used for 1.0 liter of infusate:[2][9]

$$\Delta[Na^+]_p = \frac{[Na^+]_i - [Na^+]_p}{TBW + 1} \tag{3.1}$$

The plasma sodium change ($\Delta[Na^+]_p$) to infusate (with volume V_i and sodium concentration $[Na^+]_i$) can be calculated by subtracting the original plasma sodium concentration ($[Na^+]_{p,1}$) from the plasma sodium concentration after the infusate has been administered ($Na^+]_{p,2}$):

$$\Delta[Na^+]_p = [Na^+]_{p,2} - [Na^+]_{p,1} = \frac{{Na_p}^+ + {Na_i}^+}{TBW + V_i} - \frac{{Na_p}^+}{TBW} \tag{3.2}$$

In order to improve mathematical clarity and because this retrospective validation study looks at different types saline (which is free of potassium), potassium is disregarded in Equation (3.2). This equation can be algebraically rewritten to:

$$\frac{TBW\left({Na_p}^+ + {Na_i}^+\right)}{TBW(TBW + V_i)} - \frac{{Na_p}^+(TBW + V_i)}{TBW(TBW + V_i)} =$$

$$\frac{TBW{Na_p}^+ + TBW{Na_i}^+ - TBW{Na_p}^+ - V_i{Na_p}^+}{TBW(TBW + V_i)} = \tag{3.2}$$

$$\frac{TBW{Na_i}^+ - V_i{Na_p}^+}{TBW(TBW + V_i)} = \frac{{Na_i}^+ - V_i\left({Na_p}^+/TBW\right)}{TBW + V_i} \tag{3.3}$$

This produces the modified Adrogue-Madias equation, which was used in our article:

$$\frac{V_i[Na^+]_i - V_i\left({Na_p}^+/TBW\right)}{TBW + V_i} = \frac{V_i[Na^+]_i - V_i[Na^+]_p}{TBW + V_i} = \frac{V_i\left([Na^+]_i - [Na^+]_p\right)}{TBW + V_i} \tag{3.4}$$

Table 1: Characteristics of the included SIADH patients and the administered intravenous fluids

Measurement	TBW (weight)	Infusate (V_i, type)	$Na^+]_{p,1}$	$Na^+]_{p,2}$	O_u
1 (M, 79 y.o.)	34 L (57 kg)	1.5L 0.9%-NaCl	133 mmol/L	131 mmol/L	766 mOsmol/L
2 (M, 78 y.o.)	37 L (62 kg)	1.0 L 0.9%-NaCl	132 mmol/L	131 mmol/L	702 mOsmol/L
3 (M, 74 y.o.)	30 L (60 kg)	1.0 L 0.9%-NaCl	130 mmol/L	129 mmol/L	614 mOsmol/L
4 (M, 74 y.o.)	30 L (60 kg)	0.5 L 0.9%-NaCl	129 mmol/L	128 mmol/L	689 mOsmol/L
5 (M, 59 y.o.)	40 L (77 kg)	1.0 L 0.9%-NaCl	129 mmol/L	128 mmol/L	890 mOsmol/L
6 (F, 66 y.o.)	33 L (66 kg)	1.0 L 0.9%-NaCl	131 mmol/L	130 mmol/L	569 mOsmol/L
7 (F, 78 y.o.)	25 L (50 kg)	1.0 L 0.9%-NaCl	128 mmol/L	127 mmol/L	660 mOsmol/L
8 (F, 82 y.o.)	27 L (54 kg)	1.5 L 0.9%-NaCl	128 mmol/L	128 mmol/L	496 mOsmol/L
9 (F, 78 y.o.)	25 L (50 kg)	0.10 L 2.5%-NaCl	127 mmol/L	128 mmol/L	677 mOsmol/L
10 (M, 59 y.o.)	60 L (100 kg)	0.15 L 2.5%-NaCl	106 mmol/L	107 mmol/L	336 mOsmol/L
11 (F, 87 y.o.)	43 L (86 kg)	1.5 L 0.9%-NaCl	131 mmol/L	132 mmol/L	386 mOsmol/L
12 (M, 69 y.o.)	47 L (79 kg)	0.15 L 2.5%-NaCl	122 mmol/L	123 mmol/L	645 mOsmol/L
13 (M, 69 y.o.)	47 L (79 kg)	0.10 L 2.5%-NaCl	123 mmol/L	124 mmol/L	559 mOsmol/L
14 (F, 84 y.o.)	35 L (70 kg)	0.10 L 2.5%-NaCl	121 mmol/L	122 mmol/L	354 mOsmol/L
15 (F, 85 y.o.)	29 L (58 kg)	0.15 L 2.5%-NaCl	122 mmol/L	124 mmol/L	345 mOsmol/L

Table 2: Comparison of the Voets (V) equation and the modified Adrogue-Madias (A-M) equation for prediction of the change in plasma sodium concentration in response to intravenous fluid therapy in SIADH patients

n	Measured $\Delta[Na^+]_p$	Predicted $\Delta[Na^+]_p$ according to V*	Predicted $\Delta[Na^+]_p$ according to A-M**	SIADH	Causative condition
1	-2 mmol/L	-1.9 mmol/L	+0.9 mmol/L	Yes	Citalopram use
2	-1 mmol/L	-1.2 mmol/L	+0.6 mmol/L	Yes	Pain due to leg ischemia
3	-1 mmol/L	-0.8 mmol/L	+0.8 mmol/L	Yes	Pneumonia
4	-1 mmol/L	-0.5 mmol/L	+0.4 mmol/L	Yes	Pneumonia
5	-1 mmol/L	-1.7 mmol/L	+0.6 mmol/L	Yes	Quetiapine use
6	-1 mmol/L	-0.4 mmol/L	+0.7 mmol/L	Yes	Non-small cell lung carcinoma
7	-1 mmol/L	-1.3 mmol/L	+1.0 mmol/L	Yes	Pain due to hip fracture
8	0 mmol/L	+0.4 mmol/L	+1.4 mmol/L	Yes	Unknown
9	+1 mmol/L	+0.6 mmol/L	+1.2 mmol/L	Yes	Pain due to hip fracture
10	+1 mmol/L	+0.9 mmol/L	+0.8 mmol/L	Yes	Pneumonia
11	+1 mmol/L	+1.6 mmol/L	+0.8 mmol/L	Yes	Unknown
12	+1 mmol/L	+0.5 mmol/L	+1.0 mmol/L	Yes	Psychosis
13	+1 mmol/L	+0.4 mmol/L	+0.6 mmol/L	Yes	Psychosis
14	+1 mmol/L	+1.1 mmol/L	+0.9 mmol/L	Yes	Pneumonia
15	+2 mmol/L	+2.0 mmol/L	+1.6 mmol/L	Yes	Viral respiratory tract infection

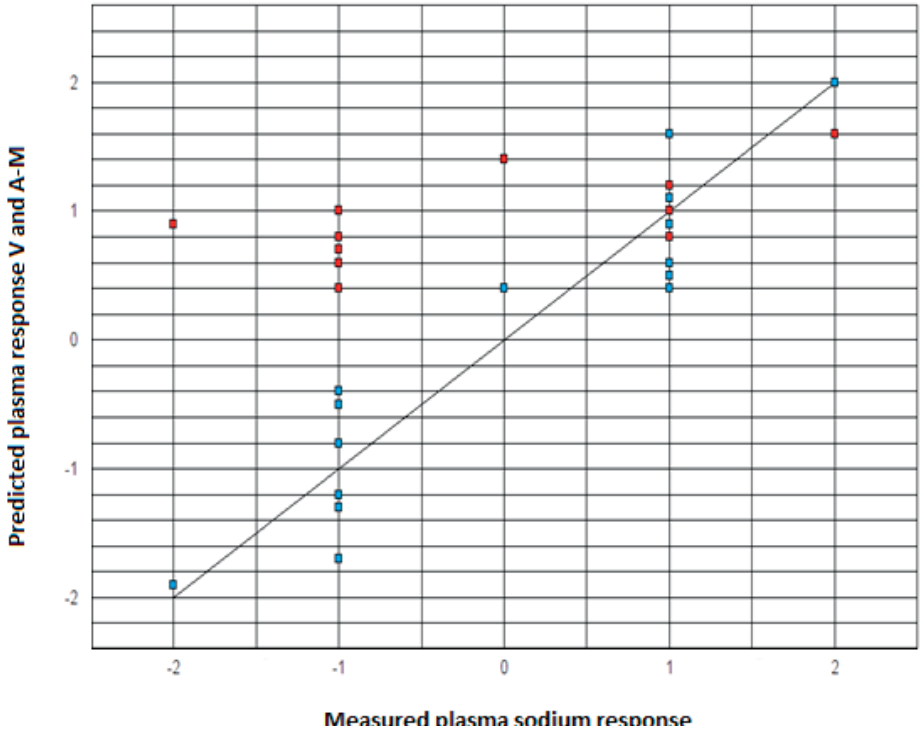

Figure 1: Scatter plot showing a comparison of the Voets (V) equation (blue dots) and the modified Adrogue-Madias (A-M) equation (red dots) for prediction of the change in plasma sodium concentration in response to intravenous fluid therapy in the included SIADH patients (scatter plot was created using www.onlinecharttool.com).[10]

