Challenges in Diuretic Therapy: A Case Based Discussion

Internal Medicine Grand Rounds

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This is to acknowledge that Kamalanathan Sambandam, M.D. has disclosed that he does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Sambandam will be discussing off-label uses in his presentation.

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Biography:
Dr. Sambandam received his undergraduate degree at Rice University in Houston, Texas followed by his Doctor of Medicine at the University of Texas Medical Branch at Galveston. His Internal Medicine and Nephrology Subspecialty training was conducted at Barnes-Jewish Hospital/Washington University in Saint Louis. His main administrative roles include Program Directorship for the Nephrology Fellowship at UTSW and Medical Directorship of the Parkland Memorial Hospital Renal Clinics. His clinical and research interests lie in the fields of diuretic resistance and non-diabetic glomerular disease. He is the center Principal Investigator for two NIH-sponsored studies, the Nephrotic Syndrome Study Network and the Cure Glomerulonephritis Network.

Purpose and Overview:
The discussion will review some of the obstacles that are encountered during the course of diuretic therapy for states of volume excess. The physiologic principles that underpin these challenging scenarios will be examined. Building upon on this foundation of understanding, the review will provide pragmatic solutions to these clinical problems. With this knowledge, the practitioner will gain the tools necessary to overcome these common impediments to effective volume control in the hypervolemic syndromes.

Educational Objectives:
1. Understand some of the mechanisms of loop diuretic resistance in the treatment of nephrotic syndrome. Know how to overcome this resistance with and without the use of albumin infusions.
2. Understand some of the mechanisms that maintain a metabolic alkalosis during diuretic therapy for the hypervolemic syndromes. Understand the limits of carbonic anhydrase inhibitor therapy in this situation as well as the importance of potassium chloride supplementation in correcting the alkalosis.
3. Move beyond an understanding of hyponatremia that is based solely on volume status to one that views it as a disproportion between total body sodium and potassium content and total body water. From this foundation, understand how potassium supplementation and, occasionally, liberalized sodium intake, may be appropriate for managing the hyponatremia of hypervolemic states.

Introduction

Renal sodium retention characterizes the pathophysiology of a large and diverse set of diseases encountered by the clinician, including heart failure, acute and chronic kidney disease, cirrhosis, and diseases of excess capillary permeability such as sepsis, malignancy, and malnutrition. Diuretics are the primary means of addressing sodium retention and the hypervolemia that results. As such, diuretics are some of the most commonly prescribed medications. Though they are typically effective for achieving improvements in hypervolemia, they are not without challenges. Table 1 lists the aspects of diuretic therapy that may impair the ability to achieve good volume control. The following discussion employs a case-based approach and focuses on 3 of the obstacles that are listed: the *diuretic resistance that characterizes nephrotic syndrome*, *diuretic associated metabolic alkalosis*, and *diuretic associated hyponatremia*. The goal is to provide the reader with an understanding of the physiologic basis of some of these challenges in diuretic therapy. Building upon this foundation, pragmatic solutions to these problems are then discussed. Armed with this knowledge, it is hoped that the clinician can overcome these obstacles to achieve optimal volume control and better patient centered outcomes.

- Resistance to diuresis
  - Heart failure
  - Cirrhosis
  - Nephrotic syndrome*
  - Renal insufficiency
- Worsening renal function with diuresis
- Metabolic alkalosis* or acidosis
- Hypokalemia or hyperkalemia
- Hyponatremia* or hypernatremia
- Hypomagnesemia
- Hyperuricemia
- Ototoxicty
- Idiosyncratic side effects (pancreatitis, interstitial nephritis)

Table 1: Patient factors that may impair effective volume control with diuretic therapy. These include pre-existing factors or consequences of diuretic therapy. Those factors that are marked by an asterisk (*) will be the subject of this discussion.

Case 1: The Diuretic Resistant Patient with Nephrotic Syndrome

Mr. X was a 57-year-old male with a recent diagnosis of membranous nephropathy at an outside hospital. He was found to have 21 g of proteinuria at diagnosis and discharged with oral furosemide 120 mg twice daily and instructions to establish care at the county hospital. He presented to the emergency room with severe body swelling. On exam he had edema extending to the hips and shifting dullness. His neck veins were flat. His admission laboratories were most notable for a serum creatinine of 1.6 mg/dL and an albumin of 1.7 g/dL. On day 0, the patient was bolused with furosemide 80 mg and started on a continuous infusion of 20 mg/h. Over the subsequent 4 days, the furosemide drip was increased to 40 mg/h and IV chlorothiazide was added. Only 0.5 kg of weight loss was achieved by day 4. His creatinine was relatively stable at 1.8 mg/dL. At this point, the use of should salt-poor, hyperoncotic albumin infusions were proposed as a means to address his diuretic resistance. Is this necessary?

