

PRACTICAL ISSUES IN THE MANAGEMENT OF HEART FAILURE: DIURETIC THERAPY

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Introduction

Of the expanding number of pharmacological strategies available to manage heart failure, diuretics receive the least attention. This is despite the fact that they remain the most effective means of providing prompt relief of symptoms in this syndrome. Possibly as a result of this lack of attention, the full potential of diuretic therapy may not be realised or indeed they can be misused. In either setting, patient care can be compromised leading to unnecessary complications.

This review of diuretic therapy will address many of the practical questions we need to answer in the day-to-day use of these agents in heart failure.

Are diuretics the first-line therapy for heart failure?

When patients present they are invariably symptomatic as a result of congestion. In such settings, diuretic should be first-line therapy in order to achieve rapid symptom response. However, even if symptoms totally resolve with diuretic, it is critical to continue investigations to confirm the diagnosis of heart failure, determine the cause, assess systolic function of the left ventricle to clarify the need for ACEI and/or beta blocker therapy and ensure the patient and family members are educated in critical components of self-care in this syndrome.

If a patient is found to have asymptomatic reduction in left ventricular function (i.e. a reduced ejection fraction), then diuretic would not be required and focus should be placed on clarifying the aetiology, initiating therapy with ACEI inhibition and referring for beta blocker titration.

Which diuretic and how to assess the initial diuretic dose?

Diuretics exerting their action on the ascending loop of Henle are the most effective approach in relieving congestion. Thiazide diuretics as a single therapy do not produce as impressive a diuresis. Use of a combination diuretic such as Frumil is often chosen to minimise potassium loss. The initial dose of a loop diuretic is based on the patient's symptoms, previous exposure to diuretic, renal function and age. An initial dose of frusemide 40mg equivalent (bumetanide 1mg) is generally chosen.

How to assess the correct maintenance dose

It is important to carefully assess response to the initial amount of diuretic, as it is rare that this dose will prove to be the correct maintenance dose. Excess diuresis should be avoided, as it further activates many of the neurohumoral abnormalities in heart failure potentially aggravating the disease process. Over-diuresis is suggested by symptoms of postural hypotension, clinical evidence of reduced venous pressure (low jugular venous pressure [JVP]) and biochemical evidence of climbing blood urea. Insufficient diuresis is indicated by continuing symptoms and evidence of congestion.

It is also important to note that the diuretic dose often requires adjustment in response to certain clinical circumstances. For example, intercurrent illness can reduce the need for diuretic (e.g. gastroenteritis) or indeed lead to a temporary increase in diuretic, especially when events such as pneumonia exacerbate heart failure. Climatic changes often influence diuretic dose with reduced requirements in hotter months. Finally, clinical response to other agents in heart failure, most notably ACEI and beta blockers, may lead to a permanent reduction in dose of diuretic. Therefore, careful and regular assessment of diuretic dose is required.

What to do if refractory to oral diuretic?

When clinical response is unsatisfactory, several issues need to be addressed. Assuming compliance is not a problem, the other common causes for failing to achieve an adequate diuresis are poor renal function, prominent right heart failure, concomitant medical therapy or the development of diuretic resistance.

Declining renal function will reduce responsiveness to loop and thiazide diuretic. In such circumstances, careful review of the patient's case to exclude reversible causes of renal dysfunction (drug-induced such as ACEI or NSAID or vascular such as renal artery disease) should be undertaken in an effort to improve diuretic responsiveness.

Right heart failure, diagnosed as an elevated JVP, significantly impairs absorption of loop diuretics as a result of bowel congestion, thereby reducing their clinical efficacy. The most effective means of overcoming this problem is a once-off or short course of intravenous diuretic, with careful monitoring of renal and electrolyte profile. This can pose practical problems in a general practitioners surgery and may be most effectively carried out on an outpatient basis in the setting of a hospital heart failure unit. Our own experience with this approach has been very encouraging, stabilising the clinical situation, aborting a possible admission and allows for the successful resumption of oral diuretic therapy.

Diuretic resistance can occur outside the above situations. With more protracted use of loop diuretic, heightened absorption of sodium and water can occur in the distal convoluted tubule negating the block of sodium absorption in the loop of Henle. This can be overcome by the addition of a thiazide diuretic acting on the distal convoluted tubule prescribed 30 minutes before taking the loop diuretic (see Figure 1). In adopting this approach, careful monitoring of renal and electrolyte profile is mandatory as profound potassium and sodium loss can occur.

When is intravenous diuretic useful?

