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Physiologic Mechanisms of Water and Electrolyte Disturbances After Transsphenoidal Pituitary Surgery

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Abstract

Background—Disturbances in water and electrolyte homeostasis are common after transsphenoidal surgery. These disorders are variable and unpredictable, increasing patient risk and complicating postsurgical treatment. Clinically, it is generally accepted that damage to the pituitary is the cause, but the mechanisms behind the response variability and underlying pathophysiology remain unknown.

Objective—To test the hypothesis that changing the degree of damage to the pituitary stalk produces a spectrum of water and electrolyte disturbance along which all presentations of postsurgical water and electrolyte disturbances can be identified.

Methods—We used HumMod, a large mathematical model of physiology, to simulate pituitary stalk damage at differing fractions: 20%, 40%, 60%, and 80%. The damaged neurons were modeled to undergo a 5-day countdown to degeneration and release stored antidiuretic hormone as they die, as is proposed to occur.

Results—Lower pituitary damage (20%) resulted in transient polyuria and intermediate damage (40%) was associated with delayed polyuria and diabetes insipidus. Higher levels of damage (60% and 80%) showed a triphasic pattern of diabetes insipidus.

Conclusions—We postulate that our model provides a plausible mechanistic explanation for some varieties of postsurgical water and electrolyte disturbances, in which increasing damage to the pituitary potentiates the likelihood of a full triphasic response. However, our simulation shows that merely modifying the level of damage does not produce every presentation of water and electrolyte imbalance. This theory suggests that other mechanisms, which are still unclear and not

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a part of this model, may be responsible for postoperative hyponatremia and require further investigation.

Keywords

Antidiuretic hormone; Mathematical modeling; Transsphenoidal pituitary surgery

Introduction

Transsphenoidal surgery is a minimally invasive procedure for accessing pituitary tumors or sellar masses. One of the most frequent postsurgical effects is the disturbance of salt and water homeostasis secondary to disruption of the posterior pituitary gland or nearby infundibulum. The patterns of water and electrolyte disturbances after transsphenoidal surgeries can be generally categorized as periods of polyuria or hyponatremia, attributable to an abnormally low or abnormally high secretion, respectively, of antidiuretic hormone (ADH). These derangements may not escalate to the level of clinically defined central diabetes insipidus (DI) or syndrome of inappropriate antidiuretic hormone (SIADH) but may still require acute or chronic management. Six profiles of polyuria or hyponatremia have been reported: brief or sustained polyuria, immediate or delayed hyponatremia, and biphasic or triphasic DI.¹ Therefore, these disturbances are variable in both their presentation and their time of appearance. The tendency for early hospital discharge after surgery makes these problems especially relevant. Symptomatic disturbances may lead to hospital readmission 1–20 days after surgery,² significantly increasing the total hospital cost of this procedure and adversely affecting quality metrics.

Although most water and electrolyte disturbances are acute, clinicians have long sought to find reliable risk factors or markers that predict prolonged water and electrolyte disturbances after these surgeries. Considerable effort has been made to establish correlations between the tumor type or specific disease and the complication rate.^{1,3–6} In addition, associations have been found with sex, age, body mass index, nadir sodium, surgeon experience, and the amount of intraoperative manipulation of the neurohypophysis.^{7–9} Ultman et al.¹⁰ suggest that there is a single initiating factor, pituitary stalk damage, which may account for the full spectrum of homeostasis disorders after transsphenoidal surgery, with the degree of damage determining the particular profile. However, the mechanisms behind the response variability and underlying pathophysiology remain unknown, likely in part, because assessing the degree of damage in vivo is a difficult experimental task and is usually subjective in a surgical setting.