Relevant Physiology

The rationale for employing albumin infusions in the setting of diuretic resistant nephrotic syndrome is based on 2 principles: ameliorating the enhanced renal sodium retention that characterizes this condition as well as improving loop diuretic delivery to the kidney. The mechanisms of sodium retention in nephrotic syndrome are complex. It is often understood that

the sodium retention results from a vascular underfilling due to low intravascular oncotic pressure. In this case, the plasma volume would contract, as Starling's forces (the balance between intravascular and interstitial hydrostatic and oncotic pressure) would predict. The reduced circulating volume would then result in increased renal tubular reclamation of sodium and water. This would be mediated in part by renin-stimulated angiotensin II and aldosterone excess as occurs in states of low effective circulating volume. However, the plasma volume of individuals with nephrotic syndrome has been studied by several groups by analyzing the distribution volume of radiolabeled albumin [1]. In such analyses, the plasma volume was found to be low in only 1/3. In the remaining individuals, the plasma volume was normal or even high. In addition, the plasma renin activity was typically not high in most subjects. There are other possible mediators of sodium retention in nephrotic syndrome. One analysis found that sodium reclamation was stimulated in the distal nephron through the action of plasmin on the Epithelial Sodium Channel (ENaC). The delivery of plasmin to luminal ENaC occurred as a result of the enhanced filtration of the plasma derived precursor protein, plasminogen, in the nephrotic state [2].

Albumin infusions may still mitigate the enhanced tubular reclamation of sodium in nephrotic syndrome despite the presence of a normal to high plasma volume in most. This was the case in a study of 10 nephrotic patients with an average serum albumin concentration of 1.7 g/dL given a bolus of 75 g of 20% albumin [3]. The mean blood volume was slightly above normal prior to the infusion. After the infusion, the blood volume was effectively expanded to 136% of normal at 4 h and remained at 120% of normal at 20 h (Figure 1). In response, there was a suppression of plasma renin activity and aldosterone with an increase in natriuresis.

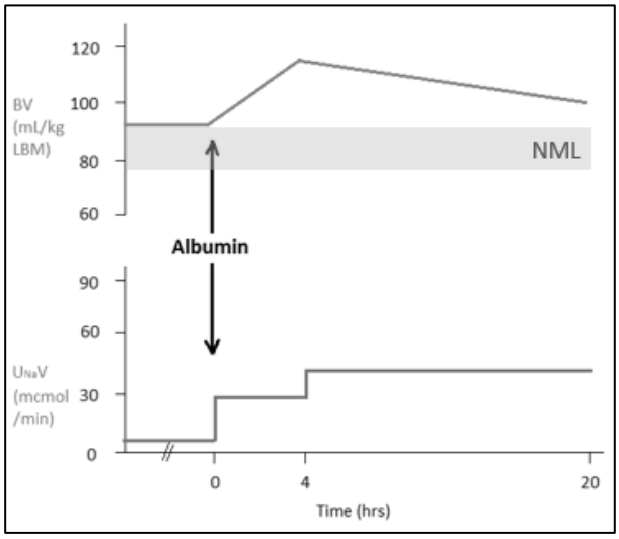

Figure 1: Effect on blood volume and natriuresis of a 75 g infusion of hyperoncotic albumin in 10 nephrotic patients.

In addition to enhancing natriuresis via volume expansion, the other rationale for the use of albumin infusions in nephrotic syndrome is as a means to increase loop diuretic delivery to the kidney. Most diuretics, including all loop diuretics, are highly protein bound with a resulting small volume of distribution (V_d). With the hypoalbuminemia that characterizes the nephrotic syndrome, the V_d is increased as more of the administered drug distributes to the extravascular space. The result is a lower serum level for a given furosemide dose, less delivery of furosemide to the renal tubular lumen where it acts, and less natriuresis. The administration of hyperoncotic albumin will transiently raise the serum albumin and thus at least partially repair the increase in V_d. The effect of combination albumin and loop diuretic therapy in nephrotic syndrome has been studied in a few small crossover studies [4]. Results have been variable, but on balance, combining a sufficient dose of albumin with a moderate to large dose of loop diuretic does augment the natriuretic response.

A deeper understanding of pharmacokinetic principle of volume of distribution allows for a dose adjustment to surmount this obstacle without the administration of hyperoncotic albumin.

