

Case and Review

Diuretic Resistance Treated with Low-Dose Hydralazine: A Case Report and Review of the Literature

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Keywords

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Abstract

We present a case of severe diuretic resistance and edema from acute cardiorenal syndrome complicating heart failure with preserved ejection fraction (HFpEF) and mild alcoholic liver disease. High doses of intravenous (iv) furosemide plus iv doses of chlorothiazide failed to increase the daily urine output (UV) above 1,500 mL or the fractional excretion of sodium (FE_{Na}) above 2%. The addition of a relatively low dose of hydralazine (10 mg thrice daily PO) during 5 days of constant iv infusion of furosemide plus iv bolus chlorothiazide doubled the UV and FE_{Na} while reducing the serum creatinine concentration from 3.3 to 2.0 mg/dL. Hydralazine may have restored a response to the diuretics by increasing the renal blood flow and thereby the renal diuretic delivery, or by reducing the filtration fraction or reducing the renal congestion and thereby reducing the proximal reabsorption during blockade of distal reabsorption with diuretics. Further mechanistic studies of low-dose hydralazine for diuretic resistance are warranted.

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Introduction

Diuretic resistance is a failure to clear congestion or edema despite a full diuretic dosage. It is associated with worse short- and long-term outcomes [1]. Here, we present a case of diuretic-resistant volume overload where the addition of a low dose of hydralazine restored

the responsiveness to diuretics and relieved the congestion. We discuss a potential role of low-dose hydralazine in diuretic-resistant heart failure, review the literature, and propose physiological mechanisms.

Case Report

The patient was a 52-year-old female with a past medical history of hypertension, obesity, heart failure with preserved ejection fraction (HFpEF), and mild alcoholic liver disease. She was admitted to the hospital with a 3-day history of altered mental status. She was afebrile. Her BP was 109/59 mm Hg, O₂ saturation 98% on room air, and weight 134 kg. Her serum creatinine concentration (Scr) had increased from 0.8 to 3.6 mg/dL over 1 month, and she had gained 30 kg of weight over 5 months. Other investigations included BUN 41 mg/dL, serum sodium 131 mmol/L, and serum potassium 6.7 mmol/L. Hyperkalemia was treated successfully with iv furosemide plus insulin with glucose. She was managed initially for presumed hepatorenal syndrome (HRS) with infusions of human salt-poor albumin, midodrine, and octreotide but had no significant improvement. The nephrology team was consulted on the third hospital day.

Physical examination revealed jugular venous distention of >5–8 cm H₂O, decreased breath sounds at the lung bases, and 2+ pitting edema of the lower extremities up to the lower abdomen. Laboratory values included a hemoglobin of 8.7 g/dL, platelet count of 109,000/ μ L, serum sodium 140 mmol/L, serum potassium 3.8 mmol/L, serum chloride 106 mmol/L, serum total CO₂ 23 mmol/L, BUN 47 mg/dL, Scr 3.47 mg/dL, and proBNP 1,170 pg/mL with normal values for blood glucose, calcium, and liver enzymes but a reduced plasma albumin of 2.5 g/dL. Urinalysis revealed a specific gravity of 1.017 without proteinuria or casts. Urine sodium and chloride concentrations were <10 mmol/L, and fractional excretion of Na⁺ (FE_{Na}) was 0.1%. The preserved renal concentrating ability, low FE_{Na}, and absence of proteinuria or casts suggested a hemodynamic basis for her increase in Scr.

A chest X-ray revealed signs of pulmonary edema. An echocardiogram from 2 weeks prior revealed a preserved ejection fraction of 60–65% but diastolic dysfunction. Abdominal sonography was negative for ascites.