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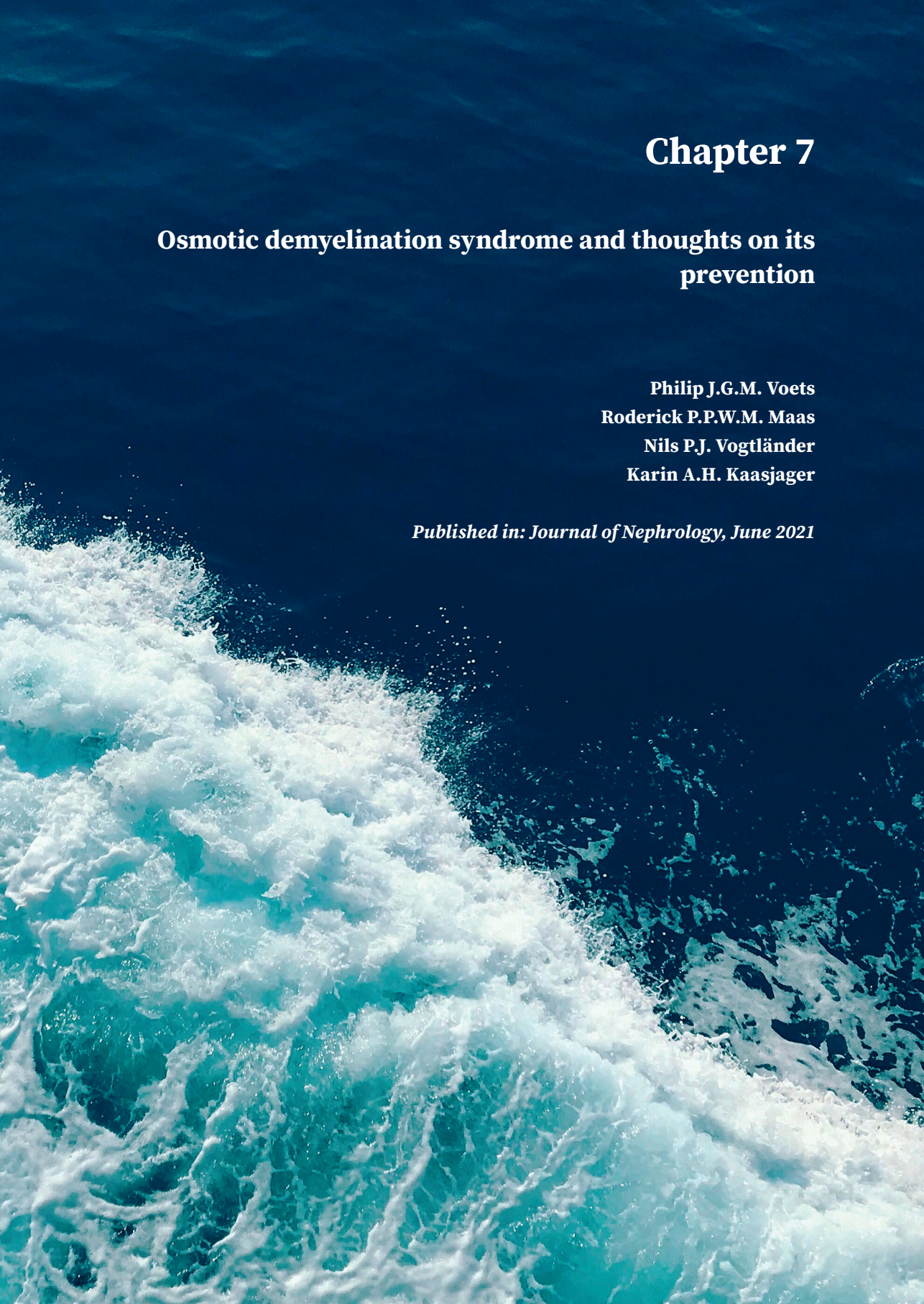

Chapter 7

Osmotic demyelination syndrome and thoughts on its prevention

Philip J.G.M. Voets
Roderick P.P.W.M. Maas
Nils P.J. Vogtländer
Karin A.H. Kaasjager

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1. INTRODUCTION

Osmotic demyelination syndrome (ODS) is a devastating clinical repercussion of the body's inability to accurately respond to a rapid rise in plasma tonicity that can occur in malnourished individuals with a long-standing hyponatremia that was corrected too rapidly (Figure 1).[1][2] Here, after presenting a patient who unfortunately developed ODS, we discuss insights into its prevention.

A 46-year-old female patient with a medical history of hypertension, for which she used hydrochlorothiazide, presented to the Emergency Department with confusion and lethargy. Over the past few weeks, she had consumed excessive amounts of alcohol, accompanied by poor oral intake. Her general physical examination was unremarkable, except for a heart rate of 110 beats per minute. She was normotensive and weighed 62 kilograms. Neurological examination revealed disorientation, restless behavior, and a staggering gait, but no paresis or appendicular ataxia. A CT scan excluded structural intracerebral abnormalities. Her plasma sodium concentration turned out to be 95 mmol/L with a measured plasma osmolarity of 198 mOsmol/L. Her plasma potassium concentration was also low at 2.9 mmol/L and she was normoglycemic. Urine osmolarity on admission was 248 mOsmol/L, implying non-osmotic ADH release in the context of profound hyponatremia, with a urine sodium concentration of 36 mmol/L. Hypothyroidism and hypocortisolism were ruled out. The internist concluded that her hypotonic hyponatremia was probably caused by chronic hydrochlorothiazide use and poor oral intake and ordered boluses of hypertonic saline (3.0%-NaCl), striving for a maximum correction rate of the plasma sodium concentration of 10 mmol/L in the first 24 hours. Her plasma sodium concentration and urine output were strictly monitored (Table 1). Her plasma sodium concentration increased by 5 mmol/L in the first seven hours, which prompted conversion to a 5%-glucose infusion. After six hours of stable plasma sodium concentrations, infusion was switched to 2.5%-glucose/0.45%-NaCl. The correction was then suddenly accompanied by massive diuresis and a decrease in urine osmolarity to 46 mOsmol/L. Seventeen hours after presentation, her plasma sodium concentration was 105 mmol/L. As a rescue strategy, intravenous desmopressin was administered along with 5%-glucose infusion. The following days, her plasma sodium concentration gradually increased toward normonatremia. A week later, however, she developed severe

tetraparesis and respiratory insufficiency requiring intubation. A brain MRI scan showed T_2/FLAIR-hyperintense, T_1-hypointense signals centrally in the pons, basal ganglia, and thalami, confirming the diagnosis of ODS.

2. LESSONS FOR THE CLINICAL NEPHROLOGIST

Our case demonstrates the dramatic neurological sequelae of an overly rapid correction of a profound hypotonic hyponatremia of multifactorial aetiology, which –although anticipated– could not be prevented.[1,2,3] Here, saline infusion removed the hydrochlorothiazide-induced hypovolemic antidiuretic hormone (ADH) stimulus, which resulted in a considerable increase in renal free water clearance and a steep rise in plasma sodium concentration. This dangerous phenomenon is commonly referred to as "auto-correction".[4] It should be noted that the mechanism of thiazide-associated hyponatremia is probably more complex than simple hypovolemia-mediated ADH release and has recently been shown to also involve disrupted prostaglandin E_2 transport in the renal tubular epithelium.[5] Furthermore, reintroduction of solutes in the form of saline after a prolonged period of inadequate intake strongly increased the patient's urine output, adding to the auto-correction.[4] Her poor intake may also have contributed to intravascular volume depletion. The depth of the patient's plasma sodium concentration and her responsiveness on presentation imply that the hypotonic hyponatremia was chronic in nature. Therefore, her pontine cells will have had ample time to adapt to the chronic plasma hypotonicity by decreasing their cytoplasmic solute content, but not enough time to adjust to the rapid rise in plasma sodium concentration when the hypovolemic ADH stimulus was removed. It could be argued that her "malnourished" pontine cells were already less capable of adjusting their intracellular solute content in response to any increase in extracellular tonicity.[1] Hypokalemia has also been described as a risk factor for the development of ODS, probably because it often reflects a poor nutritional status or hypovolemic activation of the renin-angiotensin-aldosterone system, both of which predispose for auto-correction.[1] In our case, however, the observed hypokalemia was most likely the result of chronic hydrochlorothiazide use and malnutrition.

3. PROACTIVE DESMOPRESSIN CLAMP, THE VOETS EQUATION AND HYPERTONIC SALINE

In order to forestall neurological complications, guidelines recommend a maximum allowable correction rate of the plasma sodium concentration of 8 to 10 mmol/L in the first 24 hours, followed by 8 mmol/L per 24 hours over the next days.[2,3] The maximum allowable correction of extreme hyponatremia should be even slower, since the relative increase in plasma tonicity is larger. A proactive "desmopressin clamp" (PDC) with hypertonic saline boluses is an effective, safe, but relatively unfamiliar treatment strategy for patients with severe hypotonic hyponatremia who are at risk for rapid auto-correction and ODS.[6,7] PDC, although counter-intuitive at first glance, is intended to control renal free water clearance through the administration of desmopressin, a synthetic ADH analogue. A rational initial dose is 2 μg i.v., after which the following doses depend on urine osmolarity and output.[6,7] The treating physician can then correct the plasma sodium concentration in a controlled fashion by administering calculated hypertonic saline boluses without being surprised by sudden water diuresis when the endogenous ADH release falls.[6,7] This proactive strategy is different from a reactive strategy or rescue strategy, as was attempted in the discussed patient.[7]

The central problem for physicians when initiating a PDC is accurately predicting the increase in plasma sodium concentration in response to saline infusate to make sure that the correction limit is not exceeded. Many physicians rely on the Adrogue-Madias equation to estimate this change.[4,6,8] A major and frequently cited issue with this model is that it solely looks at the redistribution of crystalloid infusate and disregards any subsequent renal water and solute handling. Therefore, calculations according to the Adrogue-Madias equation are short-term predictions, and their accuracy quickly breaks down as time passes.[8,9] Ignoring renal infusate handling will lead to an imprecise prediction of the "net" –clinically relevant– effect of saline infusion on the plasma sodium concentration. A novel model –hereafter referred to as the Voets equation– has recently been derived and validated for SIADH patients. This model is based on the electrolyte-free water balance that considers both infusate input and renal output under the condition of relatively fixed urine osmolarity. Therefore, it is an ideally suited model to predict the net change in plasma

sodium concentration in response to crystalloid infusate boluses with a PDC (dubbed "therapeutic SIADH").[8,9] Because sudden changes in endogenous ADH release are not an issue with a PDC, the patient essentially has a fixed urine osmolarity. For this particular scenario, the Voets equation –described below– is conceptually better suited than the Adrogue-Madias model, as previously shown for SIADH patients:[8,9]

$$\Delta[Na^+]_p = \frac{[Na^+]_p V_i}{TBW}\left(1.7\frac{O_i}{O_u} - 1\right) \tag{1}$$

Here, the parameters $\Delta[Na^+]_p$, $[Na^+]_p$, V_i, TBW, O_i, and O_u represent the predicted change in plasma sodium concentration, initial plasma sodium concentration, infusate volume, total body water, infusate osmolarity (which equals infusate tonicity for crystalloid fluids), and urine osmolarity, respectively.[8]

Suppose that a PDC is applied to the previously presented patient with total body water of 31 liters, as estimated from her body weight, and that her urine osmolarity is clamped at approximately 250 mOsmol/L, which corresponds to her urine osmolarity on admission. This is desirable as PDC merely sets the stage for a controlled correction of the plasma sodium concentration; it should not in itself induce significant changes in free water clearance. According to the Voets equation, her predicted change in plasma sodium concentration in response to a 0.50L 3.0%-NaCl bolus (osmolarity: 1,026 mOsmol/L) would be 9.1 mmol/L:[8]

$$\Delta[Na^+]_p = \frac{95 \cdot 0.5}{31}\left(1.7 \cdot \frac{1{,}026}{250} - 1\right) \approx 9.1 \tag{2}$$

By contrast, the modified Adrogue-Madias equation estimates the net effect of a 0.50L 3.0%-NaCl bolus (sodium concentration: 513 mmol/L) on the plasma sodium concentration as follows:[4,9]

$$\Delta[Na^+]_p = \frac{V_i\left([Na^+]_i - [Na^+]_p\right)}{TBW + V_i} = \frac{0.5 \cdot (513 - 95)}{31 + 0.5} \approx 6.6 \tag{3}$$

Although no prediction model is infallible and a margin of error is inevitable, this relative underestimation of 2.5 mmol/L could encourage physicians to administer larger volumes of saline to the patient than the Voets equation suggests, potentially causing an overly rapid correction of the plasma sodium concentration. In a similar vein, a 3.0%-NaCl bolus of 0.75L, required to increase this patient's plasma sodium concentration with 10 mmol/L according to the Adrogue-Madias equation, leads to an estimated change of almost 14 mmol/L when the Voets equation is applied.