The steady state V_d of furosemide for a plasma albumin concentration of 4.6 g/dL is 0.11 L/kg. In a study of patients with nephrotic syndrome and a serum albumin concentration of 2.5 g/dL, the V_d was 0.18 L/kg [5]. V_d relates to the plasma concentration ([X]) and total dose (TD) of a drug by the following relationship:

$$[X] = TD / V_d$$

Knowing the V_d of furosemide in nephrotic (V_d^{neph}) and normoalbuminemic (V_d^{nml}) patients, one can now calculate the dose adjustment required in nephrotic patients to achieve an identical plasma concentration as in normoalbuminemic patients. In the formulas that follow, TD^{neph} is the total dose of furosemide given in the setting of nephrotic syndrome and TD^{nml} refers to the total dose given to a normoalbuminemic individual:

$$TD^{neph} / V_d^{neph} = [X] = TD^{nml} / V_d^{nml}$$

$$TD^{neph} = TD^{nml} \times (V_d^{neph} / V_d^{nml})$$

$$TD^{neph} = TD^{nml} \times (0.18 / 0.11)$$

$$TD^{neph} = TD^{nml} \times 1.64$$

Therefore, one needs to increase the furosemide dose in nephrotic patients with a serum albumin of 2.5 g/L by 1.6 fold in order to achieve the same plasma level as obtained in normoalbuminemic patients. This does not necessarily imply that an identical natriuretic response will be achieved. On the contrary, it is likely that a further dose increase will be required to overcome the anti-natriuretic mechanisms at play in nephrotic syndrome. This knowledge of the effect of changes in V_d provides a starting point for dose adjustment. Refraining from the use of albumin infusions also avoids the possibility of deteriorating diuretic responsiveness after albumin infusions cease and the serum albumin declines back to baseline. This may result in rebound accumulation of volume if the loop diuretic dose is not increased in compensation for the drop in serum diuretic concentrations that is expected to occur as the V_d re-expands. It is noteworthy that none of the previously cited studies comparing combination albumin and loop diuretic therapy to diuretic monotherapy in nephrotic syndrome employed a dose adjustment based on differences in V_d as described here. It is possible that doing so would have eliminated any benefit from albumin and loop diuretic coadministration.

Case 1 Outcome

After increasing furosemide to a maximum of 60 mg/h during the subsequent 9 days, 17 kg of additional weight loss was achieved. His ascites was no longer detectable and his edema was improved, limited to below the mid-shin. His serum creatinine modestly increased to 2.3 mg/dL at the time of discharge. Albumin infusions were never employed. This allowed for the transition to an oral diuretic regimen prior to discharge that the clinician was confident would continue to be effective. There was no need to reassess diuretic responsiveness as might be required with declining serum albumin concentrations after albumin infusions cease.

Case 2: The Patient with Worsening Metabolic Alkalosis During Diuresis

Ms. Y was a 68 year-old female with morbid obesity, sleep apnea, combined chronic diastolic and systolic heart failure, and chronic kidney disease who presented with shortness of

breath. She was hypoxemic and volume overloaded on presentation with edema extending to her body wall. Her initial serum chemistries were notable for a potassium of 3.8 mmol/L, a creatinine of 2.3 mg/dL, and a bicarbonate of 29 mmol/L. Her blood gas revealed an arterial pH of 7.48 with a pCO_2 of 56 mmHg. She was admitted to the cardiac care unit and started on a furosemide drip. Over the subsequent 8 days she lost 8 kg of excess volume, however her total carbon dioxide progressively rose despite dosing 500-1000 mg acetazolamide intravenously twice daily in the prior 5 days. By day 8, her serum chemistries revealed a bicarbonate of 43 mmol/L, potassium of 3.3 mmol/L, and creatinine of 2.8 mg/dL. This severe metabolic alkalosis resulted in a cessation of her furosemide despite the fact that she still had edema to the level of her thighs and an oxygen requirement. Nephrology was at this time consulted with a request to assist with the alkalosis and consider initiating renal replacement therapy for further volume removal.

Relevant Physiology

Bicarbonate is reclaimed along the length of the nephron such that, normally, the urine is rendered bicarbonate free. Most of this bicarbonate is reclaimed not in its ionized buffer form but rather as carbon dioxide. Protons are secreted into the tubular lumen and react with luminal bicarbonate to form CO_2 and water. The CO_2 then translocates across the plasma membrane and into the cell where the reverse reaction takes place, regenerating bicarbonate. The bicarbonate is then returned to circulation by way of basolateral transport proteins. The conversion of bicarbonate to CO_2 and back is facilitated by the enzyme carbonic anhydrase (Figure 2).

