Use of diuretics in cardiovascular diseases: (1) heart failure

S U Shah, S Anjum, W A Littler

Diuretics are used extensively in hospitals and in community medical practice for the management of cardiovascular diseases. They are used frequently as the first line treatment for mild to moderate hypertension and are an integral part of the management of symptomatic heart failure. Although diuretics have been used for several decades, there is still some ambiguity and confusion regarding the optimal way of using these common drugs. In this paper, the classes and action of diuretics are reviewed, and the various indications, optimal doses, and recommendations on the effective use of these agents are discussed.

CLASSIFICATION AND MECHANISM OF ACTION

The commonly used classes of diuretics are loop, thiazide, and potassium sparing diuretics, and carbonic anhydrase inhibitors. Carbonic anhydrase inhibitors are rarely used in the management of hypertension or heart failure and hence will not be discussed in detail. This classification of diuretics is based on their site of action in the kidneys. This secondarily determines their potency and various biochemical effects (see table 1).

Loop or high ceiling diuretics, including frusemide, bumetanide, and torsemide, reversibly inhibit the Na⁺–K⁺–2Cl⁻ symporter (cotransporter) situated at the luminal thick ascending limb of the loop of Henle. A second functional class of these drugs, typified by ethacrynic acid, is also effective only from the tubule lumen but exhibits a slower onset of action, and delayed and only partial reversibility. Loop diuretics therefore act by inhibiting the reabsorption of chloride, sodium, potassium, and hydrogen ions in the ascending loop of Henle. In comparison with thiazide diuretics, loop diuretics induce relatively more urine formation and relatively less loss of sodium and potassium (see table 2).

The plasma half life of a typical loop diuretic, frusemide, is 1.5 hours; the duration of action is 4–6 hours. Diuresis starts within 10–20 minutes of an intravenous dose and peaks 1–1.5 hours after an oral dose.

The group often collectively referred to as “thiazide” diuretics are not all technically benzothiadiazine derivatives. Thiazides inhibit sodium and chloride reabsorption more distally. This cotransporter is insensitive to loop diuretics. More sodium reaches the distal tubules to stimulate the exchange with potassium, particularly in the presence of an activated renin–angiotensin–aldosterone system. Thiazides may also increase the active excretion of potassium in the distal renal tubule. Thiazides are rapidly absorbed from the gastrointestinal tract, producing diuresis within 1–2 hours, which typically lasts for 6–12 hours. Their potency is midway between loop and potassium sparing agents, which act mainly on the distal tubules. Metolazone, which is a thiazide-like diuretic, seems to affect the proximal tubule in addition to its more distal effect. It is therefore effective even in renal failure, whereas other thiazide diuretics, owing to their distal and hence less potent action, are of limited or no use. Indapamide has been shown to have mainly vasodilatory effects in smaller doses, and it works as a weak diuretic in relatively larger doses.

Potassium sparing diuretics also generally retain magnesium. Amiloride and triamterene inhibit the sodium proton exchanger, which is concerned with sodium reabsorption in the distal tubules and collecting tubules. Thereby potassium loss is indirectly decreased. They are relatively weak diuretics, which are often used in combination with thiazides and loop diuretics. An advantage of such combination is that the loss of sodium is achieved without a major loss of potassium and magnesium. Both amiloride and triamterene affect cardiac repolarisation, possibly by inhibiting delayed rectifier K⁺ currents (Iₖ), and may exaggerate the prolonged repolarisation observed with Singh–Vaughan Williams class IA antiarrhythmics.

Spironolactone and its active metabolites canrenone and potassium canrenoate competitively inhibit the binding of aldosterone to mineralocorticoid or type I receptors in many tissues, including epithelial cells of the distal convoluted tubule and collecting duct. Spironolactone is more powerful then other potassium sparing diuretics. One daily dose is usually adequate for diuresis. Recently, spironolactone has been shown to decrease mortality markedly in subjects with advanced heart failure.

Diuretics have also been shown to exert some extrarenal effects. Both loop and thiazide diuretics can induce vasodilatation when used acutely. Frusemide has been shown to relax precontracted pulmonary venous rings by directly affecting smooth muscle cells. Interestingly, this effect is apparent only in pulmonary venous and not in arterial vascular tissue and was apparent in these in vitro studies only at drug concentrations achievable transiently after bolus infusions. This vasodilatory
effect is sustainable with long term use, although it is influenced by other factors, such as dosage, route, and concomitant use of other medications. All these rapid haemodynamic changes are attenuated in patients with chronic congestive heart failure. The vasodilatory effect of these two classes of diuretics is probably related to the loss of sodium and water from the vessel wall. At least some of this vasodilatory action is mediated through the release of prostacyclin and endothelin derived relaxing factor. The mechanism responsible for the lowered peripheral resistance may also involve potassium channel activation.