Mathematical modeling is a method of investigation that allows for experimentation that cannot be directly performed in vivo. Mathematical modeling enables detailed analysis of water and electrolyte balance and its regulation by complex mathematical relationships and feedback loops spanning endocrine, renal, autonomic, cardiac, and interstitial domains. Our tool, HumMod, is an elaborate mathematical model of integrated human physiology stemming from the cardiovascular model initially established by Guyton et al.¹¹ and described by Hester et al.¹² This model is designed to simulate electrolyte and water balance through mechanisms derived from basic clinical and experimental evidence. HumMod has

been previously validated in the context of dehydration and rehydration, with particular attention given to ADH and its physiologic actions.¹³ In the current study, we used HumMod to inflict stepwise damage to the pituitary stalk. Similar to Ultman et al.,¹⁰ our hypothesis was that modulation of damage alone produces a spectrum of disease along which the full variety of reported presentations of postsurgical water and electrolyte disturbances can be identified.

Methods

Forming the backbone of the present model, HumMod is a well-established interactive physiologic simulator comprising some 10,000 variables. It is a system of algebraic and differential equations that mathematically express the relationships between physiologic variables from each organ system in the body. These relationships are based on experimentally proved cell-tissue-organ physiology and are programmed as a lumped parameter model that describes the movement of water, electrolytes, hormones, metabolites, oxygen, carbon dioxide, and other factors through physiologic and anatomic compartments. The model produces results in the form of numeric solutions of the equation system, with a set of results being produced every time step. By making specific adjustments to HumMod's baseline model of normal physiology, a variety of pathologic states can be simulated, studied, and more completely understood by looking at the complete effect the given disease has on the multitude of systems in the model.

Previous Work

Precursors of this model have been used in numerous studies to provide a more detailed understanding of the physiologic mechanisms that play a role in common clinical conditions. For example, Guyton et al. used this model to identify the primary role of the kidney in controlling long-term blood pressure,^{11,14,15} and Iliescu and Lohmeier¹⁶ used it to explore the therapeutic effects of baroreceptor stimulation and its impact on blood pressure control through actions on the kidney. In addition, our group has used this model to study dehydration and rehydration in humans¹³ as well as cardiovascular responses to changes in salt intake.¹⁷

The details of the full model structure are beyond the scope of this work because of its large size. However, we provide a summary description of 2 areas of the model that are pertinent to the present study: nonpathologic ADH synthesis and secretion, and pathologic effects of pituitary stalk damage on ADH synthesis and secretion. Many terms used in the mathematical model description serve as representations of in vivo structures. For example, in describing the mass of ADH in the magnacellular neuron projections, we refer to any ADH that is readily secreted, as opposed to the cell body mass that represents ADH not yet ready for secretion.

Normal ADH Secretion

The nonpathologic ADH model is composed of 2 storage masses (cell body and cell projection), with synthesis producing cell body mass, and secretion coming from projection mass, along with movement of the hormone between the two. This model represents the in

vivo process by which cell bodies in the hypothalamus produce the hormone and transport it through the infundibulum to nerve terminals in the posterior pituitary, where it enters the circulation.¹⁸ In the model, synthesis of the hormone in the cell bodies is governed by a feedback relation in which more mass reduces synthesis and vice versa. The movement of the hormone from the cell body to the projections (flux, Φ) is modeled as a constant times mass. Secretion from the projections is a combination of 2 stimuli: osmoreceptor stimulation by serum osmolarity and a central nervous system component controlled by atrial volumes. The osmoreceptor component accounts for about 20% of the total acute maximal stimulatory effect, although chronic disturbances that affect ADH secretion are almost entirely caused by serum osmolarity.¹⁹⁻²¹ ADH clearance is via the liver, kidney, and other tissues. The full model of normal water and electrolyte homeostasis and ADH has been described in more detail in previous work.¹³

Pathophysiologic Model

As described in the literature, triphasic DI is a rare but well-documented type of postsurgical water and electrolyte disturbance that presents as a 3-stage response involving an initial transient DI caused by interruption of the axonal stalk from the hypothalamus to the pituitary, suppressing ADH secretion for about 5–7 days in the first phase.¹⁰ In the second phase there is water retention from 2 to 14 days. These symptoms resemble SIADH and are caused by the degeneration of injured ADH-secreting neurons, which start to undergo apoptosis around this period and dump intracellular contents into the circulation. With significant damage and apoptosis, ADH secretion is significantly impaired in the long-term, resulting in chronic DI (defined as the third phase).^{1,10,22}

