Physiologic Mechanisms of Water and Electrolyte Disturbances After Transsphenoidal Pituitary Surgery

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

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.

Key words
- Antidiuretic hormone
- Mathematical modeling
- Transsphenoidal pituitary surgery

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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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 Lohmeier[16] 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 humans[13] 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]