### BIOCHEMICAL AND METABOLIC EFFECTS OF DIURETICS

Loop and thiazide diuretics may lead to deficiency of the main electrolytes, particularly potassium and sodium. Hypokalaemia and hyponatraemia to a lesser degree may secondarily cause other metabolic effects. The degree of potassium wastage and hypokalaemia is directly related to the dose of diuretic. Hypokalaemia may precipitate potentially hazardous ventricular ectopic activity and increase the risk of primary cardiac arrest, even in patients who are not on concomitant digitalis therapy and do not have myocardial irritability. Even mild hypokalaemia caused by these diuretics may result in leg cramps, polyuria, and muscle weakness. In some patients, concomitant diuretic induced magnesium deficiency prevents the restoration of intracellular potassium deficits. Hence, it is important that magnesium levels in patients with heart failure who are treated with diuretics are regularly checked and magnesium corrected if necessary. Magnesium deficiency may also be responsible for some of the arrhythmias ascribed to hypokalaemia.

Most diuretics decrease urate excretion with the risk of increasing levels of uric acid in the blood, causing gout in predisposed patients. The serum level of uric acid is elevated in as many as one third of untreated hypertensive patients. With long term high dose diuretic therapy, hyperuricaemia appears in another third of patients, probably because of increased proximal tubular reabsorption accompanying volume contraction. Diuretic induced hyperuricaemia may precipitate acute gout, most frequently in those who are obese and consume large amounts of alcohol or who have a family history of this condition.

Serum cholesterol levels often rise after diuretic therapy, but after one year no adverse effects were noted in those who responded to smaller doses. High doses of diuretics may impair glucose tolerance and precipitate diabetes mellitus, probably because they increase insulin resistance and therefore induce hyperinsulinaemia. The mechanism by which diuretics increase insulin resistance is uncertain. However, it is probably related to their lowering of potassium levels (thiazides more so than loop diuretics owing to their longer action).

There is usually a slight increase in serum calcium levels (less than 0.125 mmol/l (0.5 mg/dl)) with thiazide use, at least in part because increased calcium reabsorption accompanies the increased sodium reabsorption in the proximal tubule that is induced by contraction of the extracellular fluid volume. The rise is of little concern except in patients with previously unrecognised hyperparathyroidism, who may

### Table 1: Classification and mechanism of action of diuretics

<table>
<thead>
<tr>
<th>Diuretic</th>
<th>Principal site and mechanism of action</th>
<th>Effects on urinary electrolytes</th>
<th>Extrarenal effects</th>
<th>Common or important side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loop diuretics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frusemide</td>
<td>Thick ascending loop of Henle, inhibition of Na-K-2Cl cotransporter</td>
<td>Increases Na and Cl</td>
<td>Acute</td>
<td>Hypokalaemia, hyponatraemia, hypomagnesaemia, hypocalcaemia, hyperuricaemia, hyperglycaemia, dehydration, blood dyscrasias, rashes, lipid abnormalities, ototoxicity</td>
</tr>
<tr>
<td>Torasemide</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Thiazide related</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulphonamide diuretics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bendrofluazide</td>
<td>Distal tubule</td>
<td>Increases Na and Cl</td>
<td>Increases venous capacitance and glucose</td>
<td>Hypokalaemia, hyponatraemia, hypomagnesaemia, hypercalcaemia, hyperuricaemia, pancreatitis, rashes, increase in LDL and triglycerides (may be transient), impotence</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>Inhibition of NaCl cotransport</td>
<td>Increases K</td>
<td>Increases LDL and triglycerides May be dose related</td>
<td></td>
</tr>
<tr>
<td>Chlorothiazide</td>
<td>Additional proximal tubular action</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metolazone</td>
<td>Vasoconstrictor</td>
<td>Additional effects include reducing Cl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indapamide</td>
<td></td>
<td></td>
<td>Milder</td>
<td></td>
</tr>
<tr>
<td>Potassium sparing diuretics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Aldosterone antagonists, collecting duct</td>
<td>Reduces K, increases Na and Cl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triamterene</td>
<td>Inhibition of apical membrane Na conductance</td>
<td>Increases HCO</td>
<td></td>
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</table>