In our opinion, a PDC with hypertonic saline boluses, calculated according to the Voets equation, is a rational, safe, and effective treatment strategy for hyponatremic patients at risk for auto-correction and ODS. Obviously, frequent measurements of the plasma sodium concentration remain imperative.

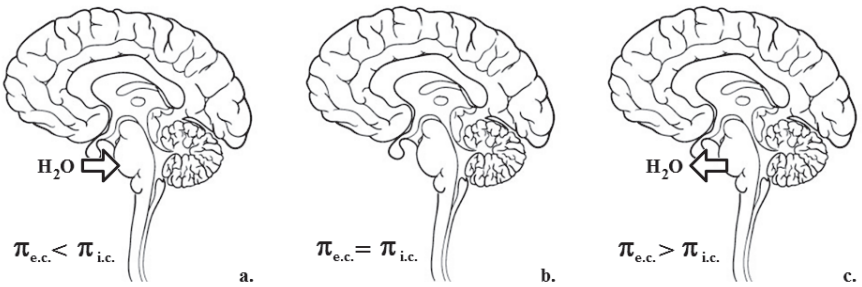

Figure 1. Osmotic water movement in the brain. If the effective osmolarity of the extracellular compartment ($\pi_{e.c.}$) is lower than the effective osmolarity of the intracellular compartment ($\pi_{i.c.}$), water moves into the brain cells (a). This occurs in hypotonic hyponatremia. If the effective osmolarity of the extracellular compartment is equal to the effective osmolarity of the intracellular compartment, no water will move between these compartments (b). This occurs when brain cells have adjusted their intracellular osmolarity to hypotonic hyponatremia by reducing their cytosolic solute content. If the effective osmolarity of the extracellular compartment is higher than the effective osmolarity of the intracellular compartment, water moves out of the brain cells (c). This occurs if long-standing hypotonic hyponatremia is corrected. If the water losses in (c) are large enough and occur relatively rapidly (>8 mmol/L/day), massive lysis of glial cells may ensue, also known as osmotic demyelination syndrome (ODS). The arrow in (a) points toward the pons, which contains fibers of the corticospinal and corticobulbar tracts and is especially vulnerable to ODS, also known as central pontine myelinolysis. ODS in other structures in the central nervous system, such as the thalami and basal ganglia, is known as extrapontine myelinolysis.[1]

Table 1: Course of the patient's plasma sodium concentration (where (A) refers to a radial artery puncture), urine osmolarity, urine output, and intervention on the day of her admission. It can be seen that an increase in the plasma sodium concentration of 10 mmol/L occurred in the frst 17 h after admission, exceeding the maximum allowable correction rate.

Hours since admittance	Plasma sodium concentration	Urine osmolarity	Urine output	Intervention
0	95 mmol/L	248 mOsmol/L	-	3.0%-NaCl (bolus of 100 mL)
1	<100 mmol/L (A)	246 mOsmol/L	125 mL/h	-
2	98 mmol/L	-	100 mL/h	Ringer's infusate (bolus of 250 mL)
3	98 mmol/L	-	100 mL/h	-
5	100 mmol/L (A)	102 mOsmol/L	200 mL/h	5.0%-glucose (bolus of 1000 mL)
10	102 mmol/L	173 mOsmol/L	-	2.5%-glucose / 0.45%-NaCl (? mL)
12	101 mmol/L	252 mOsmol/L	400 mL/h	2.5%-glucose / 0.45%-NaCl (? mL)
15	102 mmol/L	152 mOsmol/L	700 mL/h	5.0%-glucose (1000 mL/h)
17	105 mmol/L	46 mOsmol/L	850 mL/h	5.0%-glucose (? mL) / DDAVP
18	102 mmol/L	92 mOsmol/L	1150 mL/h	5.0%-glucose (? mL) / DDAVP
22	100 mmol/L	50 mOsmol/L	700 mL/h	5.0%-glucose (? mL) / DDAVP

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Chapter 8

Extracellular volume depletion and resultant hypotonic hyponatremia: a novel translational approach

Philip J.G.M. Voets
Roderick P.P.W.M. Maas

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ABSTRACT

Although several methods currently exist to determine that a person is hypovolemic, it often remains very challenging to accurately estimate the effective circulating volume or amount of intravascular volume depletion in a non-controlled setting. This depletion of intravascular volume can have many causes and is frequently accompanied by hypotonic hyponatremia as a result of hypovolemia-induced release of antidiuretic hormone from the posterior pituitary gland. Here, we derive a novel, comprehensible equation that provides a theoretical insight into the complex interrelationship between the degree of isotonic volume depletion and the resultant change in plasma sodium concentration.

1. INTRODUCTION

Intravascular volume depletion represents a common problem in everyday clinical practice and may pose a therapeutic challenge to the physician facing it. Its miscellaneous causes can broadly be divided into absolute extracellular volume loss and volume shift between the various body fluid compartments, e.g. interstitial edema in nephrotic syndrome, congestive heart failure, and cirrhosis. Irrespective of the underlying cause, contraction of extracellular fluid is frequently accompanied by hypotonic hyponatremia of varying degrees. When presented with the choice, the human body prioritizes the correction of extracellular volume depletion over maintaining plasma osmolality. Indeed, reduced effective circulating volume itself is a potent stimulus for the release of antidiuretic hormone (ADH), also known as arginine vasopressin (AVP), from the posterior pituitary gland, although –under physiological circumstances– the secretion of this hormone is regulated primarily by changes in the plasma osmolality.[1][2] ADH release stimulates the insertion of aquaporin-2 channels in the apical membrane of collecting duct epithelial cells which results in the renal retention of pure water. A relatively small part of this reabsorbed water will remain in the extracellular compartment and increase (albeit slightly) the intravascular volume at the cost of plasma dilution, while the remaining water will redistribute into the intracellular compartment.[1][2] Hypovolemia-induced release of ADH –and consequently the retention of pure water– has been shown to be the pathophysiological substrate behind the hyponatremia that can be observed in patients with different kinds of intravascular volume depletion, e.g. hemorrhage, vomiting, diarrhea, use of diuretics, cirrhosis, nephrotic syndrome and heart failure (see schematic representations in Figures 1 and 2, which can be considered variations on Darrow-Yannet-diagrams).[3][4]

Although this mechanism has been well-known for a long time, to our knowledge it has never been exploited before to deduce a quantitative relationship between the degree of volume depletion and the change in plasma sodium concentration. Such an equation would enhance our insight into the complex interrelationship between both variables and might eventually be of clinical benefit. Here, we aim to reduce this knowledge gap by deriving a novel and comprehensible equation that describes how isotonic volume depletion will theoretically affect plasma sodium concentration. It should be noted that this model provides a conceptual framework; an experimental validation of the presented model therefore falls beyond the scope of this article.

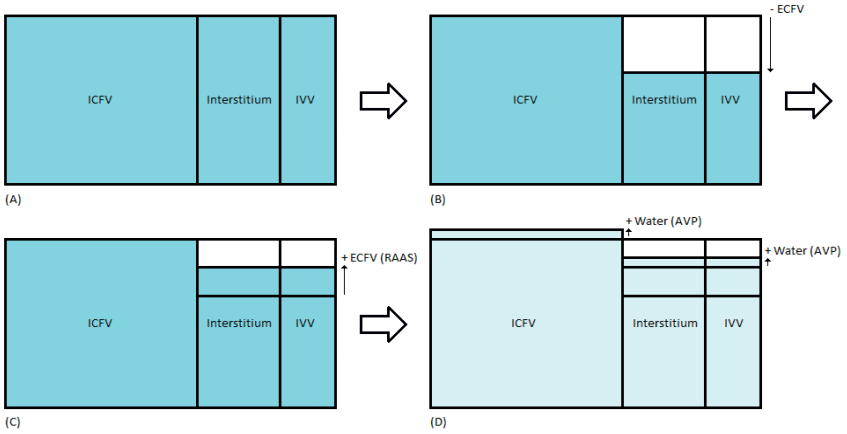

Figure 1. Schematic representation of the antidiuretic hormone (ADH) response to intravascular volume depletion due to absolute losses. Intravascular volume depletion due to absolute losses (B) stimulates the renin-angiotensin-aldosterone system (RAAS), which leads to isotonic volume repletion (C). It also stimulates the volume-mediated release of ADH, which leads to pure water retention – and at least some repletion of intravascular volume (IVV) – at the cost of hyponatremia (D). The human body chooses correction of intravascular volume over preservation of plasma osmolality.

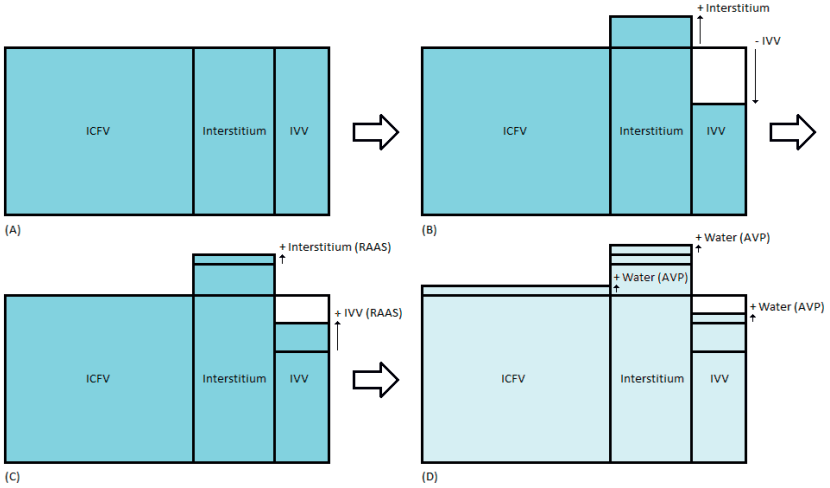

Figure 2. Schematic representation of the antidiuretic hormone (ADH) response to intravascular volume depletion due to extracellular volume shift. Intravascular volume depletion due to edema formation (B) stimulates the renin-angiotensin-aldosterone system (RAAS), which leads to isotonic volume repletion (C). It also stimulates the volume-mediated release of ADH, which leads to pure water retention –and at least some repletion of intravascular volume (IVV)– at the cost of hyponatremia (D). The human body chooses correction of intravascular volume over preservation of plasma osmolality.