The pathologic ADH model is composed of a variable that determines the percentage of the stalk that is damaged, and the effects of that on the cell bodies and projections. When the stalk is damaged, that percentage of cell bodies and cell projections is also marked as damaged. This process results in 3 instantaneous changes and 1 change that occurs after a fixed interval. First, ADH flux between damaged cell bodies and damaged projections stops immediately. Second, ADH synthesis in damaged cell bodies ceases. Third, the damaged cell projections die immediately, and their stored ADH is not released. Fourth, after 5 days, the damaged cell bodies begin to die at a constant rate, taking 2 days to disappear completely. As they die, they release all of their stored ADH. Explicitly, the initial mass of the ADH in the damaged slow mass is $\text{Mass}_{\text{cell body}}^{\text{damaged,initial}} = \text{Fraction}_{\text{damage}} \cdot \text{Mass}_{\text{cell body}}$. After a 5-day delay,

$$\frac{d\text{Mass}_{\text{cell body}}^{\text{damaged}}}{dt} = -\text{Mass}_{\text{cell body}}^{\text{damaged,initial}} \cdot \frac{\varepsilon}{3000} \cdot \frac{1}{\text{Fraction}_{\text{damage}}}$$

where $\varepsilon=1$ if $\text{Mass}_{\text{damaged}}^{\text{hyp}} > 0$ and 0 otherwise. This process results in a weakened ADH production system, and the size of the remaining system determines whether the simulation has prolonged issues with water or electrolyte balance.¹⁰ Overall, the model can be described as a permanent partial damage model of ADH-secreting neurons.

The assumptions made in this model are that 1) damaged projections do not release their ADH, 2) cell bodies begin to die in 5 days, and all cell death is accomplished in 2 days, and 3) cell bodies release their ADH only as death occurs, resulting in the secretion of ADH from damaged cell bodies proportional to the level of damage incurred. In simulations not shown, allowing damaged projections to release their ADH on death results in an initial spike in ADH that is resolved within hours with no significant change to body salt and water homeostasis. The second assumption affects when and for how long antinatriuresis takes place. Experimentally, the damaged section of slow mass in rats begins apoptosis by day 10 and dies by day 20.^{23,24} Our choice of 5 days fits better with human observations of water retention in 2–14 days, but the outcome of the model is not sensitive to the specific number of days. The third assumption is supported by clinical evidence; in cases of triphasic or biphasic DI, as well as isolated hyponatremia, the ADH stored in the damaged cell is released after cell death at a rate that correlates with the rate of apoptosis.^{10,22}

Protocol

Our protocol consisted of damage to the ADH secretion system as outlined earlier, yielding a fixed fraction of dying cells: 20%, 40%, 60%, or 80%. That is to say, the variable in the above equation was modulated to 0.2, 0.4, 0.6, and 0.8. We simulated routine intravenous hydration by applying 0.9% saline at a rate of 1.5 mL/minute over the course of the first 24 hours after damage. In addition, water intake was not restricted and was directly proportional to thirst, which is responsive to serum osmolarity (primary stimulus) and plasma volume status (secondary stimulus). The model was run for 14 days after the damage, with data recorded every 12 hours.

The code, entire model, and protocols are freely available online via GitHub (www.github.com/hummod/avphummod.git). The complete model is available at hummod.com/projects.

Results

Our simulations resulted in patterns of water-electrolyte disturbance that can be grouped into clinical conditions defined by urine volume and water intake, which are shown in Figure 1A and B. All 4 pituitary damages showed at least a small increase in urine volume on day 1 after the surgery. In the 20% pituitary damage simulation, there was a transient polyuria. With 40% damage, urine volume returned to normal but increased further at day 7, resembling a delayed polyuria with some degree of permanent DI. Both 60% and 80% pituitary damage showed a triphasic pattern of urine volume change representing triphasic DI. Urine volume and water intake were directly proportional (Figure 1A and B).