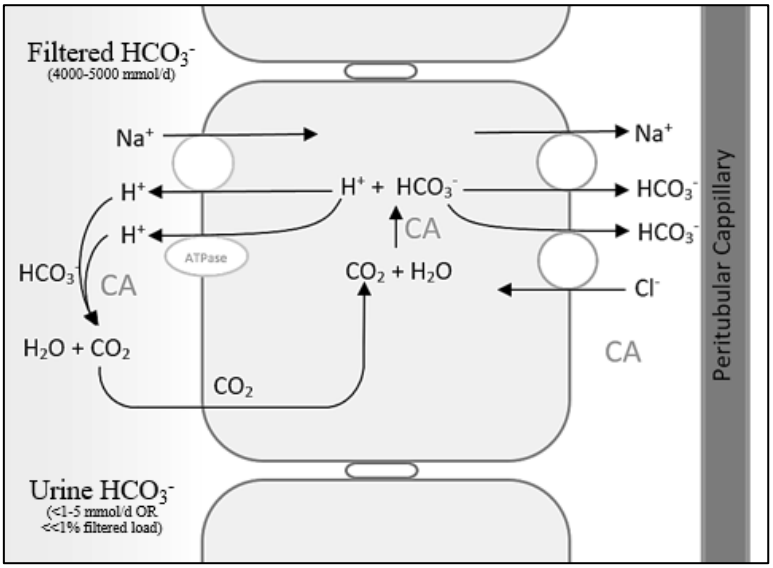

Figure 2: The basic physiology of bicarbonate reclamation from the renal tubular lumen. Note this relies on the interconversion between bicarbonate and carbon dioxide under the influence of carbonic anhydrase (CA).

Normally this process of bicarbonate transport is extremely effective, resulting in much less than 1% of the filtered load of bicarbonate reaching the final urine. With an intact glomerular filtration rate, the kidneys filter roughly 4500 mmol of bicarbonate per day but lose less than 5 mmol per day in the urine.

With the administration of acetazolamide, carbonic anhydrase is inhibited. With complete inhibition, the fractional excretion of bicarbonate can be increased to 25% of the filtered load. Twenty-five percent of 4500 mmol is approximately 1000 mmol. If this patient were to achieve a fractional excretion of 25% with acetazolamide dosing, one would predict that the serum bicarbonate would rapidly fall from the severely elevated value of 43 mmol/L to the normal range in a single day. Why then did this patient not correct her serum bicarbonate as acetazolamide was dosed? There are 3 reasons for this: Firstly, the patient had impaired renal function. With a creatinine of 2.8, her estimated glomerular filtration rate was approximately 20 mL/min per 1.73 m^2, or about 1/6 of normal. Her filtered load of bicarbonate would have

therefore been roughly 1/6 that of an individual with a comparable serum bicarbonate and a normal glomerular filtration rate, dramatically reducing the amount of bicarbonate that is available for excretion. Secondly, her reduction in effective circulating volume resulted in increased tubular solute reclamation, including bicarbonate. Lastly, a total body potassium depletion caused by her loop diuretic therapy further contributed to alkalosis. This last mechanism deserves further explanation and is described in Figure 3 and the discussion below.

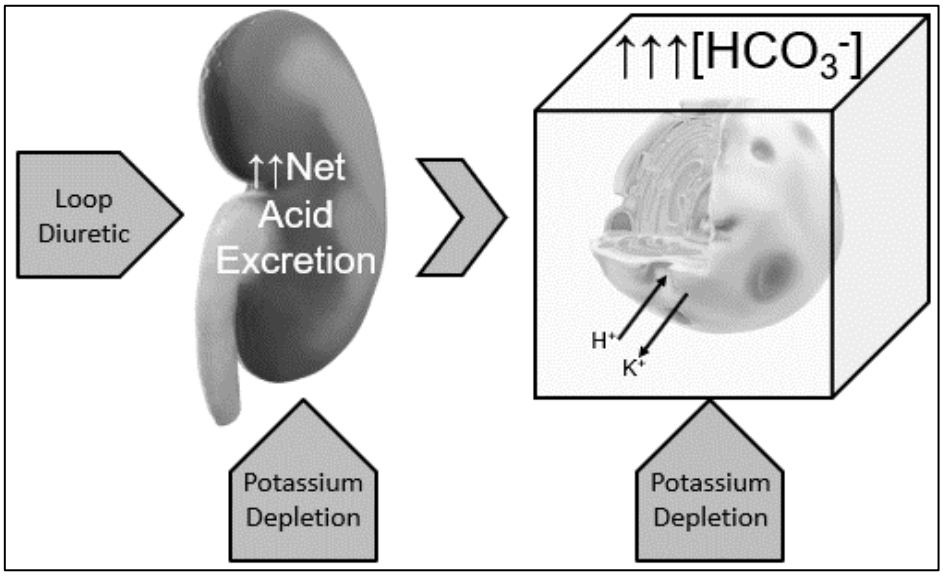

Figure 3: The synergistic effect of loop diuretic therapy and potassium depletion in the development and maintenance of a metabolic acidosis. Loop diuretics and potassium depletion both augment urinary acid excretion. Potassium depletion further augments the serum bicarbonate concentration by driving extracellular protons into cells.