2. MATHEMATICAL DERIVATION

Dunn and Brennan first demonstrated a clear and strong exponential relationship between the percentage of isotonic intravascular volume depletion ($[\Delta IVV]$) and the plasma ADH concentration ($[ADH]$) in an experimental rat model in 1973 (see Figure 3).[5] This relationship has since become widely accepted and has been cited by the leading textbooks of human physiology.[2] [6] Mathematically, this exponential relationship can be expressed as follows:

$$[ADH] = k_1 \exp(k_2 \Delta IVV) \tag{1}$$

The antidiuretic effect or water reabsorption in the collecting duct as a result of an increase in the plasma ADH concentration follows a concentration-response relationship according to Michaelis-Menten kinetics (as is the case for the vast majority of the endocrine concentration-response relationships) and can therefore be described by the following equation (see Figure 4):[7][8][9][10]

$$R([X]) = \frac{R_{max}[X]}{[X] + [X]_{50}} \tag{2}$$

In which R, $[X]$, R_{max}, and $[X]_{50}$ represent response (i.e., change in total body water ($[\Delta TBW]$), concentration of an agent, maximum response, and the hormone concentration at which 50% of is reached, respectively. A linear-logarithmic model accurately approximates the Michaelis-Menten model in the clinically relevant shoulder of the curve:[11][12][13]

$$\frac{R_{max}[X]}{[X] + [X]_{50}} \approx k_3 \ln([X]) + k_4 \tag{3}$$

In which K_3 and K_4 represent different constants, chosen in such a way that the linear-logarithmic model fits the Michaelis-Menten model. The right-hand side of Equation (3) is also known as the solution to Weber-Fechner's law (the original equation being: $dR \propto d[X]/[X]$), which is frequently applied to describe concentration-response curves in physiology and biochemistry.[14]

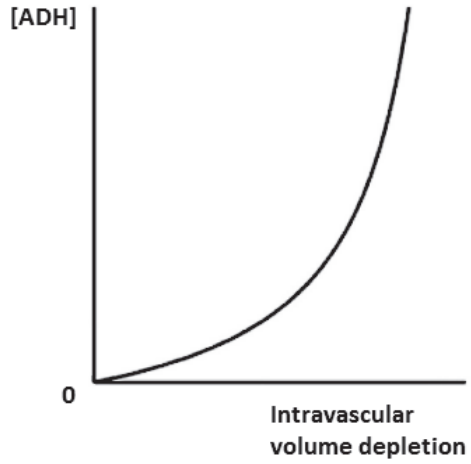

Figure 3. Exponential relationship between depletion of the intravascular volume (x-axis) and the plasma ADH concentration (y-axis). Adapted from: Hall J.E. and Guyton A.C.[2]

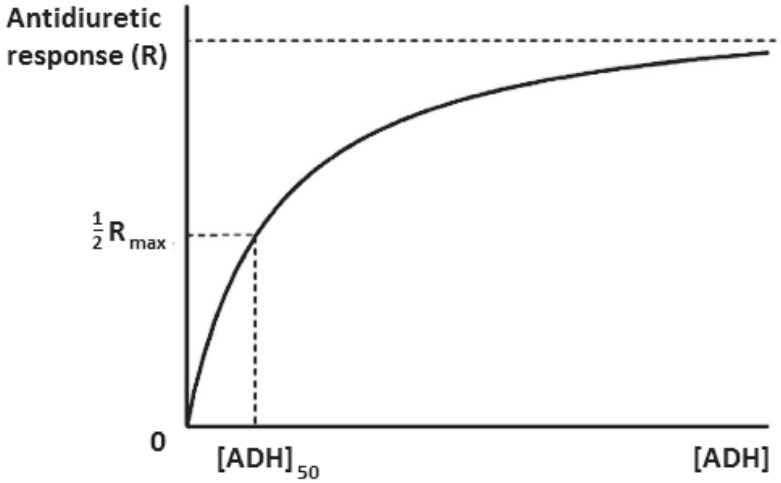

Figure 4. Graphic representation of the Michaelis-Menten-like relationship between plasma ADH ([ADH]) concentration and ADH-mediated antidiuretic effects or water retention.[7]

The relationship between total body water change as a result of renal pure water retention (ΔTBW) and the plasma ADH concentration can therefore be approximated as follows:

$$\Delta\ TBW\ \approx\ k_3\ \ln([\ ADH\ ])+k_4 \tag{4}$$

Indeed, linear-logarithmic models for the relationship between plasma ADH concentration and its antidiuretic effects have previously been described.[15] The equation above can be further simplified by substitution of Equation (1):

$$\Delta TBW = k_3 \ln(k_1 \exp(k_2 \Delta IVV)) + k_4 = k_3(k_2 \Delta IVV + \ln(k_1)) + k_4 = k_5 \Delta IVV + k_6 \tag{5}$$

Where $k_5 = k_2 k_3$, and $k_6 = k_3 \ln(k_1)+k_4$. ADH-mediated retention of pure water decreases the plasma sodium concentration ($[Na^+]_p$, in mmol/L), as described by the simplified Edelman equation: $[Na^+]_p = (Na_e^+ + K_e^+)$ / TBW, but does not alter the total amount of exchangeable body sodium and potassium ($Na_e^+ + K_e^+$):

$$Na_e^+ + K_e^+ = [Na^+]_{p,1} TBW = [Na^+]_{p,2}(TBW + \Delta TBW) \tag{6}$$

In which $[Na^+]_{p,1}$ represents the original plasma sodium concentration and $[Na^+]_{p,2}$ represents the plasma sodium concentration after plasma dilution by renal pure water retention. Equation (6) can be rearranged in order to obtain:

$$\Delta TBW = TBW \frac{[Na^+]_{p,1}}{[Na^+]_{p,2}} - TBW = TBW \left(\frac{[Na^+]_{p,1}}{[Na^+]_{p,2}} - 1 \right) \tag{7}$$

Equation (7) is essentially equivalent to the equation for total body water deficit, because there is an overlap between the mathematical derivations of both expressions. Equating the Equations (5) and (7) produces:

$$k_5 \Delta IVV + k_6 = TBW \left(\frac{[Na^+]_{p,1}}{[Na^+]_{p,2}} - 1 \right) \tag{8}$$

Total body water can be fairly accurately estimated from body weight (W, in kilograms):[2]

$$TBW = kW \tag{9}$$

In which value for the constant of proportionality k depends primarily on gender and age (usually between 0.5 and 0.6). Substitution of this relationship in Equation (8) and some algebraic rearrangement produces an expression for the percentage of intravascular volume loss in terms of the change in plasma sodium concentration (here, the constants have been renamed for the sake of clarity: $k_1 = k/k_5$ and $k_2 = k_6/k_5$):

$$\Delta IVV = K_1 W \left(\frac{[Na^+]_{p,1}}{[Na^+]_{p,2}} - 1 \right) - K_2 \tag{10}$$

Alternatively, the equation above can easily be rewritten to express the change in the plasma sodium concentration ($\Delta[Na^+]_p$) in terms of the degree of volume depletion as follows:

$$\Delta[Na^+]_p = [Na^+]_{p,2} - [Na^+]_{p,1} = [Na^+]_{p,1} \left(\frac{K_1 W}{K_1 W + K_2 + \Delta IVV} - 1 \right) \tag{11}$$

3. DISCUSSION

In the previous section, a straightforward equation has been derived that provides a means to approximate the degree of volume depletion in a hypovolemic patient based on body weight and the change in plasma sodium concentration due to hypovolemia-induced release of ADH. This is convenient, because although several methods currently exist to determine that a person is hypovolemic (e.g., heart rate, blood pressure, central venous pressure, fractional sodium excretion, urea-to-creatinine ratio), it often remains challenging to estimate the effective circulating volume or amount of volume depletion. In turn, this is important to efficiently commence and regulate fluid replacement therapy. The proposed model provides a novel, quantitative insight into the complex interrelationship between the intravascular fluid volume and disturbances in the plasma sodium concentration, which was first experimentally investigated by Edelman et al. in 1958.[16]

The derived model rests on two main pillars. The first is the ubiquitously cited exponential relationship between blood volume depletion and hypovolemia-induced ADH release from the pars nervosa of the posterior pituitary gland, which was first described in 1973 in a Sprague-Dawley rat model ($r = 0.89$, $p < 0.001$).[2][5][6] Although several other physiological regulatory mechanisms (such as the renin-angiotensin-aldosterone system or RAAS) are activated by hypovolemia in addition to ADH release, these only result in isotonic correction of the extracellular fluid volume and therefore do not contribute to dilution of the plasma sodium concentration and hyponatremia (see Figures 1 and 2). Since the hypovolemia-mediated ADH release was measured in (human) in vivo models, the observed exponential release pattern has to be considered a net effect that takes these additional physiological responses into account. The second pillar is the Michaelis-Menten-like kinetics of the renal effects of ADH. The Michaelis-Menten model was originally conceived to describe enzyme-substrate kinetics, but was soon found to be more broadly applicable, especially to endocrine ligand-receptor interactions.[8][9][10] Indeed, a characteristic Michaelis-Menten-like curve has repeatedly been observed to describe ADH's antidiuretic effects.[7] Because complex mathematics often limit applicability in physiological and clinical practice, a linear-logarithmic approach is chosen as

it increases the mathematical transparency of the final equation and therefore improves its convenience. Mathematically, the Michaelis-Menten kinetics can be accurately approximated by a linear-logarithmic (Weber-Fechner) model in the shoulder of the curve, which suitably corresponds to the physiologically relevant range of hypovolemia-induced ADH concentrations.[11][12][13] One of the well-described and currently more significant applications of the Weber-Fechner model is to describe concentration-response curves that represent ligand-receptor interactions.[14] Maximum water reabsorption already occurs at a plasma ADH concentration of 5 pg/mL and above whereas the Weber-Fechner concentration-response curve would theoretically only start to deviate from the saturated Michaelis-Menten curve at very high plasma ADH concentrations.[17] Since it is highly unlikely that these values will be reached as a result of a mere reduction in effective circulating volume, there is no reason to assume that this limits the application of the presented equations. Hyponatremia usually sets in rapidly within several minutes, because the translocation of aquaporins from the intracellular vesicles to the apical cell membrane as a result of the binding of ADH to the V_2-receptors allows for a swift onset of effect, pending the synthesis of additional aquaporin-2 molecules by the collecting duct epithelial cells.[18][19] The specific time of onset of hypovolemia would therefore not limit the applicability of the proposed model. Correction for an additional increase in total body water as a result of thirst-induced oral water intake can be easily implemented into the model by adding a factor to the right-hand side of Equation (5). However, it is the ADH-mediated renal water retention that appears to be the principal pathophysiological mechanism responsible for hypovolemic hyponatremia.[3][4] The measured plasma sodium concentration $[Na^+]_{p,2}$ corresponds to the degree of hypovolemia and often deviates strongly from the physiological reference values. It can be determined at any point in time and will then theoretically reflect the current, hypovolemic status of a patient. Since under euvolemic circumstances, the human body efficiently maintains the plasma sodium concentration between 135 mmol/L and 145 mmol/L (with only minor fluctuations due to stringent regulatory systems), we propose the physiological reference average of 140 mmol/L as a suitable value for $[Na^+]_{p,1}$. This is in line with the recommendations from earlier studies.[20] Alternatively, in case a plasma sodium concentration has recently been determined in the patient under euvolemic circumstances, we suggest to use this value for $[Na^+]_{p,1}$. This will limit the risk of either overestimation or underestimation of the actual

degree of hypovolemia. Furthermore, since it is a well-known fact that the human body prioritizes its extracellular volume regulation over the regulation of plasma osmolality (i.e., in the case of combined or conflicting stimuli for ADH release, the hypovolemic stimulus tends to override the osmotic stimulus for the release of ADH) it seems plausible that the Equations (10) and (11) could even be applied in the context of minor conflicting osmotic stimuli.[21] However, it stands to reason that conditions that clearly perturb the relationship between hypovolemia and ADH release (such as the syndrome of inappropriate ADH secretion or diabetes insipidus) and the inability of the kidneys to generate an osmotic medullary gradient (such as a treatment with loop diuretics) are exclusion criteria for the application of this model.

