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Acid-Base and Electrolyte Teaching Case

Diuretic Resistance

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Diuretic resistance is defined as a failure to achieve the therapeutically desired reduction in edema despite a full dose of diuretic. The causes of diuretic resistance include poor adherence to drug therapy or dietary sodium restriction, pharmacokinetic issues, and compensatory increases in sodium reabsorption in nephron sites that are not blocked by the diuretic. To illustrate the pathophysiology and management of diuretic resistance, we describe a patient with nephrotic syndrome. This patient presented with generalized pitting edema and weight gain despite the use of oral loop diuretics. Nephrotic syndrome may cause mucosal edema of the intestine, limiting the absorption of diuretics. In addition, the patient's kidney function had deteriorated, impairing the tubular secretion of diuretics. He was admitted for intravenous loop diuretic treatment. However, this was ineffective, likely due to compensatory sodium reabsorption by other tubular segments. The combination of loop diuretics with triamterene, a blocker of the epithelial sodium channel, effectively reduced body weight and edema. Recent data suggest that plasmin in nephrotic urine can activate the epithelial sodium channel, potentially contributing to the diuretic resistance in this patient. This case is used to illustrate and review the mechanisms of, and possible interventions for, in diuretic resistance.

INDEX WORDS: Diuretic resistance; pathophysiology; edema; oral loop diuretic; nephrotic syndrome; triamterene; eNaC; epithelial Na^+ channel; *SCNN1B*; proteinuria; kidney disease; cryoglobulinemic membranoproliferative glomerulonephritis; hepatitis C virus.

Note from Feature Editor Jeffrey A. Kraut, MD: This article is part of a series of invited case discussions highlighting the diagnosis and treatment of acid-base and electrolyte disorders.

INTRODUCTION

Generalized edema can develop in nephrotic syndrome, chronic kidney disease (CKD), heart failure, and liver cirrhosis. Usually patients with edema respond to dietary sodium restriction in combination with a loop diuretic.[1] However, some patients become resistant to diuretics. Diuretic resistance is defined as failure to achieve the therapeutically desired reduction in edema even when a maximal dose of diuretic is employed. Box 1 summarizes the main causes of diuretic resistance,[2] which include poor adherence to diet or drug therapy, pharmacokinetic issues, and compensatory increases in sodium reabsorption in nephron sites that are not blocked by the diuretic.[3] Establishing the cause of diuretic resistance is important because it directly informs the options for intervention. For example, diuretic resistance is often treated effectively by combining a loop diuretic with another type of diuretic.[4] We present a patient to illustrate the causes, pathophysiologic mechanisms, and treatment of diuretic resistance.

CASE REPORT

Clinical History and Initial Laboratory Data

A 55-year-old man was admitted because of edema and dyspnea. He had a history of chronic hepatitis C virus infection (genotype 1A) without evidence for liver cirrhosis (no fibrosis or portal hypertension on ultrasound and no fibrosis on elastography). Secondary to hepatitis C virus infection, he developed membranoproliferative glomerulonephritis with 2 episodes of nephrotic syndrome. These episodes of nephrotic syndrome resolved after treatment with a combination of glucocorticoids and loop diuretics, but resulted in progressive glomerular filtration rate (GFR) loss. His estimated GFR prior to admission was 37 mL/min/1.73 m^2 (as calculated by the CKD-EPI [CKD Epidemiology Collaboration] equation[5]). His outpatient medication consisted of bumetanide (1 mg 2 times daily), losartan (25 mg once daily), and spironolactone (25 mg once daily). At presentation, he was alert but was concerned about edema and dyspnea. On physical examination, blood pressure was 145/110 mm Hg, while his body weight had increased by 20 kg. He had ascites, but his liver was not enlarged. Generalized pitting edema reaching up to his scrotum was present. Based on the presence of edema and his laboratory results, the recurrence of nephrotic syndrome was established (Table 1).

Additional Investigations

A kidney biopsy was performed (42 glomeruli, 18 with global sclerosis). Light microscopy showed thickened glomerular

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Box 1. Common Causes of Diuretic Resistance

- Incorrect diagnosis (eg, venous or lymphatic edema)
- Nonadherence to recommended sodium and/or fluid restriction
- Drug not reaching the kidney
  - ◇ Nonadherence
  - ◇ Dose too low or too infrequent
  - ◇ Poor absorption
- Reduced diuretic secretion
  - ◇ Tubular uptake of diuretic impaired by uremic toxins
  - ◇ Decreased kidney blood flow
  - ◇ Decreased functional kidney mass
- Insufficient kidney response to drug
  - ◇ Low glomerular filtration rate
  - ◇ Decreased effective intravascular volume despite elevated total extracellular fluid volume
  - ◇ Activation of the renin-angiotensin system
  - ◇ Nephron adaptation
  - ◇ Use of nonsteroidal anti-inflammatory drugs

Based on Hoorn et al.[2]

basement membrane and increased mesangial and endocapillary cellularity. Immunofluorescence showed positivity for immunoglobulin G (IgG), IgM, C3, and κ and λ light chains in a granular pattern. Electron microscopy was not performed.