Figure 1C shows the broad trends in plasma ADH concentration throughout the simulations, and Figure 1D is a magnified scale for appreciation of finer changes in ADH. Lower plasma ADH concentration corresponded with more severe polyuria and polydipsia (Figure 1). Only transient changes in plasma ADH were seen in the transient polyuria simulation (20% pituitary damage). The other 3 simulations experienced a large increase in plasma ADH around day 5, corresponding with neuronal degeneration. This process brought urine volume to minimal levels for a few days. In the triphasic DI simulations (60% and 80% damage

groups), there was a sequential decrease, increase, and then permanent deficiency in circulating ADH.

Plasma osmolarity and sodium levels increased during periods of polyuria and polydipsia, although these values never reached abnormally high values (Figure 2A and B). The changes in these parameters corresponded with the changes in plasma ADH concentration. In addition, more dilute urine was produced during periods of low ADH levels, and vice versa (Figure 2C).

In the simulations with overt polyuria (>40% pituitary damage), there were decreases in plasma volume (Figure 3A) and extracellular fluid volume (Figure 3B). This was accompanied by a compensatory increase in fluid intake. Although volume status eventually came into balance in all simulations, by day 14 plasma volume and ECFV were permanently decreased in proportion to the degree of damage. Total extracellular sodium mass mirrored plasma volume (Figure 3C).

Mean arterial pressure (MAP) increased corresponding to periods of high ADH beginning on day 5 (Figure 4A). During the triphasic DI simulation (80% pituitary damage), there was a mild decrease in MAP during the first day that was not seen in other simulations and that was associated with extreme polyuria. Cardiac output increased in all simulations during the first day and was associated with an increase in plasma volume caused by perioperative fluid loading (Figure 4B). Conversely, total peripheral resistance (TPR) decreased during the first day (Figure 4C). Similar to MAP, TPR also increased during the period of high ADH levels. Despite these fluctuations, all cardiovascular parameters returned toward their respective baseline values.

Renal function is shown in Figure 5 and tubular water reabsorption in Figure 6. Decreases in glomerular filtration rate (GFR) were seen in the simulations that were associated with low ADH levels (Figure 5A). During periods of high ADH, GFR remained at near-normal levels. Aside from minor fluctuations on day 1, renal blood flow (Figure 5B) and sodium excretion (Figure 5C) remained relatively stable. In general, tubular water reabsorption correlated inversely with plasma ADH. The most pronounced difference between the presence and absence of ADH was seen in the distal tubule (Figure 6C) and collecting duct (Figure 6D).

Atrial natriuretic peptide (ANP) changed in accordance with plasma volume, increasing in response to antidiuresis and decreasing in association with DI-induced polyuria (Figure 7A). The most consistent change in the renin-angiotensin system was the decrease in angiotensin II (Figure 7B) and aldosterone (Figure 7C) on day 1 after the surgery, corresponding with the increases in plasma volume and sodium retention (Figure 3).

Discussion

The results of our simulation show that a variety of presentations of postsurgical water and electrolyte disturbances can be elicited by modifying the degree of pituitary damage. Specifically, the 3 phenotypes produced were transient polyuria, delayed polyuria with permanent DI, and triphasic DI. The triphasic DI simulations involved an initial DI, an interphase that resembles SIADH, and then permanent DI. However, in contrast to our

hypothesis, we show that merely modifying the level of pituitary damage does not produce a continuum of disease that includes all postsurgical water and electrolyte disturbances, namely severe hyponatremia, either isolated or in tandem with low ADH in the second phase of triphasic DI.

Several clinically pertinent observations can be made from our simulations. In the immediate postoperative period, we showed polyuria with 2 different causes: iatrogenic fluid loading and early-onset DI. There is overlap of the increases in urine volume, and this represents a potential confounding factor for the diagnosis of DI. In addition, we show that a drastic change in water intake is required for a patient with sudden, central DI to remain relatively normonatremic and normo-osmotic. In our simulation of early-onset DI (80% damage), water intake increased by a factor of 8 on postoperative day 1 (Figure 1B). These results reinforce the credence that water intake should be controlled by the patient's own thirst and that treatment with desmopressin should be used cautiously because of the possibility of neuron degeneration.