### Table 2: Relative potency of various diuretics, and effects on loss of fluid and electrolytes

<table>
<thead>
<tr>
<th>Diuretic</th>
<th>Volume (ml/min)</th>
<th>Na</th>
<th>K</th>
<th>Cl</th>
<th>HCO</th>
<th>Ca</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1</td>
<td>15</td>
<td>15</td>
<td>60</td>
<td>1</td>
<td>Variable</td>
</tr>
<tr>
<td>Thiazide</td>
<td>3</td>
<td>15</td>
<td>25</td>
<td>150</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Frusemide</td>
<td>8</td>
<td>140</td>
<td>10</td>
<td>155</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Triamterene</td>
<td>3</td>
<td>130</td>
<td>5</td>
<td>120</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Amiloride</td>
<td>2</td>
<td>130</td>
<td>5</td>
<td>110</td>
<td>15</td>
<td>0</td>
</tr>
</tbody>
</table>
experience a much more marked rise. Conversely, the diuretic induced positive calcium balance is associated with a reduction in the incidence of osteoporosis in the elderly.20

An increase in the incidence of impotence has been noted in men taking thiazide diuretics.21 A significant increase in renal cell carcinoma among diuretic users was found in a search of nine case-control and three cohort studies.22–25 Although the risk ratio was 1.55, the absolute incidence of renal cell carcinoma was only 0.065%, which was not statistically significant. The overall positive effects of diuretic use therefore far outweigh their hazards.

**USE IN HEART FAILURE**

Fluid retention is a consistent finding in almost all acute and most chronic heart failure patients. It manifests as pulmonary and peripheral oedema. Fluid retention impairs the transportation of oxygen, nutrients, and waste products, ultimately leading to organ failure.26 Diuretics have been used to improve pulmonary and peripheral symptoms and signs of congestion.27 There is, however, no specific long term mortality data available for the use of diuretics in heart failure. Diuretics can result in neuroendocrine activation, with potential long term consequences. However, no significant negative effects have so far been found.

In patients with acute left heart failure, pulmonary oedema is the main abnormality and is usually treated with intravenous loop diuretics. The improvement in symptoms and the accompanying reduction in filling pressures occurs even before diuresis is initiated and have been attributed to vasodilatation.28 However, the exact mechanism of these acute effects of diuretics is still not fully understood.

**Box 1: How to minimise side effects**

- Use the smallest possible doses and tailor individual therapy.
- Hypokalaemia can be avoided by using concomitant angiotensin converting enzyme inhibitor, angiotensin receptor blocker, β-blocker, or potassium sparing agents.
- Combination of aminoglycosides and loop diuretics should be avoided because of the risk of ototoxicity.
- A low sodium diet (less than 2.4 g sodium) and fluid restriction (less than 1.5 l fluid) can reduce the need to use higher doses in advanced heart failure.
- Non-steroidal anti-inflammatory drugs blunt the effects of diuretics and angiotensin converting enzyme inhibitors, and should be avoided.
- Xanthine oxidase inhibitors should be used in patients with gout.
- Elderly patients should be commenced on a smaller dose and the dose slowly titrated to avoid many complications. Mild diuretics, such as slow release indapamide, are useful as antihypertensive agents because of their excellent safety profile.
- In patients with advanced heart failure and low blood pressure, use a diuretic infusion rather than bolus doses.
- In patients with hypertension, use a moderately long acting (12–18 hour) diuretic, such as hydrochlorothiazide, because longer acting drugs, such as chlorothalidone, may increase potassium loss.
- Increase dietary potassium intake and restrict the concomitant use of laxatives.

**HOW TO USE DIURETICS EFFECTIVELY IN HEART FAILURE (SEE TABLE 3)**

Diuretics are the mainstay of therapy for symptomatic chronic heart failure but are now rarely used as monotherapy. Together with angiotensin converting enzyme inhibitors, β-blockers and digoxin, they improve patients’ symptoms and in most cases also improve their effort tolerance.29 In asymptomatic patients (New York Heart Association class I; NYHA I) with echocardiographic evidence of left ventricular systolic dysfunction, an angiotensin converting enzyme inhibitor rather than a diuretic should be used as a first line agent.30 However, in more symptomatic cases (NYHA II–IV) diuretics are usually needed in addition to other agents. Thiazide diuretics can be used in milder cases, particularly if there is no renal impairment. However, in more symptomatic patients (NYHA III–IV) and in patients with renal impairment, loop diuretics are more useful owing to their relatively strong diuretic action and fewer side effects (see table 2). Thiazide diuretics are not effective in patients with renal failure (creatinine levels of more than 180 μmol/l).31 In such patients, the dose of loop diuretics should be doubled for better diuresis. However, metolazone, which is a thiazide like diuretic, works efficiently in patients with renal failure owing to its additional action on the proximal tubule.32

In patients with substantial oedema, a combination of diuretics is much more useful than a high dose of a single agent. Hence a combination of a high dose loop diuretic and a thiazide diuretic with or without a potassium sparing agent is much more potent than a high dose of either of these. This is due to the “sequential blocking” effect of these agents, thereby blocking all potential reabsorption sites for the glomerular filtrate. Metolazone is a very powerful agent and together with loop diuretics can cause a substantial loss of electrolytes and fluid. It is therefore advisable that metolazone therapy should be initiated in hospital, where daily renal profile and other parameters can be checked and the patient closely monitored. A smaller dose of 2.5 mg daily works in most patients and has fewer biochemical and haemodynamic effects. Once stable, patients on metolazone can be monitored in the community, with renal profile being measured perhaps once every fortnight and later less frequently.