While rarely needed, the outpatient administration of intravenous diuretic should be recognised as a useful strategy. As

stated above, it can be used to combat diuretic resistance when explained by right-sided heart failure. It can also be used to expedite recovery from a clinical deterioration when oral diuretic is not proving as effective as needed. Finally, when patients refuse hospitalisation, a surrogate for inpatient management can be attempted using regular clinic intravenous therapy.

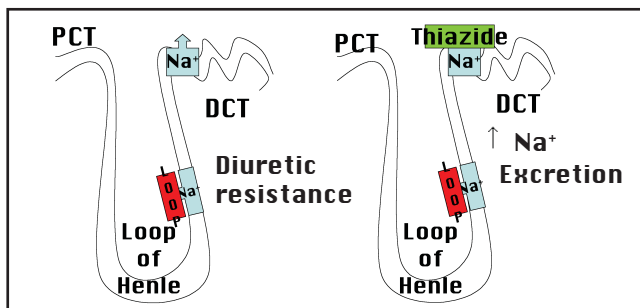


Figure 1. Sequential nephron blockade

When should we use aldosterone antagonists?

Recent information has outlined the value of spironolactone in the management of heart failure associated with reduced left ventricular systolic dysfunction. Its benefit is likely not due to its activity as a weak diuretic but as a direct inhibitor of the actions of aldosterone, a hormone which promotes fibrosis, baroreceptor dysfunction and sympathetic activity in heart failure. Therefore, while not a strong diuretic, its use may have multiple benefits, not least in maintaining potassium homeostasis. However, in the

setting of renal dysfunction, concomitant use of ACEI or angiotensin receptor blockers, careful monitoring of renal function and electrolytes is mandatory.

Complications of diuretic therapy?

In general, diuretics can be safely used without significant complications. On occasion, problems do arise which need to be addressed. Common issues include the following.

Disturbance in renal/electrolyte profile

Potassium loss can be readily addressed using potassium-sparing diuretics, especially spironolactone because of its proven mortality benefit in patients with reduced ejection fraction heart failure. Nowadays there is little reason to prescribe potassium supplements for this reason.

Reduced sodium concentration can be seen with diuretic therapy, especially in patients with more severe heart failure, where it reflects excessive activation of the renin angiotensin aldosterone system. Minor reductions in sodium ($>128\text{mEq/l}$) are generally of no clinical consequence. More significant reductions can result in non-specific symptoms and may require adjustment of diuretic therapy. In such settings, use of diuretic-sparing therapy can be of benefit, including nitrates to reduce venous pressures and attempting to maximise dose of ACEI therapy.

An elevation in urea and less commonly in creatinine can be seen with diuretic therapy. Modest elevations can be accepted if other parameters do not point to excess diuretic use (i.e. normal or still elevated venous pressure). More significant elevations

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PRESCRIBING INFORMATION ROI. Indications: Treatment of stable chronic moderate to severe heart failure with reduced systolic ventricular function (ejection fraction $\leq 35\%$, based on echocardiography) in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides. **Dosage:** The patients should have stable chronic heart failure without acute failure during the past six weeks and a mainly unchanged basic therapy during the past two weeks. It is recommended that the treating physician should be experienced in the management of chronic heart failure. **Warning:** The treatment of stable chronic heart failure with bisoprolol has to be initiated with a titration phase. **Adults:** Starting dose of 1.25mg a day for one week, then gradual up-titration, if well-tolerated, in defined steps, to a maximum dose of 10mg once daily. **Elderly:** No dosage adjustment required. **Children:** Not recommended. After initiation of treatment with 1.25 mg, the patients should be observed over a period of approximately 4 hours (especially as regards blood pressure, heart rate, conduction disturbances, signs of worsening of heart failure). During the titration phase, in case of worsening of the heart failure or intolerance, it is recommended first to reduce the dose of bisoprolol, or to stop immediately if necessary (in case of severe hypotension, worsening of heart failure with acute pulmonary oedema, cardiogenic shock, symptomatic bradycardia or AV block). Treatment with bisoprolol is not recommended to be stopped abruptly since this might lead to a transitory worsening of heart failure. If discontinuation is necessary, the dose should gradually be decreased. There is no information regarding pharmacokinetics of bisoprolol in patients with chronic heart failure and with impaired liver or renal function. Up-titration of the dose in these populations should therefore be made with additional caution. **Contra-indications:** Acute heart failure or during episodes of heart failure decompensation requiring i.v. inotropic therapy, cardiogenic shock, second or third degree AV block, sick sinus syndrome, sinoatrial block, bradycardia with < 60 beats/min before the start of therapy, hypotension, severe bronchial asthma or severe chronic obstructive pulmonary disease, late stages of peripheral arterial occlusive disease and Raynaud's syndrome, untreated phaeochromocytoma, metabolic acidosis, hypersensitivity to bisoprolol or to any of the excipients. **Precautions:** Bronchospasm, bronchial asthma, obstructive airways disease, concomitant treatment with inhalation