Immediate polyuria occurs in up to 30% of cases and has been speculated to be the result of routine intravenous hydration associated with surgery.¹ All simulations included an initial saline administration, which was associated with an iatrogenic polyuria on day 1 that was permanent in 2 of 4 scenarios. Similarly, clinical studies have also noted patients with prolonged polyuria.¹ The model predicted permanent polydipsia and polyuria with >40% pituitary damage, with no abnormalities seen during 20% damage. This finding implies that the threshold of our model for pituitary damage leading to observable permanent ADH insufficiency is between 20% and 40%.

Water and electrolyte homeostasis was shifted to various degrees in the present simulations. Although no severe electrolyte derangements occurred (e.g. hypernatremia or hyponatremia), there were large shifts in the amount of water intake and output in the simulations. The intact thirst mechanism allowed immediate adjustment of water intake in accordance with a changing plasma osmolarity. In HumMod, DI is represented by lower levels of plasma ADH, which result in increases in urine output and thirst. Similarly, the typical clinical presentation of DI is polyuria and polydipsia with the absence of sodium or osmolar abnormalities if there is free access to water.²⁵ The range of polyuria depicted from our simulations (4–8 mL/minute) is consistent with the levels seen clinically during DI.^{18,25} We also observed a period of anti-diuresis when extremely high levels of ADH combined with low thirst and urine volume resembled clinical SIADH. However, plasma sodium and osmolarity were prevented from decreasing to abnormal levels because thirst was suppressed, suggesting that there may be mechanisms not accounted for in our model that are responsible for clinically high or low plasma osmolarity after pituitary surgery.

The exact mechanism that produces the wide range of water and electrolyte disturbances in patients undergoing pituitary surgery remains unclear. In rodents, damage to the pituitary stalk during transsphenoidal surgery causes loss of ADH in areas associated with magnocellular cell bodies.¹⁰ Moreover, the magnitude of the decrease in ADH in this study was correlated with the degree of water and electrolyte disturbances.¹⁰ This finding is further supported by clinical observations that preservation of the pituitary stalk in resection

of craniopharyngioma is associated with lower rates of permanent DI.^{26,27} In some cases, a remnant stalk after surgery is able to compensate for the lost posterior pituitary by secreting ADH, forming a pseudoposterior lobe.^{26,27} Similarly, in our model, damaged hypothalamic neurons undergo degeneration nearly a week later and are then permanently impaired. In our model, the amount of cellular damage modified the magnitude and length of each phase and increased the likelihood of all 3 components of triphasic DI to appear. These observations reinforce previous hypotheses for the mechanism of triphasic DI and help account for why this derangement is so rare (1%–3% of surgeries) yet consistent in its presentation.¹⁸

The change in ADH secretion in damaged magnocellular neurons cannot be verified in the literature directly. Therefore, we made several assumptions in the design of the model. The most influential of these assumptions involved the initiation and time course of cell body death after damage. In an imaging study in rats, cell body death begins at 10 days, is accelerating at 20 days, and is complete by 30 days. To our knowledge, no imaging studies in humans are available. However, the ADH-secreting period after these surgeries has been reported to last 2–14 days in humans, with nadir appearance on days 5–7.²² In our simulation, we chose 5 days for the delay between severing and the initiation of cell death, with cell death rate fixed. This strategy led to longer periods of SIADH as the pituitary damage increased. The second assumption was that terminals, on being severed from their cell bodies, would not secrete any ADH. Because of the clearance rate of ADH, physiologic evidence of this process in humans remains unknown and would likely be difficult to confirm experimentally.