Non-volatile acid is secreted from the body via the urine in the form of protonated urinary buffers such as phosphate and ammonium iron (NH_4^+). The most important and dynamic of these is ammonium ion, with the kidneys modulating the excretion rate of this species according to the physiologic need of the organism. The term Net Acid Excretion (NAE) refers to the sum of these urinary buffers minus the urinary bicarbonate excretion rate (the loss of bicarbonate in the urine counteracts the elimination of an equimolar amount of acid and so is subtracted in calculating NAE). The metabolic consequence of NAE is the generation and replenishment of the body's bicarbonate content. The administration of loop diuretics increases NAE through augmenting proton secretion in exchange for sodium absorption in both the thick ascending limb [6] as well as the collecting duct (see Figure 4). Loop diuretics also increase urinary potassium excretion. The depletion of potassium further increases NAE when there are high aldosterone levels [7, 8], as is characteristic in states of low effective circulating volume. This excess NAE results in a metabolic alkalosis. Potassium depletion increases the serum bicarbonate concentration by a second mechanism: transcellular cation shift. When potassium shifts out of cells to replace losses of extracellular potassium in the urine, the resulting electrical gradient favors a compensatory shift of sodium and protons to the intracellular space (see Figure 3). A reduction of extracellular proton content results in a further worsening of the metabolic alkalosis.

Aggressive potassium supplementation will tend to reverse the augmented NAE and intracellular proton translocation that perpetuates the metabolic alkalosis. The addition of a potassium sparing diuretic (such as amiloride, triamterene, spironolactone, or eplerenone) will limit urinary potassium losses as well as blunt the increase in NAE that occurs with loop diuretic therapy. These effects are mediated through reducing the favorable electrical gradient for luminal potassium and proton secretion in the collecting duct (Figure 4). Potassium sparing diuretics inhibit distal nephron sodium absorption, thus reducing the negative electrical potential

difference that favors both potassium and proton losses in the urine. The reduction in NAE serves to mitigate the rise in serum bicarbonate but does not reduce the extracellular bicarbonate concentration per say. That would require enhanced urinary bicarbonate elimination via carbonic anhydrase inhibition, which may have limited effectiveness for the reasons previously outlined. It should therefore be apparent that aggressive potassium supplementation and the initiation of potassium sparing diuretics should ideally be employed early, rather than delayed until after a significant metabolic alkalosis develops. It is the author's experience that without these interventions, the development of metabolic alkalosis is practically universal once the goal 4-5 L/d diuresis is achieved, as is required to realize timely clinical improvement in most markedly overloaded patients. For this reason, the author recommends that these interventions be initiated at a threshold serum bicarbonate concentration of 22 mmol/L, once this rate of diuresis is achieved. In the case presented, potassium supplementation and potassium sparing diuretic therapy were initiated on day 8 when the serum bicarbonate was already 43 mmol/L. The result was predictable: over the next 3 days, the serum bicarbonate remained at 42 mmol/L.

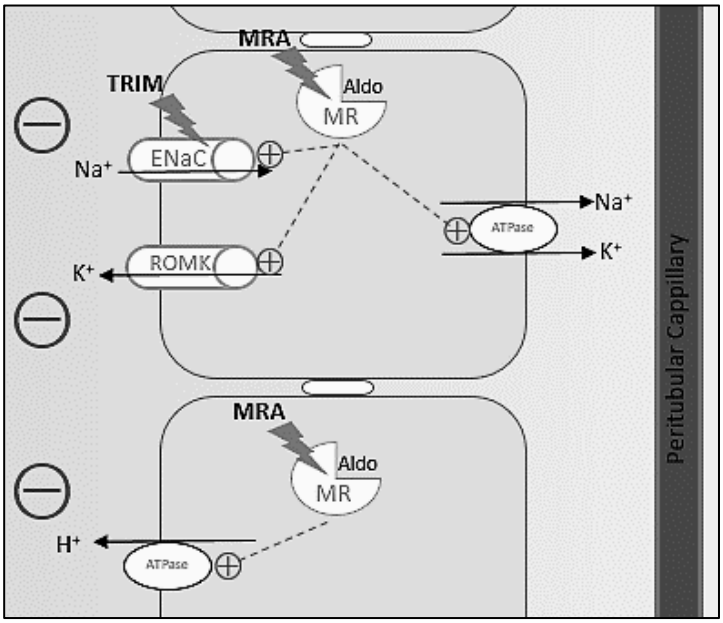

Figure 4: Distal nephron potassium and proton secretion depends on the luminal negative potential difference generated by sodium absorption. By inhibiting this process, mineralocorticoid antagonists (MRA) and triamterene (TRIM) or amiloride will reduce urinary proton and potassium losses.