anaesthetics, diabetes mellitus, strict fasting, ongoing desensitisation therapy, first degree AV block, Prinzmetal's angina, peripheral arterial occlusive disease, psoriasis, thyrotoxicosis. Allergic reactions may be worsened. **Pregnancy and lactation:** Bisoprolol should not be used during pregnancy unless clearly necessary. Use during breastfeeding is not recommended. **Drug interactions:** Calcium antagonists, clonidine, monoamineoxidase-A inhibitors, class-I and class-III antiarrhythmic drugs, parasympathomimetic drugs, other β -blockers, insulin and oral antidiabetic drugs, anaesthetic agents, digitalis glycosides, prostaglandin synthetase inhibiting drugs, ergotamine derivatives, sympathomimetic agents, tricyclic antidepressants, barbiturates, phenothiazines, other antihypertensive agents, rifampicin, mefloquine. **Side effects:** **Common:** Coldness or numbness in the extremities, tiredness, dizziness, headache, GI disturbances. **Uncommon:** Muscular weakness/cramps, bradycardia, AV-stimulus disturbances, worsening of heart failure, orthostatic hypotension, sleep disturbances, depression, bronchospasm. **Rare:** Nightmares, hallucinations, hypersensitivity reactions, increased liver enzymes, hepatitis, increased triglycerides, potency disorders, hearing impairment, allergic rhinitis, dry eyes, psoriasis-like rash, alopecia. **Presentations:** Cardicor film-coated tablets contain either 1.25mg, 2.5mg, 3.75mg, 5mg, 7.5mg or 10mg bisoprolol fumarate (2:1). Calendar Pack 28 tablets. Price in Republic of Ireland: 1.25mg €8.76; 2.5mg €8.11; 3.75mg €10.01; 5mg €10.51; 7.5mg €12.13; 10mg €13.43. **Product licence no.:** PL 0493/0179-84. **Product authorisation number and holder:** 654/7/1-6: Merck Pharmaceuticals, (A Division of Merck Ltd), Harrier House, High Street, West Drayton, Middlesex UB7 7QG, United Kingdom. **Legal category:** POM. **Date of preparation:** January 2003. Full prescribing information available on request from: Merck Pharmaceuticals, (A Division of Merck Ltd), 2004A Orchard Avenue, Citywest Business Campus, Naas Road, Dublin 24. Tel: 01 466 1900. **Reference 1.** CIBIS II, *Lancet* 1999; 353 (9146): 9-13.



(>25% above baseline) often require adjustment of diuretic regimen and/or adjustment of other therapies (is the patient taking non-steroidal anti-inflammatory drugs [NSAIDs]?).

Excess diuresis

Care should be exercised to avoid over-diuresis, as the resultant activation of the renin angiotensin aldosterone system may have a negative impact on overall prognosis. Accordingly, clinical review focusing on venous pressure, accompanied by analysis of urea and creatinine, should be undertaken at regular intervals (three to six months), even in clinically stable patients.

Gout

This recognised complication of diuretic therapy is particularly problematic in heart failure as it may result in the prescription of NSAIDs. The latter can result in a deterioration in renal function and precipitate fluid retention. Prophylaxis of gout in those at risk should be a focus of therapy and minimise the need for NSAID therapy. Alternatively, the use of diuretic-sparing therapies, such as nitrates, may lessen the likelihood of precipitating gout.

Other tricks with diuretics?

Reduce with ACE titration

When initiating ACEI therapy a reduction in diuretic for a few days may be of use in minimising hypotension and decline in renal function. In stable patients this can

generally be done without problems.

Cough: ACEI or congestion?

This is a relatively common clinical problem. Rather than immediately implicate the ACEI, care should be taken to exclude occult congestion (not evident clinically or radiographically). Unless one has the benefit of serial measurements of brain natriuretic peptide to help solve this issue, the only practical solution is to prescribe a short term increase in diuretic which will resolve any lingering congestion.

Diuretic sparing

Nuisance problems with diuretic therapy include frequent disturbance of sleep due to diuresis. Focusing diuretic therapy in the morning minimises this issue but if symptoms return towards the evening, use of nitrates may provide the needed symptomatic benefit without producing significant diuresis. Nitrate patches at night may also help reduce the tendency to PND without disturbing sleep for diuresis.







Conclusion

This review hopefully covers many of the major practical issues related to diuretic therapy in heart failure. This remains a very flexible therapy which when used to its fullest can make management of heart failure more effective.

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