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The current art of diuretic therapy for heart failure: a personal viewpoint

Abstract

Diuretic therapy for heart failure is not that simple. There are nowadays several diuretics and natriuretics, with potential interactions, and different doses and ways of use. Furosemide plays a key role in the treatment of acute decompensated heart failure and chronic heart failure.

Keywords: Diuretics, furosemide, heart failure

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Introduction

Heart Failure is nowadays epidemic, being the main cause of hospitalization in adults.[1] There are several classifications, but there is a great distinction in two syndromes, acute decompensated heart failure (ADHF), and chronic heart failure, in patients who daily deal with congestion and frequent titration of diuretics (CHF). For an optimum myocardial work, one of the key targets is the loading conditions, preload and afterload. In this viewpoint I will review the current challenges of diuretic therapy.

Discussion

Differences between diuretic, natriuretic, aquaretic: By definition, diuretics are drugs that increase daily urine production by acting directly in the nefrone, interfere in renal physiology, and modify the hydroelectrolitic composition of the urine and blood, provoking also an acid-base state alteration. There are 5 classic groups of diuretics, osmotic, loop, thiazides, potassium sparing, and carbonic anhydrase inhibitors. The term "natriuretic" refers to substances that increase diuresis mainly by sodium excretion, and they can be endogenous (natriuretic peptides) or exogenous (natriuretic peptide agonists nesiritide and ularitide, or neprylisin inhibitors that increase levels of endogenous natriuretic peptides, sacubitril, ecadotril, candoxatril). The A1 receptor of adenosine antagonist rollophyline also exerts natriuretic effect,[2] as well as the sodium-glucose cotransporter type 2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ipragliflozin, luseogliflozin, and tofogliflozin). Finally, aquaretic refers to drugs that lead to an increase in diuresis mainly by clearance of water, like the antagonists of the V2 receptor of arginine-vasopressin, tolvaptan, conivaptan, and lixivaptan.

Furosemide for heart failure

Routes of administration: The enteral absorption of furosemide is diminished when congestion provokes interstitial edema in the intestine wall. This factor, associated with the delayed onset of action, favors other routes of administration. Most of the times, intravenous furosemide is used, but the timing for downgrading to oral use is not exactly known and it may lead to therapeutic failure and early readmissions. The intramuscular administration leads to erratic drug concentration and effects, and currently there are other ways of administration under investigation, as transjugal and transdermal (currently approved in veterinary). The subcutaneous furosemide used with small infusion pumps,[3] has a modification in its pH that avoids tissue damages, and has similar bioavailability that intravenous furosemide, this is potentially beneficious for HF patients who have multiple readmissions for short IV shots (usually called "frequent flyers", or INTERMACS class 4 patients).

Time door-to-furosemide in ADHF: Some indirect data from recent ADHF large trials revealed that an early and fast decongestion may improve outcomes (mortality, length of stay, and tissue damage). A Japanese group published recently the results of an observational study,[4] describing a correlation between the minutes of delay in using the first IV dose of furosemide and outcomes. They suggest the term "door to furosemide" (D2F), less than 1 hour as an optimal D2F time.

Boluses vs continuous infusion: Furosemide has two main mechanisms of action: Inhibition of the degradation of prostaglandins (by blocking prostaglandin dehydrogenase) leads to venous vasodilatation, rapidly lowering preload. For the diuretic effect, this drug must get to the renal tubules through a saturable acid secretion mechanism, and so a significant part of the dose may be metabolized without getting to its biophase. In that sense, different authors suggest a continuous infusion of furosemide instead of boluses. However, the results in small trials revealed no big differences, a bit more daily urinary volume but with higher rates of hypokalemia.[5]

Interdoses interval: After 6-8 hous, there is no effect of furosemide, and the reactivation of renin angiotensis aldosterone effects are seen when the drug is used every more hours.

High vs Low dose: Another issue of concern is the dose to use when a patient worsens its clinical status. The Dose Trial[6] data suggested a benefit when the high dose (2.5 times more than usual care) is used. For chronic patients, it is usual to note a progressive increase in daily doses, and it is attributed to tubular hypertrophy. In different countries the main daily dose varies, and the oral furosemide pills range from 20 milligrams up to 500 milligrams. Other key factor in the dosing of furosemide for HF outpatients is dietary salt intake and how strict are clinicians about recommendations for low sodium diet.

Combination with other diuretics: Patients with heart failure and reduced ejection fraction must receive a potassium sparring diuretic like spironolactone or eplerenone as a guideline reccomendation, with mild diuretic effect at the usual doses (12.5 to 50 mg). The association with furosemide neutralizes potassium balance. On the other hand, the use of thiazide-like diuretics is potentially harmful, worsens renal function and may provoke severe hyponatremia and hypokalemia. If clinicians decide to use that combination, the patient must be examined frequently and lab tests should be performed on regular basis. I personally don´t use that combination.

Natriuretics

Natriuresis with natriuretic peptides: Atrial natriuretic factor was the first hormone described in the early ‘80s by DeBold. For the first time heart was recognized as an endocrine organ and not just as a pump. More than 30 years later, we understood lots of things about natriuretic peptide system. Both ANP and BNP are released to circulation when there is an increase in loading conditions and myocardial stretching, and natriuretic peptide receptor type A is expressed in different cells. Also UNP (urodilatin) belongs to this system, it is released from renal tubules and acts as a paracrine binding to the same NPR-A in the distal tube. The binding of natriuretic peptides to the receptos stimulates guanylate cyclase, with second messengers that finally lead to sodium pass through membranes in the proximal and collector tubules. There is also a hemodynamic diuretic effect by vasodilation of afferent arteriole and constriction of efferent arteriole, which increases glomerular filtration rate. The pharmacologic strategies for increasing natriuretic peptide system effect are direct agonism of NPR-A (nesiritide, ularitide), or inhibition of neprylisin so the half-life of endogenous natriuretic peptides is increased (sacubitril, ecadotril, candoxatril are neprylisin inhibitors).[7]

Natriuresis with SGLT2 inhibition: In the recent years, a group of drugs that inhibit renal reabsorption of glucose was developed. The co-transporter of sodium and glucose type 2 is naturally expressed in the luminal membrane of epithelial cells from the segments S1/S2 of the proximal tubules (that is the place where 97% of the filtrated glucose is reabsorbed). The SGLT2 inhibitors, called gliflozins, provoke glucosuria and natriuresis, increasing diureris by dual effect, natriuretic and osmotic. The efficacy of gliflozins fot type 2 diabetes mellitus was proved in large randomized trials, where an improvement in glucose and glycated haemoglobin was found, but also in major endpoints of cardiological concern, like body weight, lipid levels, an mainly reduction in heart failure events (symptoms, hospitalizations, and mortality due to heart failure). There are currently ongoing trials with gliflozins for heart failure patients with and without diabetes.[8]

Conclusion

In conclusion, diuresis for heart failure patients is tricky, and deserves more attention, especially because of the development of drugs that potentiate the effect of furosemide.

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