What was done next is a rarely employed strategy for managing metabolic alkalosis. Typically in such cases, diuresis is paused even though the patient may remain hypervolemic. In other cases, further volume removal is pursued through the use of renal replacement therapy. In the present case, a more novel yet sound solution grounded in principles of physiology presented itself: the administration of an acid load. When an acid is administered, the proton is buffered by bicarbonate to form carbonic acid. Carbonic acid then converts to carbon dioxide and water, the former being expelled by the lungs. The net result is a fall in the serum bicarbonate, thus repairing the metabolic alkalosis. There are several options for acid loading in the management of the patient with refractory and severe metabolic alkalosis when potassium chloride is ineffective and volume expansion with sodium chloride is undesirable due to the presence of volume overload. These are summarized in Table 2.

Case 2 Outcome

Throughout hospital days 9 through 11, aggressive potassium chloride supplementation was administered and the potassium sparing diuretic triamterene was given. Though an additional 3.3 kg of weight loss was realized by day 11, the serum bicarbonate had remained essentially unchanged at 42 mmol/L. In addition, the serum potassium had risen to 5.1 thus preventing further potassium administration. The serum creatinine remained stable at 2.7

mg/dL. At this point, the initiation of renal replacement therapy was considered as a means to continue to remove volume without further exacerbating the alkalosis. Instead, a strategy of acid loading was pursued. Given the fact that hydrochloric acid, ammonium chloride, and arginine chloride were not on formulary in the hospital and thus required 3 days to obtain, an alternate means was employed. Given the availability of sodium thiosulfate and its propensity to cause metabolic acidosis, this was used as the acidifying agent. Over the subsequent 5 days, 4 doses of 25 g of sodium thiosulfate were given while the patient continued to receive furosemide, acetazolamide, and triamterene. By day 16, an additional 8.2 kg of weight loss was realized. At this point the serum bicarbonate had improved to 37 mmol/L with an anion gap of 18, a serum potassium of 4.8 mmol/L, and a creatinine of 2.5 mg/dL. The patient was successfully weaned off of oxygen and the clinical exam revealed only trace pedal edema at this point. Renal replacement therapy was not required.

Table 2: Options for extracellular fluid acidification in clinical practice.

Drug	Acidifying Mechanism	Dosing and Estimated $\Delta[HCO_3^-]^{\S}$	Other Concerns
Potassium chloride	Translocation of protons to the ECF in exchange for potassium	↓0.5 mmol/L $[HCO_3^-]$ / 1 mmol KCl per L TBW* Administer IV or PO	Effect on serum potassium limits dose
Hydrochloric acid	Direct proton loading	↓1 mmol/L $[HCO_3^-]$ / 1 mmol HCl per L TBW Administer as a 100 or 200 mmol/L IV infusion.	Must be given via central access, with glass IV tubing
Ammonium chloride	Metabolism of ammonium to urea by the liver consumes bicarbonate	↓1 mmol/L $[HCO_3^-]$ / 1 mmol NH_4Cl per L TBW Administer as a 100-400 mmol/L IV infusion.	Can also be given in research settings as an oral load Avoid in hepatic insufficiency given risk of hyperammonemia
Arginine hydrochloride	Metabolism of arginine to ornithine and urea in the urea cycle consumes bicarbonate	↓1 mmol/L $[HCO_3^-]$ / 1 mmol ArgHCl per L TBW Administer IV or PO undiluted as 142 mmol/300 mL vial	Excessive IV infusion rates may cause flushing and nausea
Sodium thiosulfate	Unclear May engage mitochondrial sulfide oxidation pathway forming the weak acid hydrogen sulfide	Unknown If hydrogen sulfide is responsible, would predict ↓1 mmol/L $[HCO_3^-]$ / 1 mmol sodium thiosulfate per L TBW Administer IV 25 g/100 mL (158 mmol/100 mL)	High anion gap acidosis occurs Hypotension, flushing, and nausea may occur

*TBW refers to the estimated total body water, estimated as 0.5 X body weight (kg) in euvolemic females and 0.6 X body weight (kg) in males. §Assumes no renal function, indicating only the consumption of bicarbonate buffer. *Estimated from studies in anephric rats [8].*