Diagnosis

Diuretic resistance caused by the recurrence of nephrotic syndrome secondary to hepatitis C virus–related cryoglobulinemic membranoproliferative glomerulonephritis.

Clinical Follow-up

The patient was admitted for intravenous loop diuretic treatment with a continuous infusion of 10 mg/d of bumetanide (Fig 1). Despite this treatment, he did not lose weight and therefore a thiazide type diuretic (chlorthalidone) was added after the first week. Because this combination also failed to lower his body weight, loop diuretics were combined with the epithelial sodium channel (ENaC) blocker triamterene (100 mg/d). In addition, he was treated with rituximab (1 g intravenously in weeks 2 and 3 of admission) because of the recurrence of membranoproliferative glomerulonephritis secondary to hepatitis C virus infection. The combination of diuretics and B-cell depletion therapy resulted in resolution of edema, an increase in serum albumin level to 2.7 g/dL, a reduction in body weight, and an improvement in kidney function. However, proteinuria was largely unchanged, in the nephrotic range (protein excretion, 10 g/d). Although interferon-free therapy was not available during the treatment of this patient, he is currently treated with sofosbuvir and daclatasvir.

Table 1. Laboratory Data

Parameter	Value	Reference Range
Serum chemistry		
Sodium, mEq/L	141	136-145
Potassium, mEq/L	5.4	3.5-5.1
Creatinine, mg/dL	3.9	0.74-1.3
eGFR, mL/min/1.73 m^2	16	
Albumin, g/dL	1.8	3.5-5.0
Cryoglobulins, g/L	0.02	<0.01
Urine chemistry		
Protein, g/d	14	<0.14
Sodium, mEq/d	9	-

Note: Conversion factor for creatinine in mg/dL to μmol/L, ×88.4.

Abbreviation: eGFR, estimated glomerular filtration rate.

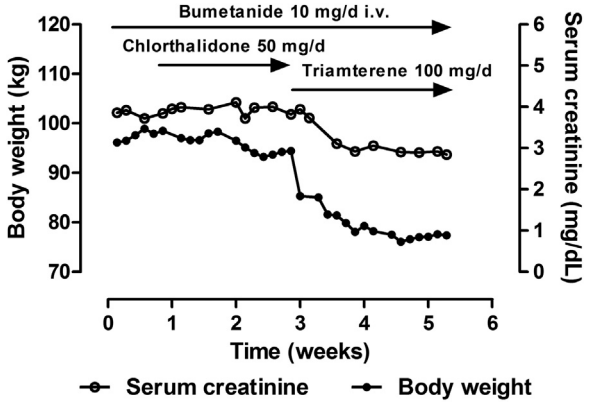

Figure 1. Patient's course in terms of body weight and serum creatinine levels during admission. Treatment periods with diuretics are indicated. Abbreviation: i.v., intravenous. Conversion factor for creatinine in mg/dL to μmol/L, ×88.4.

DISCUSSION

This case illustrates several of the possible causes of diuretic resistance and strategies to overcome it. In addition to discussing diuretic resistance in this specific patient with nephrotic syndrome, we also discuss mechanisms pertaining to diuretic resistance in CKD, heart failure, and liver cirrhosis.

There are several classes of diuretics, dictated by their site of action in the nephron (Fig 2).[2] They include diuretics that act on the proximal tubule, carbonic anhydrase inhibitors; loop of Henle, loop diuretics; distal tubule, thiazide diuretics; or collecting duct, distal potassium-sparing diuretics. Distal potassium-sparing diuretics can be further subdivided into either ENaC blockers or mineralocorticoid receptor blockers (eg, spironolactone or eplerenone). Except for mineralocorticoid receptor blockers, diuretics act from the tubular lumen by blocking the function of sodium transport proteins in the apical plasma membrane of kidney epithelial cells. This implies that for these diuretics to act, they must first be secreted in tubular fluid. Thus, diuretics are delivered to their site of action by tubular secretion rather than glomerular filtration. Tubular secretion of diuretics primarily occurs in the proximal tubule. For most diuretics, the secretory pathways have largely been identified and involve organic anion transporters and multidrug resistance proteins.[6] The importance of this secretory process is illustrated by the observation that decreased diuretic secretion into the tubular lumen is often one of the causes of diuretic resistance (Box 1).