Limitations

Our model and protocols do not allow differences between thirst and water intake, which is an important factor in promoting clinical abnormalities in sodium or osmolar balance. We did not observe hyponatremia, either immediate or delayed, or biphasic DI (defined as DI followed by an antidiuretic episode). Because of the constant water and sodium intake during the simulations, we were unable to simulate brief periods of water unavailability that would be seen in a patient (e.g., sleep). This factor most likely would have increased the severity of the water and electrolyte disturbances seen in our model. In addition, although some consider stand-alone hyponatremia to be an isolated second phase along the triphasic spectrum, patients showing isolated delayed hyponatremia or a biphasic response have normal plasma levels of ADH and ANP.¹ Separate studies have suggested that other factors may contribute to some degree of postsurgical hyponatremia, including brain natriuretic peptide, cerebral salt wasting, and hypocortisolism.^{28,29} In stand-alone SIADH, hyponatremia does not occur unless total water intake is greater than output,³⁰ similar to the findings of this simulation. In light of this factor, along with the fact that most patients have an intact thirst and osmoregulation system,²⁵ it stands to reason that the impressive incidence of postsurgical hyponatremia reported in the literature may be, at least in part, caused by ADH-independent mechanisms.

Another limitation in this study was the lack of experimental data with which to compare the model. This deficiency of data comes from the fact that patients vary greatly in their health and physiology, leading to different responses and treatments after surgery. Also, in the

remainder of the literature, although qualitative descriptions are common, the population is too heterogeneous to allow statistical comparisons or insight into a particular patient group.

Conclusions

Results from this model give mechanistic insight into many varieties of postsurgical water and electrolyte disturbances, an area in the clinical literature in which detailed studies are lacking. Stepwise cellular damage to the pituitary produced different responses and culminated with a full triphasic DI. Our simulation shows that merely modifying the level of pituitary damage does not produce a continuum of disease on which all presentations can be identified. Other elements that are still unclear and not factored into this model, namely those responsible for postoperative hyponatremia, require further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations and Acronyms

ADH	Antidiuretic hormone
ANP	Atrial natriuretic peptide
DI	Diabetes insipidus

GFR	Glomerular filtration rate
MAP	Mean arterial pressure
SIADH	Syndrome of inappropriate antidiuretic hormone
TPR	Total peripheral resistance

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Figure 1.

Profiles of urine volume (**A**) and water intake (**B**) in response to varying degrees of pituitary damage. 20% pituitary damage produces transient polyuria, 40% a delayed polyuria with a degree of permanent diabetes insipidus, and 60 and 80% a triphasic diabetes insipidus. The corresponding plasma antidiuretic hormone (ADH) concentrations are shown full-scale (**C**) and with a magnified scale (**D**) to show fine changes

Figure 2.

Plasma osmolarity (**A**) and sodium (**B**) levels increased during periods of polyuria and polydipsia, although these values never reached abnormally high values. Urine osmolarity (**C**) decreased during periods of low antidiuretic hormone levels, and vice versa.

Figure 3.

During periods of overt polyuria (>40% pituitary damage), there were decreases in plasma volume (A) and extracellular fluid volume (B), but this was accompanied by a compensatory increase in fluid intake. Total extracellular sodium mass (C) mirrored plasma volume.

Figure 4. Mean arterial pressure (A), cardiac output (B), and total peripheral resistance (C) changed in accordance with fluctuating volume status but returned toward baseline values.

Figure 5.

Decreases in glomerular filtration rate (A) were seen in the simulations that involved the lower antidiuretic hormone levels of diabetes insipidus. Aside from minor fluctuations on day 1, renal blood flow (B) and sodium excretion (C) remained relatively stable.

Figure 6.

Tubular water reabsorption in the proximal tubule (PT) (A), Loop of Henle (B), distal tubule (DT) (C), and collecting duct (CD) (D). The most pronounced difference between the presence and absence of antidiuretic hormone was seen in the distal tubule (C) and collecting duct (D).

Figure 7.

Atrial natriuretic peptide (ANP) increased in response to antidiuresis and decreasing in association with diabetes insipidus–induced polyuria (A). The most consistent change in the renin-angiotensin system was the decrease in angiotensin II (B) and aldosterone (C) on day 1 after the surgery.