Case 3: The Patient with Worsening Hyponatremia During Diuresis

Mr. Z was a 65-year-old male with chronic systolic heart failure from cardiac amyloidosis and chronic kidney disease who presents with swelling and shortness of breath. He has required hospitalizations for similar presentations 2 other times in the last 3 months. The exam reveals distended neck veins, shifting abdominal dullness, and 3+ lower extremity edema to the hips. His initial blood chemistries revealed a serum sodium of 130 mmol/L, potassium of 4.0

mmol/L, and creatinine of 1.5 mg/dL. He is started on a furosemide drip, low-salt diet, and fluid restriction. By hospital day 5 his weight has dropped by 6.2 kg. His jugular venous pulsation is down to 8 cm of water, however he still has 3+ edema to the knees and ascites. His serum sodium has dropped to 124 mmol/L with a serum potassium of 3.5 mmol/L, bicarbonate 27 mmol/L, and creatinine 1.5 mg/dL. Due to the worsening hyponatremia, his furosemide was held and nephrology was consulted.

Relevant Physiology

The traditional diagnostic approach to hyponatremia emphasizes an initial assessment of volume status. This primary focus on volume status often leads the clinician to ascribe a causative role for the hypervolemia in the development of hyponatremia. Grounded in this incorrect concept, the clinician will often focus efforts at volume removal with diuretics and assume that the serum sodium will increase as weight is lost. This is a classic example of a *cum hoc ergo propter hoc* ("with this, therefore because of this") fallacy. A deeper understanding of the physiology of dysnatremias reveals the truth, and allows one to explain the worsening hyponatremia with diuresis that was encountered in this case. This requires a discussion of Edelman's equation.

In 1958, Edelman and colleagues published their experience relating the serum sodium to the body's proportional content of electrolytes and water [10]. They examined 98 hospitalized patients with and without edema and with varying disturbances in serum sodium concentration, including both hypernatremia and hyponatremia. They were able to empirically show that the serum sodium concentration was directly proportional to the sum of the total body content of "exchangeable sodium" and "exchangeable potassium" and was indirectly proportional to the total body water. The exchangeable sodium and potassium referred to the sodium and potassium contained in the body that is able to enter the aqueous phase. For example, the bulk of the exchangeable potassium is in the intracellular space and is included in the calculation. A simplified formula describing Edelman's empiric observations is as follows:

$$[Na]^s = (Na^e + K^e) / TBW$$

where $[Na]^s$ is the serum sodium concentration in mmol/L, Na^e is the exchangeable sodium content in mmol, K^e is the exchangeable potassium content in mmol, and TBW is total body water in L. How the sodium concentration can vary with the proportional content of sodium and water is intuitive. How potassium content affects the serum sodium may not be so clear. Though Edelman did not elucidate the mechanism by which potassium influences the serum sodium, it is presumed that this results from transcellular shifts mediated by the sodium potassium ATPase pump. Added potassium exchanges for sodium as it translocates into the cell. The result is an increase in the extracellular sodium concentration.

From Edelman's equation, derangements in the serum sodium can now be better understood. On hospital day 0, the patient presented with a mild hyponatremia ($[Na]^s_0$) and volume overload. As the presence of third-spaced fluid is typically strong evidence of total body sodium excess, one can describe the initial hyponatremia observed in this case in the following mathematical terms:

$$[Na]^s = (Na^e + K^e) / TBW \quad \rightarrow \quad \downarrow[Na]^s_0 = (\uparrow\uparrow Na^e_0 + K^e_0) / \uparrow\uparrow\uparrow\uparrow TBW_0$$

where Na^e_0, K^e_0, and TBW_0 refer to exchangeable sodium, exchangeable potassium, and total body water on day 0, respectively. Note that ↓ and ↑ refer to total body depletion and excess respectively, with the severity of the perturbation indicated by the number of arrows present. Here one can see that although his total body sodium content is in excess, his initial serum sodium is still low because there is a proportionally greater excess of total body water. With the administration of furosemide therapy and sodium and fluid restriction, the patient in this case exhibited worsening hyponatremia ($[Na]^s_F$). This can now be explained in mathematical terms:

$$\downarrow[Na]^s_0 = (\uparrow\uparrow Na^e_0 + K^e_0) / \uparrow\uparrow\uparrow\uparrow TBW_0 \quad \rightarrow \quad \downarrow\downarrow[Na]^s_F = (\uparrow Na^e_F + \downarrow K^e_F) / \uparrow\uparrow\uparrow TBW_F$$

where Na^e_F, K^e_F, and TBW_F refer to body electrolyte and water content after loop diuretic therapy. One can see that furosemide administration in this case resulted in a reduction in his excess sodium content as well as potassium depletion. His total body water excess was also improved. However, the net effect on the serum sodium was a further decline due to a larger proportional drop in his electrolyte content when compared to the reduction in his water content. It should be noted that there typically must be some free water intake for this trend to occur with loop diuretic therapy, though it need not be immoderate.