In conclusion, we believe that our equation can be a means for physiologists and clinicians to get a quantitative understanding of how depletion of the intravascular volume relates to plasma sodium concentration. After experimental validation to reliably determine the appropriate values for the constants K_1 and K_2, our model might theoretically even have a role in guiding rational fluid replacement therapy. By draining an increasing percentage of blood (intravascular volume) from rats and measuring the corresponding change in plasma sodium concentration, the ratio $[Na^+]_{p,1} / [Na^+]_{p,2}$ could be plotted against ΔIVV in a linear fashion (see Equation 10). If the weight of the rat is known, this would make it theoretically possible to estimate values for the constants K_1 and K_2 by determining the slope of the graph and its intersection with the y-axis, respectively.

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Chapter 9

COVID-19 and dysnatremia: a comparison between COVID-19 and non-COVID-19 respiratory illness

Philip J.G.M. Voets
Sophie C. Frölke
Nils P.J. Vogtländer
Karin A.H. Kaasjager

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ABSTRACT

Objective: To investigate the occurrence of disorders of the water and sodium balance in Coronavirus disease 2019 (COVID-19) in our clinic.

Methods: In this retrospective chart review, patients were included if a PCR test result for SARS-CoV-2 was obtained and if at least one plasma sodium concentration measurement was obtained during the period March to June 2020. The occurrences of hyponatremia and hypernatremia were compared between 193 SARS-CoV-2-positive and 138 SARS-CoV-2-negative patients. A χ^2–test was used to determine statistical significance and the corresponding p-values were calculated.

Results: Hypernatremia was significantly more frequently observed in COVID-19 patients, in 38% (74 out of 193), versus only 8% of the-CoV-2-negative patients (11 out of 138) (p <0.01). Hyponatremia was observed in 34% of the included COVID-19 patients (65 out of 193) versus 24% of the SARS-CoV-2-negative patients (33 out of 138). In 12% of all COVID-19 patients (23 out of 193) both hyponatremia and hypernatremia were observed at some point during their admission. Among the non-COVID-19 patients, only 4% showed these plasma sodium concentration fluctuations (5 out of 138). The mortality rate among these hospitalized COVID-19 patients was 23% (45 out of 193). Correcting for double-counting, more than 71% (32 out of 45) of the deceased COVID-19 patients developed dysnatremia (hyponatremia, hypernatremia or both) versus 57% (84 out of 148) of the surviving COVID-19 patients.

Conclusion: Disorders of the water and sodium balance –and especially hypernatremia– seem to be a common occurrence in COVID-19 patients. This has important implications for the treatment of COVID-19 patients.

1. INTRODUCTION

The ongoing pandemic known as coronavirus disease 2019 (COVID-19), which is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has swept across the globe in a matter of weeks and has stirred health care professionals and governments everywhere to the highest degree.[1][2] Its impact on everyday life, ranging from social distancing to the widespread ban on social gatherings, is unmistakeable and profound. Being a new infectious disease, very little is known about the complications of COVID-19, both short-term and long-term.[1] Recently, a lot of attention has been garnered by the remarkably high incidence of pulmonary edema and pulmonary embolisms in COVID-19 patients as opposed to similar (viral) respiratory tract infections.[3][4] A recent meta-analysis in 24.410 COVID-19 patients showed that their predominant symptoms were fever (78%), cough (56%), and fatigue (31%), with 19% of all hospitalised patients requiring non-invasive ventilation, and 9% requiring invasive ventilation.[2] A growing body of evidence shows that COVID-19 is also accompanied by several extra-pulmonary phenomena, such as disorders of the water and sodium balance.[5][6][7]

In this report, we have investigated the occurrence of dysnatremia in COVID-19 patients as compared to non-COVID-19 respiratory illness, rather than healthy controls, based on data from the patient database of the University Medical Centre Utrecht (UMCU). By comparing the results in COVID-19 patients to the results in other respiratory illnesses, we were better able to determine whether plasma sodium outcomes should be considered "COVID-19-specific" or rather the result of respiratory illness in a broad sense. We believe that the results of our retrospective chart review will help raise clinical awareness in every physician treating COVID-19 patients, especially now the world is coping with this ongoing pandemic.

Below, we discuss our findings.

2. METHODS

For this retrospective chart review, we have used patient data collected for the COvid-19 PAtients CHaracteristics (COVPACH) study, which has registered the laboratory test results of all hospitalized COVID-19 patients in the UMC Utrecht, including patients admitted to the Intensive Care Unit (ICU), during the period March to June 2020. Ethical review was waived by the Medical Ethical Committee (MEC) of the UMC Utrecht (MEC reference number: 20-284). Consent was obtained using an opt-out procedure, in accordance with the hospital guidelines and with approval of the institutional research board. The medical records of these patients were accessed anonymously and none of the authors were their treating physicians. Patients were included in our study if the following two conditions were met:[1]

1. A PCR test result for SARS-CoV-2 was obtained
2. At least one -but preferably more than one- plasma sodium concentration measurement was obtained (at any time during admission).

For every included patient, his or her medical records were checked for additional biochemical parameters, such as plasma osmolality, urine osmolality and urine sodium concentration. Hypernatremia was defined as a plasma sodium concentration of 146 mmol/L or above, and hyponatremia was defined as a plasma sodium concentration of 134 mmol/L or below. In total, 331 hospitalized patients with clinical suspicion of COVID-19 were screened via a SARS-CoV-2 PCR test. A total of 193 patients tested positive for SARS-CoV-2. The 138 patients who tested negative but were exhibiting the symptoms of a non-COVID-19 respiratory tract disease (such as a bacterial pneumonia or a non-COVID-19 viral respiratory tract infection), were used as a control group to compare the occurrence of dysnatremia in patients with COVID-19 and those with another respiratory illness. Finally, in order to analyse the association between dysnatremia and mortality in COVID-19, the occurrences of dysnatremia (corrected for double-counting) in deceased patients and patients who stayed alive were compared. Both patient groups were compared in terms of mean age, gender, body-mass-index (BMI), blood pressure, and plasma creatinine concentration. These results are summarized in Table 1.

Statistical analysis: A χ^2–test was used to determine statistical significance and the corresponding p-values were calculated. A statistical power analysis was performed in order to evaluate the required patient group sizes.

3. RESULTS

Hypernatremia was observed in 38% of the included COVID-19 patients (74 out of 193) versus only 8% of the-CoV-2-negative patients (11 out of 138), which is a strong significant difference (p <0.01). On several occasions, the plasma sodium concentration in these patients reached critical values as high as 174 mmol/L. The obtained spot urine samples of these hypernatremic patients showed urine osmolalities ranging from 509 mOsmol/L to 819 mOsmol/L, with average urine osmolality was 604 mOsmol/L. Additional analysis showed that hypernatremia in COVID-19 patients occurred significantly more frequently during ICU admission than outside the ICU (p <0.01). Our calculations showed that, using a two-sided test, a 5% significance level (α = 0.05), and a statistical power of 80% (β = 0.20), a minimum sample size of 27 per group (n = 54) was required to detect this difference. Therefore, our group size was sufficiently large.

Hyponatremia was observed in 34% of the included COVID-19 patients (65 out of 193) versus 24% of the SARS-CoV-2-negative patients (33 out of 138). This difference, while indicative of a COVID-19-specific effect, did not reach statistical significance at a cut-off p-value of <0.01 (p = 0.06). Even though hyponatremia turned out to be a common phenomenon among COVID-19 patients, it also turned out to be relatively mild. In none of these patients did the plasma sodium concentration drop below 127 mmol/L. The obtained spot urine samples of these hyponatremic patients showed urine osmolalities ranging from 274 mOsmol/L to 598 mOsmol/L and urine sodium concentrations ranging from 11 mmol/L to 207 mmol/L. Their average urine osmolality was 432 mOsmol/L and their average urine sodium concentration was 50 mmol/L.

Interestingly, in 12% of all COVID-19 patients (23 out of 193) both hyponatremia and hypernatremia were observed at some point during their admission, with some patients even displaying frequent fluctuations of their plasma sodium concentration. Among the non-COVID-19 patients with a respiratory illness, only 4% showed these plasma sodium concentration fluctuations (5 out of 138). Taking the aforementioned results together –and counting the 23 COVID-19 patients who developed both hyponatremia and hypernatremia during their admission as one case of dysnatremia in order to prevent double-counting– 60%

of all COVID-19 patients (65 plus 74 minus 23 equals 116 out of 193) developed dysnatremia, defined as hyponatremia, hypernatremia or both, versus 28% of the patients in the control group 33 plus 11 minus 5 equals 39 of 138). Dysnatremia occurred significantly more in COVID-19 patients than in patients who were tested negative (p <0.01).

The mortality rate among these hospitalized COVID-19 patients from the COVPACH study turned out to be 23% (45 out of 193). Dysnatremia was observed in little more than 71% of the deceased COVID-19 patients (32 out of 45) versus almost 57% (84 out of 148) of the COVID-19 patients who lived, once again correcting for double-counting, but this difference did not reach statistical significance at a cut-off p-value of <0.01.

The main results of this study are summarized in Table 2.

4. DISCUSSION

In this study, we have presented the results of the retrospective chart review in which we have investigated the occurrence of hypernatremia among 193 SARS-CoV-2-positive compared to 138 clinically suspected but SARS-CoV-2-negative patients from our clinic. In our opinion, comparing the COVID-19 patients to patients with a non-COVID-19 respiratory illness, rather than comparing them to healthy controls (i.e., those without afflicted respiratory systems), was indicative of the COVID-19-specific biochemical characteristics and not simply of the characteristics of respiratory illness in a broader sense. Our findings clearly demonstrate that disorders of the water and sodium balance are a common –but probably underreported– phenomenon in COVID-19, with 38% of the aforementioned patients developing hypernatremia during their admission, 34% developing hyponatremia and a total of 60% developing some form of dysnatremia (hyponatremia, hypernatremia or both, correcting for double-counting). Among the 138 patients who showed signs of COVID-19, but were found to be SARS-CoV-2-negative, hypernatremia, hyponatremia, and dysnatremia occurred in 8%, 24%, and 28%, respectively. The fact that 12% of all analyzed COVID-19 patients developed both hyponatremia and hypernatremia during their hospital admission –without a noted temporal relationship with any administered intravenous fluids– might reflect the severity of COVID-19 on a cellular level. In many ways, this loss of the human body's ability to maintain electrolyte homeostasis is reminiscent of the putative "sick cell syndrome" that can be observed in critically ill or terminal patients in the Intensive Care wards (supposedly as a result of sodium-potassium antiporter dysfunction due to intracellular ATP depletion). One could even hypothesize that dysnatremia could be considered an (early) indicator of impending bodily imbalance and exhaustion in a broad sense.