The patient was diagnosed with an exacerbation of HFpEF. Acute tubular necrosis was considered unlikely because of the absence of a specific cause for acute tubular necrosis, the urine studies, and the significant volume overload. HRS also was considered unlikely because of the lack of ascites, the failure to respond to the specific HRS therapy, and the high level of proBNP that favored the primary diagnosis of HF. Therefore, diuretic therapy was intensified to furosemide 80 mg plus chlorothiazide 250 mg, both given iv twice daily. Her urine output (UV) increased modestly from 350 to 550 mL, and diuretics were escalated to a continuous iv infusion of furosemide (20 mg/h) plus iv bolus doses of chlorothiazide (500 mg twice daily), but this failed to increase UV above 1,500 mL or FE_{Na} above 2% and did not improve her symptoms or change her Scr (shown in Fig. 1). During stable diuretic therapy on hospital day 6, hydralazine (10 mg thrice daily PO) was added. Within 24 h, her Scr began to decrease to a nadir after 5 days of 1.98 mg/dL, and her UV and FE_{Na} doubled. Her clinical state improved sufficiently on day 11 to begin an oral regimen of furosemide (80 mg twice daily) plus spironolactone (200 mg daily) and hydralazine (20 mg three times daily). Over the hospital course of 19 days, the patient lost 23 kg in weight, and her Scr improved to 1.3 mg/dL. At follow-up after 3 months while she was prescribed furosemide 80 mg twice daily plus spironolactone 200 mg daily, her symptoms remained well controlled, her weight was reduced by a further 10 kg, and her Scr was at baseline at 0.9 mg/dL. Her SBP remained stable at 110–120 mm Hg.

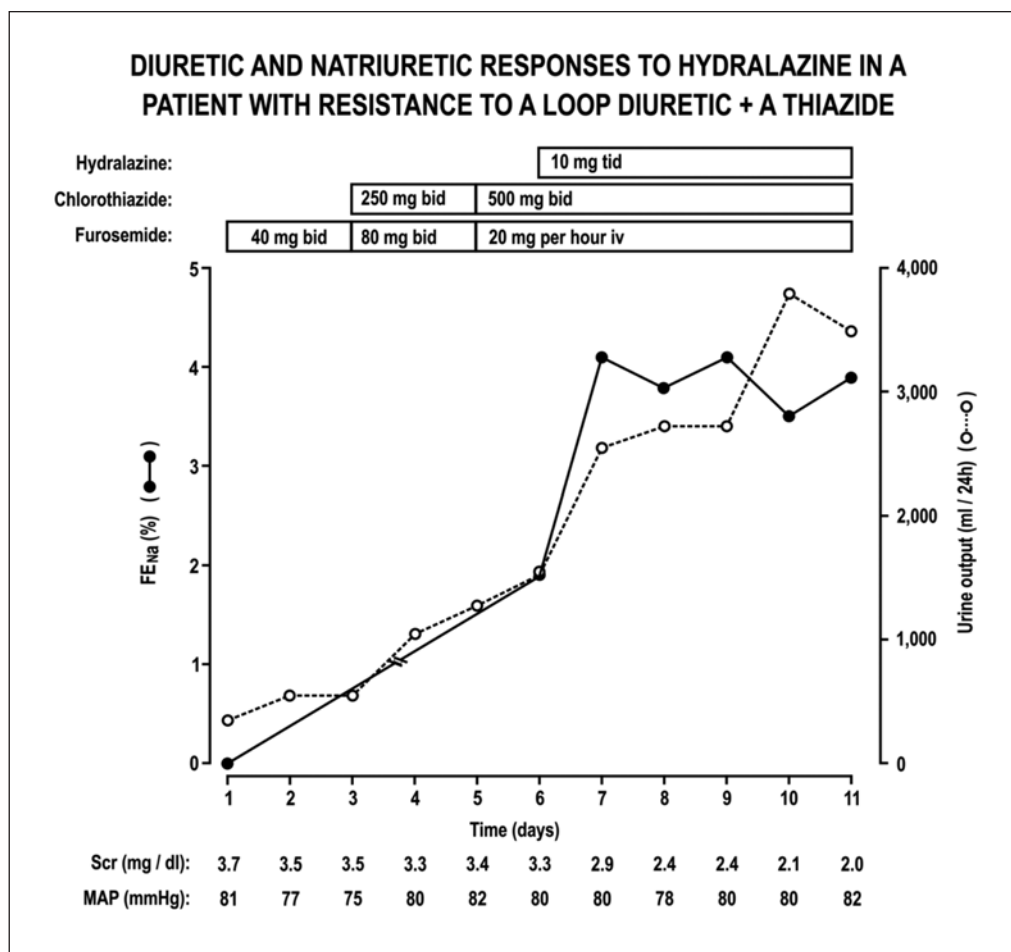


Fig. 1. Diuretic and natriuretic responses to hydralazine in a patient with resistance to a loop diuretic + a thiazide. Day 1 is the first day of nephrology consult. FE_{Na} , fractional excretion of sodium; Scr, serum creatinine; MAP, mean arterial pressure; bid, twice daily; tid, thrice daily.

