



Diuretic Dosing in Heart Failure and Chronic Kidney Disease

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Abstract

Diuretics are commonly used in patients with heart failure, chronic kidney disease, or both for volume management. However, their effectiveness is dependent upon their proper utilization, like any other medication. In chronic kidney disease, higher doses of diuretics are needed to reach the threshold to induce diuresis. Diuretics with especially short-half lives, like furosemide, induce a state of salt retention for the remainder of the day, an entity known as post-diuretic salt retention, and usually require at least twice daily dosing. Furosemide is also noteworthy for its widely variable bioavailability in its oral formulation. Intravenous furosemide and other oral loop diuretics have more reliable bioavailability. For patients exposed to loop diuretics chronically, a phenomenon known as “braking” which may occur in reduce diuresis but is overcome by administering thiazide diuretics before the loop diuretic.

Keywords: Diuretics; Dosing; Heart failure; Chronic kidney disease

Introduction

Diuretics are one of the most commonly used drugs in medicine. Patients with renal or heart failure often need diuretics for the acute and chronic management of volume. However, when used inappropriately, they may not work as intended or at all. We present a case of a patient who, unintentionally, did not use his diuretics as prescribed, leading to weight gain and a hospital admission. His case was further complicated by inadequate diuretic utilization while being hospitalized leading to the nephrology service being consulted for the possibility of ultrafiltration.

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Case Presentation

A man in his 60 s with heart failure with a preserved ejection fraction and advanced chronic kidney disease was admitted to the hospital after several months of worsening lower extremity edema. The patient's creatinine had been 3.5 mg/dL several months prior but had increased to 4.5 mg/dL at the time of admission. The patient had been on furosemide 40 mg by mouth twice daily but stated he did not have a urinary response to this. The patient was admitted for volume overload and was given furosemide 40 mg orally, which did not induce diuresis. During this time, it was discovered that the patient was supposed to be taking furosemide 80 mg by mouth twice daily but was only taking half the dose due to an error in dispensing from his outpatient pharmacy. As such, the patient was given another 40 mg orally-four hours after the first dose-but still did not achieve a urinary response. He was then given 5 mg of metolazone, a thiazide diuretic, and two hours after the second dose of furosemide to no avail. Given the lack of response, the nephrology service was consulted for the consideration of ultrafiltration for the management of his volume overload.

Clinical Follow-Up

With the assistance of the nephrology service, the patient was trialed on several oral diuretic combinations and dosages until a regimen was found that resulted in a negative fluid balance, effective diuresis, and patient comfort. The patient was ultimately placed on torsemide 60 mg by mouth twice daily and metolazone 5 mg orally thrice weekly 30 minutes before taking torsemide. The patient was seen in follow-up several times after discharge and after two months had lost 27 kg of weight on the same diuretic regimen without any worsening of his renal function or the need for dialysis.

Discussion

Loop diuretics are an important part of volume management in both heart failure and Chronic

Table 1: Common Pitfalls in Diuretic Dosing.

Not increasing the frequency of an effective diuretic dose
Failure to restrict salt intake
Failure to restrict water intake
Not giving a high enough dose to induce diuresis
Not adding a thiazide diuretic when a chronic loop diuretic fails
NSAID use
Medication nonadherence

Kidney Disease (CKD). The available loop diuretics are furosemide, bumetanide, torsemide, and ethacrynic acid. Loop diuretics are highly protein bound to albumin and are acidic. As such, they are primarily secreted and not filtered or passively diffused into the proximal tubule by the organic acid transporter into the tubular lumen where they work by blocking the $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransporter in the thick ascending loop of Henle, where 20% to 25% of the sodium that is filtered through the glomerulus is reabsorbed [1]. In chronic kidney disease, organic anions accumulate and compete with diuretics for receptor sites of the organic acid transporter [2]. As a result, higher doses are needed to surpass competitive inhibition and attain therapeutic urinary concentrations in patients with renal failure. Additionally, in patients with heart failure, reduced blood flow to the kidney reduces drug delivery and ultimately results in peak urinary concentrations that are reduced and delayed [2]. As a result, patients with heart failure also require doses of diuretics that are higher than those used in healthy persons [3].

Of particular importance to oral furosemide is its variable oral bioavailability, which is partly attributed to meal timing but also to inherent pharmacologic factors [4,5]. The bioavailability of furosemide averages around 50% but ranges between 10% and 100% [6]. In contrast, bumetanide and torsemide have near total absorption, ranging between 80% and 100% for both. Ethacrynic acid also has an oral bioavailability of 100% but its use is limited to those with sulfa allergies given its potential for ototoxicity is higher than those of other loop diuretics [7].