Interestingly, whereas almost two out of every five COVID-19 patients developed hypernatremia, this occurred in only 8% of the non-COVID-19 respiratory illness patients. This finding contradicts earlier work by –among others– Atila *et al.*, who found that the occurrence of hypernatremia was comparable among their COVID-19 group and control group, and Hirsch *et al.*, who found a compound hypernatremia prevalence of only 7% (3.2% for mild hypernatremia, defined as a plasma sodium concentration between 145 mmol/L and 149

mmol/L, and 3.8% for severe hypernatremia, defined as a plasma sodium concentration of 150 mmol/L or above) in a large cohort of 9,946 COVID-19 patients.[5][6] Similar hypernatremia prevalence numbers have been reported by other authors.[7][8] However, we have not found any relevant difference between the Dutch approach to COVID-19 and COVID-19 treatment in other countries. Based on the appropriately concentrated urine in our group of hypernatremic COVID-19 patients (with an average urine osmolality of 604 mOsmol/L), dehydration seems a very plausible explanation for their hypernatremia.[9] It seems likely that the reluctance of many physicians to initiate intravenous fluid therapy due to the risk of (an exacerbation of) bradykinin-mediated pulmonary edema –which has generally been considered a hallmark of COVID-19– in these bedridden patients with a limited access to drinking water might be an important contributory factor in the development of the observed (and probably iatrogenic) hypernatremia.[4] The direct manipulation of the renin-angiotensin-aldosterone system (RAAS) by binding of SARS-CoV-2 to the angiotensin-converting enzyme 2 (ACE2) has also been implicated in the pathogenesis of COVID-19-related electrolyte disturbances.[8] In some cases, the relative disinclination of nurses, nutrition assistants, and other healthcare workers to enter the isolation rooms of COVID-19 patients due to the stringent and time-consuming personal protective measures might have added to this frequent occurrence of hypernatremia. Our finding that the development of hypernatremia in COVID-19 patients during ICU admission is higher than outside the ICU, supports the hypothesis of hypernatremia due to iatrogenic dehydration.[8] The use of dexamethasone to ameliorate the hyperinflammation that can accompany COVID-19 seems another contributing factor.[1] Another plausible explanation for the frequent occurrence of hypernatremia in COVID-19 patients in the ICU could be osmotic urea diuresis, which is a prime example of why the solute-free water clearance (which is negative in these patients due to the massive urinary urea excretion) should be considered misleading with regard to the analysis of dysnatremia.[10][11] As presented in the results, the plasma sodium concentration can reach alarming heights. Future studies should focus on the balance between dehydration prevention during ICU admission, and avoiding pulmonary edema in COVID-19.

Hyponatremia was frequently observed in both COVID-19 patients and patients with a non-COVID-19 respiratory illness, 34% and 24%, respectively. This hyponatremia prevalence in COVID-19 patients is comparable to previously

published results.[5][6] In comparison, a large population-based cross-sectional NHANES study from 2013 showed that the prevalence of hyponatremia among 14.697 healthy U.S. adults was approximately 1.7%.[12] In line with a small number of previously published reports, the syndrome of inappropriate antidiuretic hormone release (SIADH) seems to be the primary cause of COVID-19-associated hyponatremia, based largely on the original diagnostic criteria as proposed by Bartter and Schwartz, namely hypotonic hyponatremia with inappropriately concentrated urine (the average urine osmolality of 432 mOsmol/L suggests inappropriate release of antidiuretic hormone (ADH) in the context of hyponatremia), and euvolemia (in the absence of diuretic use, the average urine sodium concentration of 50 mmol/L suggests a lack of RAAS activation).[13][14] Since pulmonary disease is a fairly common cause of SIADH, this seems pathophysiologically plausible.[11] This being said, hypovolemia-mediated ADH release could also have played an etiological role in a minority of cases in which the urine sodium excretion was strongly reduced (<15 mmol/L), especially because many physicians have been reluctant to initiate intravenous fluid therapy in these patients due to the fear of pulmonary edema. Seeing as the urine osmolality in none of the hyponatremic COVID-19 patients dropped below 274 mOsmol/L, other factors, such as "tea and toast syndrome", seem less relevant in COVID-19-associated hyponatremia even though the nutritional status of these patients is often questionable at best.[11]

A limitation of our study is that –while the occurrence of dysnatremia during admission could be reliably established in our patient groups– our data often did not allow the analysis of a temporal relationship between the onset of dysnatremia and the clinical course of COVID-19, which would have been desirable for proving causality. Furthermore, due to a large number of confounders, such as –but certainly not limited to– patient age, smoking status, and co-morbidity, the possible causality of dysnatremia in COVID-19-related deaths could not be reliably established in our retrospective cohort of COVID-19 patients. Although a more rigorous and definitive analysis remains desirable on this issue, our data do suggest that dysnatremia occurs more frequently in patients succumbing to COVID-19 (71%) than in those surviving COVID-19 (57%). This is in line with previously published analyses, in which dysnatremia has consistently been found to be an independent risk factor for mortality in COVID-19 patients.[6][7][15][16] It seems reasonable to assume that this observation can be

reliably extrapolated to COVID-19 patients.[6][7][15][16] As discussed above, failure to maintain water and sodium homeostasis might be indicative of impending death in COVID-19 patients, regardless of causality. We also would like to stress that all of the analyzed COVID-19 patients in our study were hospitalized; our results should not be blindly extrapolated to milder cases of COVID-19 which do not require hospitalization. Lastly, we have included patients in either the COVID-19 group or the non-COVID-19 (control) group based on the results of their SARS-CoV-2 PCR tests. We realize that perhaps some PCR-negative COVID-19 patients have inadvertently been included in the control group. However, since the diagnosis of PCR-negative COVID-19 is notoriously difficult and its definition relatively vague, we feel justified in this approach although it could lead to an underestimation of our results.

In conclusion, disorders of the water and sodium balance –and especially hypernatremia, contrary to the findings of several previously published studies– seem to be a very common extra-pulmonary occurrence in COVID-19 patients, and are associated with an increase in morbidity and probably even mortality. In this retrospective chart review, we have attempted to raise awareness of this potentially dangerous complication of COVID-19, which might even reflect its severity. Hopefully, this will have appropriate implications for the treatment of and care for COVID-19 patients now that the world is coping with this ongoing pandemic.

Table 1. Characteristics of patients in COVID-19 group and control group

Mean baseline characteristics	COVID-19 group (n = 193)	Control group (n = 138)
Gender: M/F (%)	60.2/39.8	55.3/44.7
Age (years)	64.3	61.7
Body-mass-index (kg/m^2)	28.5	26.2
Systolic blood pressure (mmHg)	138	137
Diastolic blood pressure (mmHg)	73	79
Plasma creatinine level (µmol/L)	120.8	98.3
Plasma C-reactive protein level (mg/L)	147	87
Hypertension (%)	37	14
Diabetes mellitus (%)	21	4
Immunosuppressant medication use (%)	18	9

Table 2. Summary of results

Outcome	COVID-19 group (n = 193) (%)	Control group (n = 138) (%)	p-value[1]
Hypernatremia	74/193 (38)[2]	11/138 (8)	< 0.01
Hyponatremia	65/193 (34)	33/138 (24)	0.06
Dysnatremia	116/193 (60)	39/138 (28)	< 0.01
- In deceased patients[3]	32/45 (71)	4/6 (67)	
- In surviving patients[3]	84/148 (57)	35/132 (27)	

[1] A χ^2–test was used to determine statistical significance

[2] Hypernatremia in COVID-19 patients occurred significantly more frequently during ICU admission than outside the ICU (p < 0.01)

[3] The difference in occurrence of dysnatremia between deceased and surviving COVID-19 and non-COVID-19 patients did not reach statistical significance

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Chapter 10

Summary (samenvatting) and future perspectives

1. ENGLISH SUMMARY

Osmoregulation is the result of the complex interplay of several physiological processes, which control the water fluxes in the human body. A concise overview is presented in **Chapter 1**. Two thirds of the total body water is stored in the intracellular compartment, and one third is located in the extracellular compartment, which can be further divided into the plasma and the interstitial fluid. The plasma sodium concentration is the most important determinant of plasma tonicity and therefore regulates the osmotic movement of water between the fluid compartments in the human body. Somewhat counter intuitively, the plasma sodium concentration is primarily a reflection of the water homeostasis in the human body and only to a lesser extent of its total amount of sodium. A key player in maintaining the plasma sodium concentration within its reference range is the antidiuretic hormone (ADH), which stimulates renal reabsorption of pure water, back into the circulation. Under physiological circumstances, ADH is secreted by the posterior pituitary gland in response to an increase in the plasma tonicity and its release is shut off in a negative feedback fashion by the resultant renal water reabsorption and plasma dilution. Pathological ADH secretion is one of the main culprits in the disorders of the plasma sodium concentration, collectively known as dysnatremia. Dysnatremia is divided in hyponatremia (a decreased plasma sodium concentration as a result of dilution of the plasma due to a water excess) and hypernatremia (an increased plasma sodium concentration as a result of concentration of the plasma due to a water deficit). The clinical ramifications of dysnatremia are especially noticeable in the brain, where hyponatremia produces brain swelling in the rigid skull, whereas hypernatremia leads to brain shrinkage. This thesis zooms in on clinical aspects of disorders of the osmoregulation and the struggles for physicians they entail.

Disorders of the osmoregulation, although frequently encountered, have been considered vexing and enigmatic by generations of clinicians. In **Chapter 2**, some important pitfalls in their analysis and treatment are highlighted, and the attitude of clinicians towards dysnatremia is investigated by means of a survey. The “image problem” that dysnatremia suffers from might be an elephant in the room, but seems to contribute significantly to these difficulties.

In order to facilitate the initial "bed-side analysis" of monofactorial dysnatremia, a novel clinical nomogram is presented in **Chapter 3** as a practical tool for the often intractable clinical practice. This nomogram is conceptually analogous to the well-known Siggaard-Andersen nomogram for the interpretation of acid-base disorders. By mathematically deriving the relationship between plasma osmolality and urine osmolality under physiological circumstances, we were able to define monofactorial pathology of the osmoregulation within a coordinate system with the parameters "urine osmolality" and "plasma osmolality" on the x-axis and y-axis, respectively.

In **Chapter 4**, an attempt is made to derive a governing dysnatremia equation, based on an electrolyte-free water balance, and integrating urine osmolality and urine tonicity. While the presented equation is not intended for exact calculations, it could be considered a means for clinicians to get a better qualitative understanding of the relationship between the plasma sodium concentration and the physiological variables that influence it.