Discussion

The renal blood flow (RBF) and the glomerular filtration rate (GFR) are reduced in many patients with congestive heart failure (CHF) and may contribute to diuretic resistance [1]. Hydralazine leads to prostaglandin-dependent renal vasodilation [2]. There are several studies of the efficacy of hydralazine in improving renal hemodynamics, UV, or sodium excretion ($U_{Na}V$) that are summarized in Table 1. When measured, hydralazine has increased the RBF more than the GFR and thereby has reduced the filtration fraction (FF). It also has increased the cardiac output (CO). The increase in the RBF is likely a consequence of renal vasodilation [3], increased CO, and decreased systemic vascular resistance. Providing that any reductions in BP are not severe, hydralazine generally has increased the UV and the $U_{Na}V$.

Our patient had an increase in FE_{Na} and diuresis with hydralazine during blockade of Na^+ reabsorption in the loop of Henle and the distal tubule. This indicates that hydralazine was principally reducing reabsorption in the proximal tubule (PT). Although the reduction in Scr and the increase in the GFR with hydralazine might have contributed to Na^+ losses, the doubling of FE_{Na} indicates that it had reduced tubular Na^+ reabsorption.

Table 1. Summary of published clinical reports of the response to hydralazine in human subjects

Author (ref)	N	Diagnosis	Hydralazine dose, mg, and route	ΔMAP, %	ΔUV, %	ΔU _{Na} V, %	ΔGFR, %	ΔRBF, %	ΔFF, %	ΔCO, %
Reubi [9]	12	7 HTN 2 GN 4 NL	8–20, sc	-19	Increased markedly	na	ns	+39	-22	na
Wilkinson et al. [27]	12	Healthy, HTN, CP, rheumatic heart disease	0.25–0.5 mg/kg iv	-30	Diuretic action was frequent but inconstant	na	Not consistent	+38*	-23	+110
Freis et al. [28]	6	HTN	0.25 mg/kg iv	-28	na	na	na	na	na	+128
Vanderkolk et al. [10]	7	HTN	75 mg orally	-22*	na	na	ns	+36*	-22*	na
Gjorup and Hilden [5]	6	HTN	0.1–0.3 mg/kg iv	-14	+9	+15	+6	na	-24	na
Hollander et al. [8]	18	HTN, CHF, CP	14–50 mg iv	-17	+36	+400	+11	+36	Reduced	+37
Cogan et al. [12]	9	CHF (III–IV)	10–60 mg iv (5 mg every 20 min)	-11*	+26	+161	+13	+127*	-46*	+70*
Elkayam et al. [13]	9	CHF	2.5 mg iv every 20 min until SVR decreased by 25% (mean 10 ± 5 mg)	-5*	na	na	+3	+13*	-5	+39*

N, number reported; NL, normal; FF, filtration fraction; ?, mean changes from before; sc, subcutaneous; CO, cardiac output; a, receiving maintenance diuretics; iv, intravenous; na, not available; HTN, hypertension; MAP, mean arterial pressure; GN, glomerulonephritis; UV, urine output; CHF, congestive heart failure; GFR, glomerular filtration rate; CP, cor pulmonale; RBF, renal blood flow.

*Statistically significant change.