This case illustrates the importance of giving a dose large enough to reach the threshold necessary to elicit a diuretic response [6]. If the urinary concentration of a drug does not reach this threshold, no diuresis will occur. In this patient's case, he should not have been given another 40 mg dose of oral furosemide. Furosemide has a half-life of 1.5 to 2 hours; thus, by four hours he should have had a urinary response, which also accounts for the delayed peak urinary concentration caused by his heart failure. As such, it would have been prudent to have given the patient a higher dose of oral furosemide or an alternate oral loop diuretic with improved bioavailability. Intravenous formulations of furosemide or another loop diuretic would have also been acceptable.

Chronic loop diuretic therapy can cause structural changes over time that reduce the efficacy of the medication, specifically hypertrophy of the distal tubule of the nephron, leading to sodium reabsorption and reduced diuresis—a phenomenon known as “diuretic braking” [8]. As such, thiazide diuretics can be given with loop diuretics to prevent reabsorption of sodium in the distal tubule by blocking the Na/Cl cotransporter. Normally, a thiazide diuretic blocks the reabsorption of only 5% to 10% of filtered sodium, but this number increases after chronic exposure to loop diuretics [1]. The thiazide diuretic can be given at the same time or before—but not after—

the loop diuretic to allow for complete blockade of the distal tubule before it is inundated with sodium from the thick ascending limb [9]. Traditionally, metolazone is used with loop diuretics to overcome braking. Metolazone does have a long half-life of approximately two days and delayed absorption but can be substituted for other thiazide diuretics like chlorthalidone or hydrochlorothiazide [1,6].

Although not an issue in this patient's case, but another common mistake is the dosing of diuretics once a day, especially in the absence of sodium restriction and with particularly short-acting diuretics like furosemide. It is important to note that there is no true long-acting diuretic as all four loop diuretics have a half-life of less than four hours [6]. Torsemide, the longest acting diuretic, has a half-life of 4 hours. As such, once the concentration of a diuretic falls below the threshold several hours later, compensatory sodium chloride reabsorption occurs for the remainder of the day in a process called post-diuretic sodium retention. If sodium intake is high (>100 mmol/day), post-diuretic sodium reabsorption may abolish any effect of the diuretic in causing a negative sodium balance. However, if sodium intake is restricted, post-diuretic sodium reabsorption may not be high enough to fully compensate for the effect of the diuretic and negative sodium balance will still be achieved [10]. In patient with high sodium intake, adding a second or third daily dose of a diuretic overcomes this problem. Nonetheless, sodium and water restriction are important aspects of therapy in any patient with renal impairment or heart failure.

Patient adherence to diuretics is also important for effectiveness, as with any other medication. Among heart failure patients, diuretics are the class of medications with the lowest rate of patient adherence, with only 69.8% of patients being classified as adherent [11]. Although our patient was compliant with the medications he was given, he had been dispensed an incorrect dose by his pharmacy (who was contacted and notified of the error). Adherence is so important for diuretic dosing that the time it is taken even matters. Patients who take diuretics on schedule are less likely to be hospitalized for heart-failure issues [12].

Finally, also not an issue in this patient's case but important in diuretic management is the avoidance of Non-Steroid Anti-Inflammatory Drugs (NSAIDs). NSAIDs impede prostaglandin synthesis by inhibiting cyclooxygenase and thereby blocking the natriuretic response to loop diuretics [1].

This patient's case highlights multiple pitfalls in diuretic dosing in both the outpatient and inpatient setting. Of course, the patient should have been initially dispensed the appropriate dose of medication as an outpatient, underscoring the importance of adherence and appropriate oral dosing (Table 1). As an inpatient, the second dose of furosemide should have been a higher dose than the initial dose to achieve a therapeutic concentration in his renal tubules given his impaired renal function [13]. It would have also been reasonable to give furosemide intravenously to overcome variable bioavailability or to utilize a different oral diuretic, as was done in this case. Finally, the thiazide diuretic should have been given before or at the same time as the loop diuretic—and not after. Ultrafiltration would have been unreasonable given its costs and adverse effects in the absence of an appropriate diuretic trial. The multicenter, controlled trial of ultrafiltration in decompensated heart failure with cardiorenal syndrome (CARRESS-HF) showed no difference in heart failure patients receiving ultrafiltration vs. a stepwise diuretic approach [14]. Additionally, patients undergoing ultrafiltration had more adverse

outcomes, including bleeding, vascular complications, and worsening of renal function. With the appropriate use of diuretics, this patient was able to avoid ultrafiltration all-together and achieve sodium and volume balance.

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