Review Articles

Loop Diuretic Resistance in Heart Failure: Resistance Etiology−Based Strategies to Restoring Diuretic Efficacy

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ABSTRACT

Loop diuretics are a cornerstone of symptom management for nearly all patients with heart failure. Diuretic resistance is a clinical problem with similar presentation despite diverse and multiple etiologies. Although the exact incidence is not known, diuretic resistance occurs frequently and can increase the length of hospitalization. Despite the prevalence of loop diuretic prescription in heart failure and frequency of diuretic resistance, current heart failure guidelines provide nonspecific guidance on strategies to restore diuretic efficacy. Providers are left with many questions regarding the optimum diuretic titration strategy in the setting of diuretic resistance. In light of these highly prevalent uncertainties, we present a case vignette−structured literature review of the mechanisms of diuretic resistance and recommend therapeutic strategies based on the resistance etiology to improve diuretic response in acute decompensated heart failure. (*J Cardiac Fail 2014;20:611−622*)

Key Words: Cardiology, acute heart failure.

Loop diuretic therapy is the cornerstone of heart failure (HF) symptom management. Chronic oral loop diuretics are prescribed to 87%−90% of HF patients.[1−3] Symptoms of fluid retention and congestion are responsible for 90% of HF hospitalizations, and almost all (86%−97%) patients hospitalized for HF receive intravenous (IV) loop diuretics.[1,4−6] The incidence of diuretic resistance is unknown, given the lack of a consensus definition, but resistance occurs frequently and can result in a prolonged hospital stay. A retrospective analysis of the PRAISE (Prospective Randomized Amlodipine Survival Evaluation) study reported that 35% of participants displayed resistance (daily furosemide equivalent dose >80 mg).[7]

Despite the prevalence of loop diuretic use in HF and frequency of diuretic resistance, guidelines by the Heart Failure Society of America (HFSA) and the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) provide nonspecific guidance on diuretic regimen design in response to diuretic resistance.[8,9] HFSA guidelines suggest the following options to consider when congestion fails to improve in response to diuretic therapy: "sodium and fluid restriction, increasing doses of loop diuretic, continuous infusion of a loop diuretic, or addition of a second type of diuretic."[8] The ACCF/AHA guidelines recommend intensifying the diuretic regimen using either "higher doses of IV loop diuretics, addition of a second diuretic, or addition of low-dose dopamine infusion."[9] As expected, 57% of physician questions about advanced HF management in a recent survey concerned diuretic titration.[10] In light of these highly prevalent uncertainties, we present here a case vignette−structured literature review of the mechanisms of diuretic resistance and recommend therapeutic strategies to improve diuretic response in acute decompensated HF (ADHF).

Loop Diuretic Pharmacology and Pharmacokinetics

The pathway that loop diuretics travel from the gastrointestinal lumen to their site of action in the ascending loop of Henle has several key features that warrant discussion to improve understanding (Fig. 1). First, loop diuretics must

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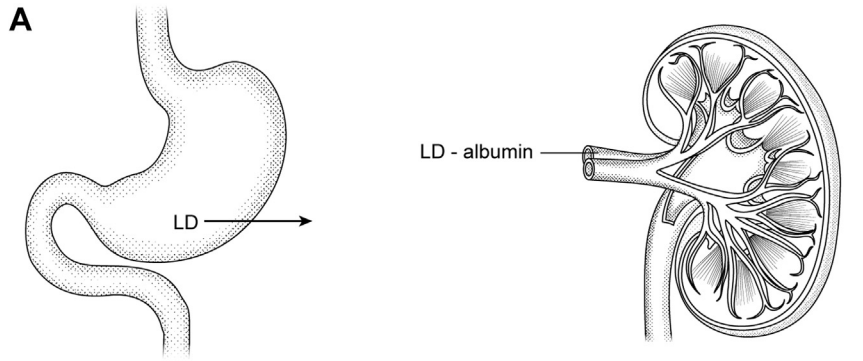

Resistance Mechanism
Intrinsic Bioavailability ADHF absorption changes Food absorption changes

Resistance Mechanism
Intra-abdominal hypertension Cardiorenal syndrome Hypoalbuminemia

Absorption	Furosemide	Bumetanide	Torsemide
Bioavailability	10–100%	80–100%	80–100%
Affected by food	Yes	Yes	No