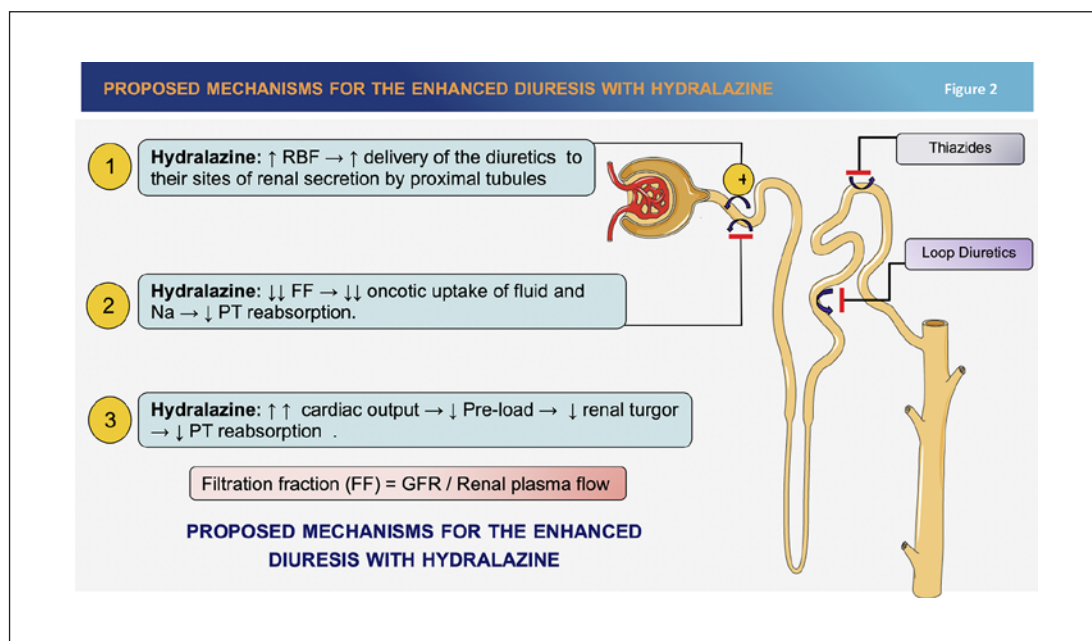


Fig. 2. Proposed mechanisms for the enhanced diuresis with hydralazine. RBF, renal blood flow; FF, filtration fraction; GFR, glomerular filtration rate.

We considered 3 mechanisms to account for the increased UV and U_{NaV} (Fig. 2). First, an increase in RBF will increase the delivery of the diuretic to the renal tubules [4, 5]. Since diuretics bind to albumin and it is required for diuretic delivery to the renal tubules, the hypoalbuminemia in our patient may have contributed to the diuretic resistance [1]. Indeed, hydralazine increases the renal clearance of furosemide [6]. However, this seems an inadequate explanation since both diuretics were being given iv at doses that are generally considered to be supramaximal [1], and an increase in diuretic dose on day 4 increased UV only marginally (Fig. 1).

Second, PT reabsorption is dependent on the oncotic pressure in the peritubular capillaries [7] that itself is dependent on the degree to which plasma water is filtered at the glomerulus that is quantitated by the FF. Hemodynamic studies with hydralazine report a consistently greater rise in RBF than in GFR, with a consequent fall in the FF [5, 8–13] (Table 1).

Third, since an increase in CO with hydralazine (Table 1) reduces preload, hydralazine should reduce renal venous pressure and renal congestion. Increased renal turgor in patients with CHF can contribute to increased PT reabsorption [14–16] and reduced RBF and GFR [17, 18].

Thus, hydralazine may have reduced the FF and the renal congestion and thereby reduced the PT reabsorption. Angiotensin-converting enzyme inhibitors have generally similar hemodynamic effects of increased RBF and reduced FF [19] that will increase the delivery of filtrate to the loop of Henle and distal nephron and thereby enhance diuretic responsiveness. However, many physicians are reluctant to use angiotensin-converting enzyme inhibitors in patients with an acute increase in Scr, as in this patient, but might select a renal vasodilatory drug such as hydralazine.

Hydralazine therapy requires care. Its variable and short half-life mandates 3 times daily dosing. Accurate therapy requires genotyping for *N*-acetyltransferase 2 status to determine whether the patient is a slow or fast acetylator [20]. Moreover, renin increases dose dependently with hydralazine [21]. Careful monitoring of the MAP and heart rate is required, since the desired effects can be compromised by sympathetic system overactivity and activation of the renin-angiotensin-aldosterone system.

The MAP should not be reduced by >25% in patients with CHF since this prevents the diuretic response [22]. Moreover, patients with HFpEF can be sensitive to blood volume depletion that requires careful use of diuretics [23]. However, the contribution of reduction in before and after load with hydralazine in patients with HFpEF should be preferable to escalating diuretic therapy since that may increase after load and thereby increase the cardiac oxygen usage [24, 25].

Although the use of vasodilator therapy to relieve systemic congestion has been reported previously, this approach has not been widely applied given the lack of a clear physiological explanation [26]. This case illustrates the potential of low-dose hydralazine to reduce reabsorption of Na⁺ in the PT and to relieve diuretic resistance. It suggests the need for further studies to establish the mechanisms involved and the general utility.

Statement of Ethics

The authors have complied with ethical standards for this case report involving a human participant. Written informed consent for publication of this case report was obtained from the patient.

Conflict of Interest Statement

The authors have no relevant financial or nonfinancial interests to disclose.

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Author Contributions

M.A. was responsible for the patient care and wrote the initial draft. C.W. revised manuscript including the data, literature review, and results.

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