In patients with significant or generalised oedema (anaesthesia) there is usually a degree of intestinal oedema affecting the absorption of oral diuretics. In these cases, the loop diuretic torsemide has been shown to be better absorbed and hence more effective than furosemide.33

**THE PHENOMENON OF DIURETIC RESISTANCE AND ITS MANAGEMENT**

The effectiveness of potent loop diuretics can decrease with worsening heart failure, thereby causing “diuretic resistance”.34 Diuretics induce the loss of electrolytes and fluid, thereby stimulating several compensatory haemostatic mechanisms, which result in increased renal sodium reten tion by all nephron segments. If dietary salt intake is sufficiently high, a daily net negative sodium balance may not be achieved even with several daily intravenous doses of a loop diuretic.35 Hence, salt intake must be restricted in patients with heart failure to obtain a negative sodium balance. This also implies that short acting diuretics, particularly loop diuretics, must be administered at least twice a day to obtain consistent daily salt and water loss unless dietary sodium intake is severely restricted.36

Certain classes of drugs, particularly non-steroidal anti-inflammatory drugs, can reduce renal function by various mechanisms. Renal prostaglandin production is required to compensate for circulating vasoconstrictor substances seen in
patients with heart failure. All non-steroidal anti-inflammatory drugs, including aspirin, can diminish diuretic efficacy by decreasing the renal synthesis of these vasodilator substances. The concomitant use of vasodilators is a common cause of diuretic resistance. In addition, all vasodilators commonly used as afterload reducing agents in patients with heart failure dilate a number of central and peripheral vascular beds. Therefore, renal blood flow may be reduced despite an increase in cardiac output, thus causing a decline in the effectiveness of the diuretic action. Vasodilator therapy may also lower renal perfusion pressure below that necessary to maintain normal autoregulation and glomerular filtration in patients with renal artery stenosis caused by atherosclerotic disease.

Diuretic resistance should be distinguished from “diuretic adaptation” or the “braking” phenomenon observed even in normal subjects given multiple doses of a short acting loop diuretic. This effect is now known to be due largely to compensatory hypertrophy of the tubular epithelium distal to the site of action of the Na\(^+-\)K\(^+-\)Cl\(^-\) cotransporter inhibitor, which increases the solute resorptive capacity of the kidney, as well as other adaptive mechanisms. Chronic and perhaps even acute treatment with loop diuretics causes rapid (roughly 60 minutes) upregulation of the thiazide sensitive Na\(^+-\)Cl\(^-\) cotransporter in the distal tubule. In addition, many patients with heart failure also have some degree of renal impairment, which shifts the diuretic concentration–effect relationship downward and to the right.

Diuretic resistance may be prevented by the use of rennin-angiotensin system inhibitors. These agents can uniquely augment the effectiveness of diuretics by mechanisms that are independent of their ability to reduce systemic vascular resistance. Diuretic resistance can also be managed by increasing the frequency of loop diuretic dosing or by switching to a continuous intravenous infusion. Concomitant administration of a more distally acting diuretic—for example, a thiazide or thiazide like diuretic, such as intravenous chlorothiazide, oral bendrofluazide, or oral metolazone—will usually also result in substantial natriuresis. This combination should, however, be used cautiously and with careful monitoring of renal function and serum levels of potassium and sodium, especially in outpatient patients.

Potassium sparing diuretics may also be able to increase the effectiveness of more proximally acting diuretics. These agents reduce the oral potassium requirement and maintain serum potassium levels well inside the normal range. Hence, most subjects receiving large doses of loop diuretics or loop diuretics plus thiazides benefit from a potassium sparing diuretic. If tolerated, spironolactone should be the potassium sparing diuretic used because of its mortality reducing effects. Observational studies suggest that potassium sparing diuretics reduce the incidence of serious ventricular arrhythmias in patients with heart failure (particularly those who are on digoxin) and hypertension (particularly in patients with left ventricular hypertrophy).
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Postgrad Med J 2004 80: 201-205
doi: 10.1136/pgmj.2003.010835

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