In a similar vein, a transparent and clinically applicable equation that can be used to calculate the estimated effect of different types and volumes of crystalloid infusate on the plasma sodium concentration in the frequently encountered syndrome of inappropriate ADH secretion (SIADH) is derived in **Chapter 5**, and retrospectively validated and compared to the widely used Adrogue-Madias equation in a cohort of SIADH patients in **Chapter 6**. Because this equation is derived on the premise of tonic ADH release, it would theoretically be a well-suited model for the prediction of the plasma sodium response to hypertonic saline boluses in the context of a proactive desmopressin clamp to prevent osmotic demyelination syndrome during the correction of hyponatremia. We have expounded on this alternative clinical application of our equation in **Chapter 7**, illustrated by a patient case where the overly rapid correction of extreme hypotonic hyponatremia unfortunately resulted in pontine and extrapontine myelinolysis, despite repeated attempts to prevent this.

Whereas central ADH release is most often stimulated by plasma hypertonicity, it also occurs as a result of hypovolemia. In **Chapter 8**, the theoretical relationship between extracellular volume depletion and resultant hypotonic

hyponatremia is discussed. The derived model rests on two main pillars. The first is the ubiquitously cited exponential relationship between intravascular volume depletion and hypovolemia-induced ADH release, and the second pillar is the Michaelis-Menten-like concentration-response relationship for ADH-mediated renal water reabsorption.

Chapter 9 presents the results of a retrospective chart study, which investigates the occurrence of dysnatremia in coronavirus infectious disease 2019 (COVID-19) patients as compared to non-COVID-19 respiratory illness, rather than healthy controls, during this as-of-yet ongoing pandemic. By comparing the results in COVID-19 patients to the results in other respiratory illnesses, rather than healthy controls, it was possible to determine whether plasma sodium outcomes should be considered "COVID-19-specific" or rather the result of respiratory illness in a broad sense. Disorders of the water and sodium balance –and especially hypernatremia, contrary to the findings of several previously published studies– seem to be a very common extra-pulmonary occurrence in COVID-19 patients.

2. NEDERLANDSE SAMENVATTING

Osmoregulatie is het resultaat van een complex samenspel van verschillende fysiologische processen die de waterflux in het menselijk lichaam reguleren. Een beknopt overzicht hiervan is te vinden in **Hoofdstuk 1**. Twee derde van het totale lichaamswater bevindt zich in de cellen en één derde buiten de cellen, een vloeistofcompartiment dat verder kan worden onderverdeeld in plasma en weefselvloeistof. De plasmanatriumconcentratie is de belangrijkste determinant van de plasmatoniciteit (een maat voor het aantal 'actieve' in bloed opgeloste deeltjes) en reguleert zo de verplaatsing van water tussen de verschillende vloeistofcompartimenten in het menselijk lichaam. Hoewel het enigszins tegenstrijdig lijkt, is de plasmanatriumconcentratie vooral een afspiegeling van de waterhuishouding in het menselijk lichaam en slechts in mindere mate van de totale natriumhoeveelheid. Het antidiuretisch hormoon (ADH), dat de opname van puur water uit de voorurine stimuleert, speelt een sleutelrol bij het regelen van de plasmanatriumconcentratie. Onder normale omstandigheden wordt dit hormoon afgegeven aan de bloedbaan door de hypofyseachterkwab (hormoonuitscheidende structuur in de hersenen) wanneer de plasmatoniciteit toeneemt. Dit leidt tot het vasthouden van water en verdunning van het plasma, waarna de ADH-afgifte via negatieve terugkoppeling afneemt. Abnormale ADH-afgifte is in veel gevallen de oorzaak van een stoornis van de plasmanatriumconcentratie, beter bekend als dysnatriëmie. Dysnatriëmie wordt onderverdeeld in hyponatriëmie (daling van de plasmanatriumconcentratie als gevolg van verdunning van het plasma door een overschot aan water) en hypernatriëmie (stijging van de plasmanatriumconcentratie als gevolg van indikking van het plasma door een tekort aan water). De klinische gevolgen van dysnatriëmie zijn voornamelijk merkbaar in de hersenen, waar hyponatriëmie zwelling van het hersenweefsel in de rigide schedel veroorzaakt, terwijl hypernatriëmie leidt tot hersenkrimp. Dit proefschrift behandelt de klinische aspecten van stoornissen in de osmoregulatie en de worstelingen van artsen hiermee.

Hoewel stoornissen van de water- en zoutbalans frequent voorkomen, worden ze al generatie op generatie enigmatisch en complex gevonden door veel clinici. In **Hoofdstuk 2** worden enkele belangrijke valkuilen bij de analyse en behandeling van deze stoornissen in kaart gebracht en wordt de attitude van

artsen en aankomend artsen tegenover dysnatriëmie onderzocht door middel van een enquête. Het "imagoprobleem" van dysnatriëmie is weliswaar een olifant in de kamer, maar lijkt significant bij te dragen aan deze moeilijkheden.

Om de initiële "bed-side-analyse" van monofactoriële dysnatriëmie te faciliteren, wordt in **Hoofdstuk 3** een nieuw klinisch nomogram gepresenteerd als praktisch handvat voor de weerbarstige klinische praktijk. Dit nomogram is conceptueel analoog aan het welbekende Siggaard-Andersen-nomogram voor de interpretatie van zuur- en basestoornissen. Door het afleiden van de relatie tussen plasma-osmolaliteit en urine-osmolaliteit onder fysiologische omstandigheden kan monofactoriële pathologie van de osmoregulatie gedefinieerd worden binnen een assenstelsel met de parameters "urine-osmolaliteit" en "plasma-osmolaliteit" respectievelijk op de x-as en de y-as.

In **Hoofdstuk 4** hebben wij gepoogd een overkoepelende dysnatriëmievergelijking af te leiden, gebaseerd op de elektrolytvrijwaterbalans, waarin urine-osmolaliteit en urinetoniciteit worden geïntegreerd. Hoewel deze vergelijking niet bedoeld is voor exacte berekeningen, kan het clinici helpen om een beter kwalitatief beeld te krijgen van hoe de verschillende relevante fysiologische parameters de plasmanatriumconcentratie beïnvloeden.

Op een vergelijkbare manier wordt in **Hoofdstuk 5** een transparante en klinisch toepasbare vergelijking afgeleid die voorspelt hoe verschillende volumina en typen zoutinfuus de plasmanatriumconcentratie beïnvloeden bij patiënten met het veelvoorkomende syndroom van inadequate ADH-secretie (SIADH). Deze vergelijking wordt in **Hoofdstuk 6** retrospectief gevalideerd in een cohort van SIADH-patiënten en vergeleken met de veelgebruikte Adrogue-Madias-vergelijking. Omdat de basisaanname van mijn vergelijking een relatief tonische ADH-afgifte is, is dit model in theorie ook zeer geschikt om de plasmanatriumrespons op hypertoon zoutinfuus in de context van een proactieve desmopressine-clamp te voorspellen. In **Hoofdstuk 7** wordt verder ingegaan op deze alternatieve klinische toepassing van onze vergelijking aan de hand van de patiëntcasus waar de te snelle correctie van extreme hypotone hyponatriëmie helaas resulteerde in pontiene en extrapontiene myelinolyse, ondanks verwoede pogingen om dit te voorkomen.

Hoewel verhoogde toniciteit van het plasma meestal de prikkel voor centrale ADH-afgifte is, kan ADH ook vrijkomen in reactie op ondervulling van het vaatbed. In **Hoofdstuk 8** wordt de theoretische relatie tussen extracellulaire volumedepletie en de resulterende hypotone hyponatriëmie besproken. Dit wiskundige model rust op twee pijlers. De eerste pijler is de exponentiële relatie tussen intravasculaire volumedepletie en hypovolemische ADH-afgifte en de tweede pijler is de Michaelis-Menten-achtige concentratie-respons-curve voor ADH-gemedieerde renale waterretentie.

Hoofdstuk 9 bespreekt een retrospectief patiëntstatusonderzoek, waarin het voorkomen van dysnatriëmie onder patiënten met bewezen coronavirus infectious disease 2019 (COVID-19) wordt vergeleken met het voorkomen van dysnatriëmie onder patiënten met niet-COVID-19-luchtwegziekte. Doordat de resultaten van COVID-19-patiënten worden vergeleken met patiënten met een andere luchtwegziekte, in plaats van gezonde controlepersonen, kunnen plasmanatriumuitkomsten beter geduid worden als “COVID-19-specifiek” en niet enkel het gevolg van luchtwegziekte in algemene zin. Stoornissen van de water- en zoutbalans –en in het bijzonder hypernatriëmie, in tegenstelling tot wat andere onderzoeken uitwijzen– lijken een veelvoorkomende extrapulmonale manifestatie in COVID-19-patiënten te zijn.

FUTURE PERSPECTIVES

Some colleagues (many, perhaps) would argue that the only correct approach to dysnatremia is simply initiating treatment, followed by frequent measurements of the plasma sodium concentration in order to determine whether or not the initiated treatment was appropriate. We have stressed –and we will continue to stress– that frequent plasma sodium measurements are essential, but we also firmly believe that such clinical pragmatism should not replace attempts to reach a deeper understanding of these disorders. While no theoretical model is infallible and no set of equations can completely capture the complexity of the human body, mathematical modeling of (patho)physiological processes can increase our understanding of them, as equations attempt to reduce these processes to their essence and –in the assumptions and boundaries of their derivations– remove any undesirable distractions or interferences. A major challenge in this regard was to keep these models both physiologically sound and mathematically transparent (and therefore clinically applicable). This theoretically oriented approach to the water and sodium homeostasis and its disorders might leave more 'evidence- or big data-minded' readers somewhat unsatisfied. A more extensive prospective validation of the presented equations and models would probably allow for further fine-tuning of proportionality constants, and perhaps even more accurate calculations. Although this is definitely a 'bucket list item', it falls beyond the scope of this thesis. What else could be the focus of future research in the field of (modeling) the water and sodium balance? Below, we have reflected on this question and we have put forward some of our thoughts:

- What are the future (clinical) implications of subcutaneous sodium storage? The presence of large amounts of glycosaminoglycan-bound, osmotically inactivated sodium has been known for several decades, but little effort has been put into the translation of its discovery to clinical medicine.[1][2] An important consequence could be that a classical "two-compartment model" –intracellular fluid compartment versus extracellular fluid compartment, with a strong focus on renal water and sodium handling– is an oversimplification and that perhaps the skin interstitium should be considered a relevant third compartment.[1][2] From a kinetic viewpoint, sodium redistribution to a third (subcutaneous) compartment would probably be a relatively time-consuming process, and it would therefore not

be expected to significantly influence the prediction of short-term plasma sodium fluctuations. This being said, introducing a third compartment could have major implications for the mathematical models describing the water and sodium kinetics in the human body. With regard to cardiovascular medicine, subcutaneous sodium buffering could change our understanding of the effects of sodium intake on blood pressure and cardiovascular health.