Starting from this description of the physiology underlying his worsening hyponatremia after furosemide therapy, one can now better understand the effect of various options to raise the serum sodium while continuing loop diuretic therapy to correct the persistent hypervolemia. These options include vasopressin antagonism and potassium and sodium supplementation. With vasopressin antagonism added to a loop diuretic, one can achieve a proportionally greater reduction in the denominator in Edelman's equation while the total body sodium excess is still corrected:

$$\downarrow\downarrow[Na]^s_F = (\uparrow Na^e_F + \downarrow K^e_F) / \uparrow\uparrow\uparrow TBW_F \quad \rightarrow \quad \downarrow[Na]^s_{F\text{-}V} = (Na^e_{F\text{-}V} + \downarrow\downarrow K^e_{F\text{-}V}) / TBW_{F\text{-}V}$$

where $[Na]^s_{F\text{-}V}$ is the serum sodium concentration and $Na^e_{F\text{-}V}$, $K^e_{F\text{-}V}$, and $TBW_{F\text{-}V}$ refer to body electrolyte and water content after continued loop diuretic therapy combined with a vasopressin antagonist. One can see that the total body sodium and water excess may be completely corrected, yet the serum sodium may remain slightly below normal as a result of an unrepaired potassium defect. Though randomized clinical trials for the use of vasopressin antagonists in hypervolemic hyponatremia have revealed efficaciousness in achieving higher serum sodium concentrations [11,12], there are disadvantages to this treatment approach. The cost of tolvaptan, the available oral vasopressin antagonist, is approximately $300 per tablet. Also, it is labeled for use for a maximum of 30 days given a small but real risk of hepatotoxicity with this medication.

An alternate approach is available. With the administration of potassium and sodium supplementation concomitantly with a loop diuretic, the expected change in serum sodium ($[Na]^s_{FNaK}$) can be once again be predicted:

$$\downarrow\downarrow[Na]^s_F = (\uparrow Na^e_F + \downarrow K^e_F) / \uparrow\uparrow\uparrow TBW_F \quad \rightarrow \quad [Na]^s_{FNaK} = (Na^e_{FNaK} + K^e_{FNaK}) / TBW_{FNaK}$$

where Na^e_{FNaK}, K^e_{FNaK}, and TBW_{FNaK} refer to body electrolyte and water content after continued loop diuretic therapy combined with liberalized sodium intake and aggressive potassium supplementation. Note that the goal is to still achieve negative sodium balance despite liberalized sodium intake by ensuring that natriuresis exceeds sodium intake. The result is an

improvement in both the serum sodium and hypervolemia. Continued effective fluid restriction is essential for this strategy of managing hyponatremia. Because of the challenges of maintaining fluid restriction and liberalized salt intake chronically, this should only be employed for a short-term period, typically in the inpatient setting.

Case 3 Outcome

After an additional 5 days of furosemide therapy combined with triamterene, aggressive potassium supplementation, and liberalized sodium intake, the patient achieved another 7.4 kg of weight loss. His serum sodium improved by hospital day number 10 to 133 mmol/L. His serum potassium was 5.0 mmol/L, bicarbonate 26 mmol/L, and creatinine 1.8 mg/dL. His edema was down to 1+ at the shins.

Conclusion

Three challenging cases of hypervolemia which highlight some of the difficulties that the clinician faces during the course of diuretic therapy were reviewed here. There was an emphasis on describing the physiologic principles that underpin these relatively common scenarios. It is hoped that the reader gained an understanding of these principles such that solutions, sometimes novel, can be devised when facing these obstacles. Nephrotic syndrome is commonly complicated by diuretic resistance. In order to overcome this, an intensified dose of loop diuretic can overcome the perturbed pharmacokinetics that are present. Albumin administration can thus be reserved for the most refractory patients, with the understanding that its effect will be transient. Metabolic alkalosis is a common complication of effective diuresis in markedly volume overloaded patients. This should be recognized promptly and interventions to mitigate the rise in serum bicarbonate such as acetazolamide, potassium sparing diuretics, and aggressive potassium supplementation should be initiated early. Rarely one may consider acid loading in severe and refractory metabolic alkalosis. Finally, worsening hyponatremia can occur despite effective diuresis. In order to continue volume removal when the patient remains hypervolemic, it is essential that careful fluid restriction is pursued and potassium depletion is repaired. When that is insufficient, some consideration can be given to liberalizing sodium intake as long as fluid intake remains restricted.

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