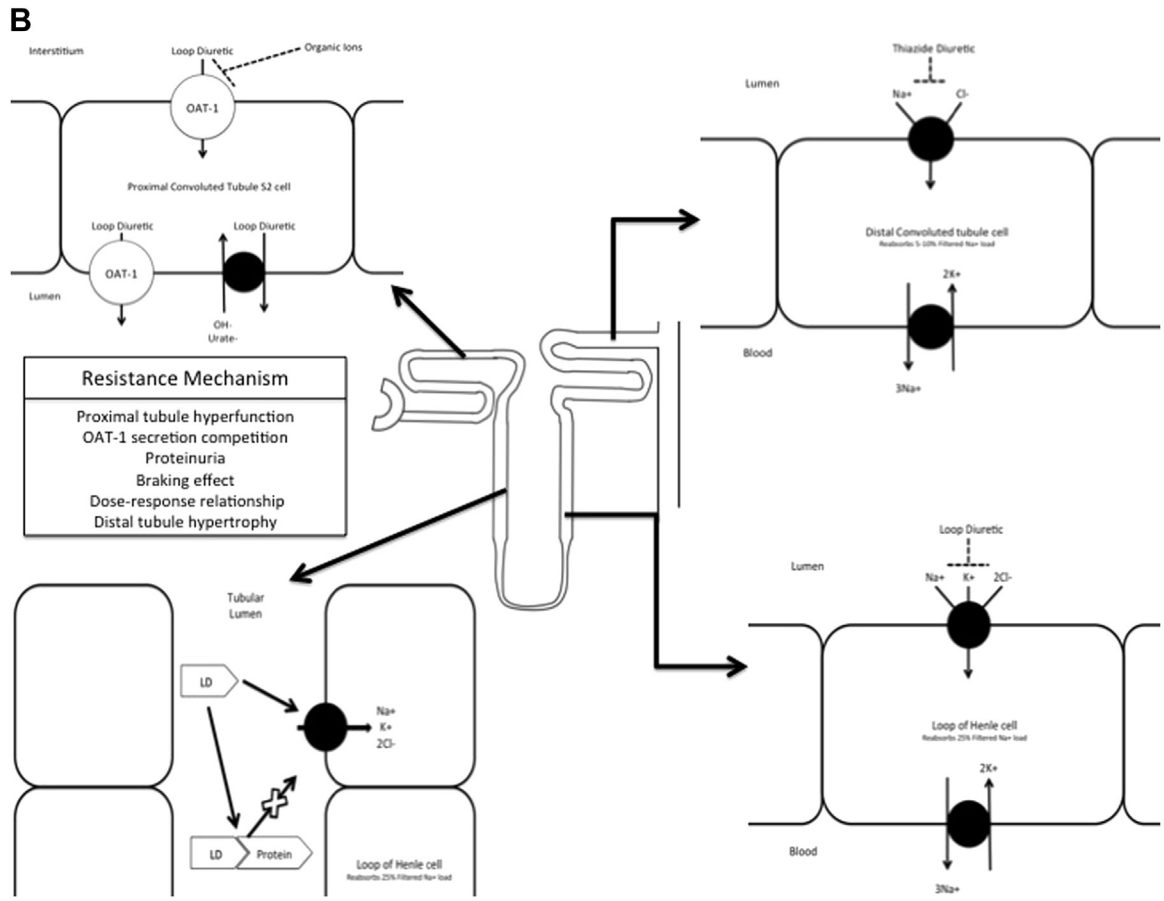

Fig. 1. A) Oral diuretic resistance may result from the intrinsic bioavailability limitations of the drug itself, altered absorption when taken with food, or altered absorption-time profiles in acute decompensated heart failure (ADHF), which are mediated by decreased gastric emptying, decreased splanchnic blood flow, and/or intestinal wall edema. Loop diuretics (LDs) are highly protein bound and are transported to the kidney bound to albumin. Hypoalbuminemina is theorized to contribute to diuretic resistance by altering diuretic entry into the lumen of the nephron and increasing the volume of distribution, which decreases delivery to the kidney. Intra-abdominal hypertension and cardiorenal syndrome are states of venous congestion and renal vein compression, which also contribute to diuretic resistance by impairing