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See related article, "Imaging of the Porous Ultrastructure of the Glomerular Epithelial Filtration Slit," on pages 2081–2089.

Managing Overly Rapid Correction of Chronic Hyponatremia: An Ounce of Prevention or a Pound of Cure?

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Rapid correction of chronic hyponatremia may lead to osmotic demyelination syndrome (ODS) and devastating neurologic sequelae.[1] The rate of rise in plasma sodium concentration (P_{Na}) in patients with chronic hyponatremia should be $<$8 mmol/L per d[2] and even lower in patients at higher risk for ODS: Those with alcoholism, cirrhosis, malnutrition, or hypokalemia.[3]

The pathophysiology of ODS is poorly understood. The brain loses organic osmolytes rapidly to adapt to hyponatremia but reclaims them slowly in response to its correction.[4] A rapid increase in P_{Na} shrinks cerebral vascular endothelial cells, which opens the blood-brain barrier, allowing lymphocytes, complement, and cytokines to enter the brain, damage oligodendrocytes, and cause demyelination.[5] Microglial activation seems to contribute to this process.[6]

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Minocycline, a tetracycline derivative, has been shown to have protective effects in experimental models of central nervous system injury, including demyelinating damage.[7] In this issue of *JASN*, two studies examine the role of minocycline in prevention of ODS caused by rapid correction of chronic hyponatremia in rats.[8,9] Data are mostly from experiments in which minocycline was started at the time of or several hours *before* correction of hyponatremia. In the study by Gankam *et al.*,[9] a large dose of minocycline was used. The administration of minocycline is associated with a marked reduction in the incidence and severity of neurologic symptoms; nevertheless, 48% of these rats died.[9] Notwithstanding, minocycline-treated rats had much better survival in the study by Suzuki *et al.*[8] Although the administration of minocycline is associated with less activation of microglia and diminished release of inflammatory cytokines, rats still develop some demyelinating brain lesions. Gankam *et al.*[9] also studied a group of rats in which minocycline was started 18 hours *after* rapid correction of hyponatremia; six of 13 rats died. In a recent study by the same group, in which hyponatremia was re-induced after rapid correction of chronic hyponatremia, only one of 16 rats died.[10]

Although both studies provide interesting insights into the role of microglial activation in ODS, the data provided do not argue strongly for a role for minocycline in the prevention of ODS in clinical practice should inadvertent rapid correction of chronic hyponatremia occur. The critical issue in the management of chronic hyponatremia is to *prevent* rapid correction. A rapid rise in P_{Na} is almost always due to a water diuresis, which happens when vasopressin action suddenly ceases, such as with volume repletion in patients with intravascular volume depletion, cortisol replacement in patients with Addison disease, resolution of nonosmotic stimuli for vasopressin release such as nausea or pain, or if *distal delivery of filtrate increases*. This last aspect of the pathophysiology of chronic hyponatremia and its correction needs emphasis. An important point is that chronic hyponatremia can develop in the absence of vasopressin action.

In the absence of vasopressin, the *maximum* urine volume is the volume of filtrate delivered to the distal nephron, which is the GFR minus the volume reabsorbed in the proximal convoluted tubule (PCT). Although it was thought that approximately 66% of the GFR is reabsorbed in the PCT, we now think it is greater. Recent data suggest that the thin descending limb of the loop of Henle of the majority of nephrons lacks aquaporin 1,[11] and therefore the entire loop of Henle of these nephrons is most likely water impermeable. Hence, a better estimate of the fraction of filtrate reabsorbed in PCT (including pars recta) is obtained from micropuncture studies of the distal convoluted tubule in rats using the tubular fluid–plasma inulin concentrations ratio. The lowest measured value is 6.[12] Therefore, five sixths (83%) of the GFR is reabsorbed in PCT, a value that is close to the estimate from lithium clearance in hu-

mans.[13] Water excretion will be less than the volume of distal delivery of filtrate, even in the absence of vasopressin, because there is appreciable water reabsorption in the inner medullary collecting duct through its residual water permeability,[14] driven by the enormous osmotic force in this setting.

Consider the implications of this physiology for a common clinical scenario. An elderly woman has ischemic renal disease and an estimated GFR of 40 L/d and is prescribed hydrochlorothiazide for hypertension. She consumes a low-salt and low-protein diet and habitually drinks a large amount of water. Because of the intake of hydrochlorothiazide and the low-salt diet, she develops a sodium deficit and a mild degree of intravascular volume depletion. If she were now to reabsorb say 90% of her GFR in PCT instead of 83%, only approximately 4 L/d will be delivered distally. Her capacity to excrete water will be substantially lower, even in the absence of vasopressin, because of water reabsorption in inner medullary collecting duct owing to large differences in osmolality between luminal fluid (she has a low osmole excretion rate) and the medullary interstitium. Hyponatremia develops if her water intake exceeds her limited capacity to excrete water.[15]

She presents to the emergency department feeling unwell and is found to have hyponatremia. Her BP is normal, but she seems to be mildly volume depleted and so receives isotonic saline for gentle volume expansion. This is enough to re-expand her intravascular volume and thereby increase distal delivery of filtrate, so a water diuresis occurs. Because of her small muscle mass, even a modest water diuresis is large enough to cause a rapid rise in P_{Na}. Furthermore, she might be at a higher risk for ODS if she also has hypokalemia or is malnourished.

If a water diuresis that may cause the P_{Na} to rise too quickly occurs, we administer dDAVP to stop the water diuresis.[16,17] If P_{Na} inadvertently rises nonetheless, lowering P_{Na} to the maximum limit for correction with the administration of D5W seems to be best strategy.[10,18]

What about a patient who presents with severe neurologic symptoms suggestive of an acute component of hyponatremia?[19] In normonatremic neurosurgical patients, a rapid rise in P_{Na} of approximately 5 mmo/L with the infusion of hypertonic saline is sufficient to lower markedly the intracranial pressure.[20] Using a similar goal of therapy, one can reduce intracranial pressure without leading to an increased risk for ODS.

Whether minocycline will add anything to our approach to treating hyponatremia will need more studies with designs similar to the clinical setting of an inadvertent rapid correction of chronic hyponatremia and with doses of minocycline that can safely be used in humans.

DISCLOSURES

None.

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