- Is it possible to estimate a patient's theoretical maximum urine tonicity ($T_{u,max}$), as used for the mathematical derivation of our equation in Chapter 4, more accurately?[3][4] The ability of the presented model to accurately predict changes in the plasma sodium concentration of SIADH patients in response to intravenous fluid largely depends on an accurate estimation of this parameter, which we have previously defined as the theoretical steady-state of the urine cation concentration after several hours of saline infusion (see Chapter 4).[3] The theoretical maximum urine tonicity was found by Musch *et al.* to have a better predictive value for this plasma sodium response to crystalloid infusate than the initial urine cation concentration.[4] Based on previous experimental work done by Musch et al. and Shimizu *et al.*, we have proposed to approximate this parameter as 60% of the initial urine osmolality under normal dietary conditions.[4][5] In theory, a more accurate approximation could simply be obtained by administering crystalloid infusate to a larger cohort of SIADH patients and comparing their steady-state urine cation concentration to their initial urine osmolality.

- Is it possible to estimate a patient's total body water more accurately? Total body water is often used to guide intravenous fluid therapy and is a very important kinetic parameter in many mathematical models (including our own) describing the water and sodium balance in the human body. For lack of a reasonable alternative, total body water estimations are frequently based on a patient's body weight (i.e., 0.6 times body weight for men, 0.5 times body weight for women). This should be considered a relatively crude "order-of-magnitude" measure and it is inaccurate if the body composition is abnormal, for instance when a patient is morbidly obese.

- What is the significance of the Gibbs-Donnan-effect (or Gibbs-Donnan-equilibrium) with respect to the predictive accuracy of models such as those presented in this thesis? The Gibbs-Donnan-effect refers to the unequal

distribution of charged particles across a semi-permeable membrane due to the presence of large charged particles that are unable to cross this membrane on only one of both sides of this membrane.[6] In the human body, an important example of this phenomenon is the unequal distribution of sodium and chloride ions between the plasma and the interstitial fluid (ISF) –despite the relatively high permeability of the capillaries for these small ions– due to the presence of anionic proteins (especially albumin) in the plasma, but not in the ISF. These large negatively charged proteins cannot freely cross the capillary walls, but exert an electrical force on the positively charged sodium ions in the ISF, drawing some of them into the plasma compartment (even though this creates a sodium concentration gradient). The movement of sodium cations from the ISF also draws some chloride anions into the plasma. The sodium concentration in the plasma is therefore slightly higher than the sodium concentration in the ISF. The influence of the Gibbs-Donnan-effect on the plasma sodium concentration is accurately described by the Nguyen-Kurtz-equation, although its daunting mathematical complexity discourages its clinical application. [6] While deriving the presented mathematical models, our primary goal was to provide a (patho)physiologically sound and correct description of the water and sodium balance without sacrificing transparency and comprehensibility. For the purpose of the derivations, we have therefore assumed that the sodium concentration in plasma is approximately equal to that in the ISF. This approach is mathematically justifiable, because our equations describe a change in plasma sodium concentration in response to intravenous fluid therapy, rather than a single plasma sodium value (such as the Nguyen-Kurtz-equation), and any influence of the Gibbs-Donnan-effect will be approximately equal for the first and the second plasma sodium value as long as the plasma protein concentration does not significantly differ between two measurements. The Gibbs-Donnan-factor (r) is approximately 1.05 for the distribution of sodium cations between the plasma compartment and the ISF compartment (i.e., $r=[Na^+]_p/([Na^+]_{ISF} \approx 1.05)$.[7] Accounting for a Gibbs-Donnan-factor leads to a clinically significant difference when a *single* sodium concentration is calculated in either ISF or plasma (e.g., 1.05·135=142 mmol/L, an absolute difference of 7 mmol/L, which can have profound clinical repercussions), but its effect can be considered fairly negligible when a sodium concentration

difference in either of these compartments is calculated (e.g., 1.05·137-1.05·134=1.05·(137-134)=1.05·3=3.2 mmol/L, an absolute difference of 0.2 mmol/L, which falls within normal assay variation). The same reasoning explains why the simplified Edelman equation (see Chapter 1) is probably a justifiable substitute for the original Edelman equation (which also includes a y-intercept, determined by osmotically inactive cations and non-electrolyte osmoles, and a slope, influenced by the Gibbs-Donnan effect) for calculations of a *change* in the plasma sodium concentration, rather than a *single value*.[7][8] Furthermore, one might hypothesize that the actual Gibbs-Donnan effect in the human body is smaller than estimated by Nguyen and Kurtz, because it is strongest near semi-permeable capillary walls and probably does not occur consistently throughout the circulatory system as a whole.[6] As can be seen in the previous chapters, neglecting the Gibbs-Donnan-effect in the derivations of our models does not seem to have adversely affected their predictive accuracy when compared to the measured changes in plasma sodium concentration. However, as mentioned before, validation of our models in larger patient cohorts remains desirable.

- What is the optimal timing for accurate measurement of the plasma sodium response to intravenous fluid therapy? In other words, how long after administering infusate can its effect on the plasma sodium concentration be evaluated reliably? This is an especially vexing problem with developing mathematical prediction models such as those presented in this thesis. When exactly should blood be drawn to compare a measured (change in) plasma sodium concentration to a predicted (change in) plasma sodium concentration? Although it is impossible to say for sure, it stands to reason that the optimal timing differs depending on the specific prediction model. In the case of an equation that simply calculates the redistribution of a crystalloid solution in the body, the plasma sodium concentration should ideally be checked relatively fast after administering a bolus of infusate since redistribution occurs rapidly. Its calculations are short-term predictions, and their accuracy quickly breaks down as time passes. In the case of the equation presented in this thesis, subsequent renal water and solute handling is taken into account, which means that the kidneys must have had enough time to process the administered infusate. This can theoretically take up to several hours, primarily depending on the type and

volume of infusate, and patient characteristics such as glomerular filtration rate and body composition. Therefore, it could be argued on theoretical grounds that both equations should not be compared (see Chapter 5), but should be considered complementary.[3][9]

- What can be done to raise awareness among clinicians of the inter-assay variation in reported plasma sodium measurements? It is a well-known fact that the results produced by the various laboratory assays for plasma sodium measurement (such as flame photometry, and direct or indirect ion-selective electrode (ISE)) can differ to a significant extent, and are thus not necessarily interchangeable with regard to their clinical interpretation.[10] Because the concentration of sodium in plasma, where it is the primary electrolyte, is very high compared to other electrolytes, even a very small percentage variation in its reported value can constitute an absolute difference of several mmol/L, whereas this absolute difference would be negligible for electrolytes with a much lower plasma concentration. For instance, Weld *et al.* have demonstrated inter-assay variations between two direct ISE methods of ≥|3| mmol/L for 13% of paired results, and ≥|4| mmol/L for 4% for paired results, and the observed discrepancy between direct and indirect ISE assays is even larger.[10] In the clinical practice, it is not uncommon that dysnatremia management is based on a heterogeneous mix of plasma sodium measurements reported by various assays. Clinicians should realize that an ideal comparison of plasma sodium values requires that the same assay is used for each measurement. Although an in-depth discussion regarding the technical aspects of these various laboratory assays falls beyond the scope of this thesis, at least some of the analytical discordance can be explained by differences in pre-analytical sample handling (e.g., whether or not dilution of the sample is required), the influence of plasma protein concentrations on the assay performance, and even test-retest reliability or repeatability of the assay in general.[10]

- How should algorithms, flowcharts and prediction models for the analysis and treatment of dysnatremia be adjusted so that they can be reliably applied to patients at the extremes of age? For instance, it is a well-known fact that the concentrating ability of the kidneys of the very young and very old differs significantly from the concentrating ability of the kidneys of a

healthy adult, which has major implications for their water and sodium homeostasis. The renal concentrating ability is impaired in newborns and infants. The maximum urine osmolality in persons aged 60 to 80 years diminishes with roughly 20% as compared to its original value.[11] Furthermore, the body composition –and more specifically, the total body water percentage– is different in the very young and very old, primarily due to an increased amount of adipose tissue. In the elderly, the hypothalamic threshold for thirst is generally much higher than in a healthy adult, which is reflected in a higher average plasma osmolality.[12] Ideally, the aforementioned physiological differences should be incorporated in an optimal approach to dysnatremia in these age groups. It stands to reason that "one size does not fit all" (as we have argued in Chapter 2).

- What can or will be the role of deep learning and artificial intelligence (AI) in the analysis of dysnatremia in the nearby future? Conceivably, deep learning and AI will be able to facilitate the clinical analysis of dysnatremia by recognizing patterns that are characteristic of a particular etiology.[13] In line with the clinical nomogram presented in this thesis and several existing diagnostic flowcharts and algorithms, pattern recognition by a physician –where clinical and biochemical parameters are often subconsciously combined and interpreted– remains important in the diagnosis of dysnatremia. For example, a combination of hypertonic hypernatremia with polyuria and an inappropriately low urine osmolality, which quickly and significantly improves after administering desmopressin, strongly favors a diagnosis of central diabetes insipidus, especially if this patient's medical history is remarkable for intracranial pathology. A well-programmed computer should theoretically be able to suggest a plausible diagnosis to a physician based on information from the electronic patient file. In anticipation of these technological developments, the importance of mathematical modeling of (patho)physiological processes in the human body could increase steeply in the nearby future. The extensive Utrecht Patient Oriented Database (UPOD), which has been collecting clinical and laboratory measurements of patients from the University Medical Centre Utrecht since 2000, could provide valuable validation datasets for this purpose.

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CURRICULUM VITAE

Philippus (Philip) Johannes Gerdiaan Maria Voets werd geboren op 6 maart 1990 te Nijmegen. Na de basisschool in Udenhout doorlopen te hebben, rondde hij het gymnasium met het dubbelprofiel Natuur & Gezondheid en Natuur & Techniek aan het Cobbenhagen-lyceum te Tilburg in 2008 *magna cum laude* af. Hierna ging hij Geneeskunde studeren aan de Radboud-universiteit Nijmegen. De Bachelor-fase en Master-fase van de Geneeskundestudie werden allebei *cum laude* afgerond. Hierna werkte hij een jaar lang als basisarts (ANIOS) Interne Geneeskunde in het Canisius-Wilhelmina-ziekenhuis te Nijmegen, waarna hij werd aangenomen voor de specialisatie tot internist aan het Universitair Medisch Centrum Utrecht in 2018. De eerste jaren als internist i.o. werden doorlopen in het Gelre-ziekenhuis Apeldoorn, waar dit promotieonderzoek gestart werd onder supervisie van internisten dr. N.P.J. Vogtländer en prof. dr. H.A.H. Kaasjager. Sinds begin 2020 is hij werkzaam als internist i.o. (AIOS) in het Universitair Medisch Centrum Utrecht en is hij inmiddels toegelaten tot de subspecialisatie Endocrinologie en zal per december 2021 starten als fellow Endocrinologie met bijzonder aandachtsgebied Metabole Ziekten.

Philip woont samen met zijn verloofde, Aukje van Beurden, in Vlijmen. Zij verwachten op het moment van schrijven van dit academisch proefschrift hun eerste kind.

LIST OF PUBLICATIONS

1. Publications that are not part of this thesis:

1. Voets PJ, van Helvoort HA. The role of equal pressure points in understanding pulmonary diseases. Adv Physiol Educ 2013;37:266-7.
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3. Voets PJ, Vogtländer NPJ, Kaasjager KAH. Understanding dysnatremia. J Clin Monit Comput 2021;35:655-9.
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