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Clinical use of diuretics

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What are diuretics? How do they work?

Diuretics are widely used in clinical medicine, particularly in hypertensive and oedematous states. By inhibiting sodium reabsorption at different sites along the nephron, they increase natriuresis with consequent clinical benefit.[1] However, clinical goals may not always be easily achieved.

Site of action classifies the commonly used agents (Table 1).[1–3] Although most (60–70%) filtered sodium is reabsorbed in the proximal tubule, agents acting at this site (eg acetazolamide) are of relatively little clinical use in oedematous states because the increased sodium loss is offset by increased reabsorption further down the nephron in the thick ascending loop of Henle. The same principle applies to the proximal tubular effect of some thiazide diuretics.

Loop diuretics[1–3]

Loop diuretics (eg furosemide, bumetanide, torasemide) are organic anions, secreted into the tubular lumen in the proximal tubule. They act on the thick ascending loop of Henle where they exhibit high affinity for the chloride-binding site of the sodium-potassium-2 chloride (Na-K-2Cl) transporter. Binding directly inhibits sodium and chloride reabsorption. This indirectly leads to decreased reabsorption of calcium and magnesium, and interferes with urine concentrating and diluting mechanisms. Up to 20% of filtered sodium can be excreted using these agents.

Ethacrynic acid is a rarely used loop diuretic indicated in patients known to have had hypersensitivity reactions to sulphonamides and related agents.

Thiazide and related diuretics[1–3]

Diuretics of another class, the thiazides and related compounds (eg bendroflumethiazide, hydrochlorothiazide, chlorthalidone, indapamide, metolazone), are also organic anions secreted in the proximal tubule. They act in the distal tubule and connecting segment. They bind to a number of transporters, principally the sodium-chloride cotransporter (Na-Cl-CT), directly inhibiting sodium reabsorption. This indirectly increases calcium reabsorption. The maximum natriuresis is less than that achieved with loop diuretics, but combination of these classes can be especially potent.

*Potassium-sparing diuretics*1-3

The potassium-sparing diuretics include amiloride, triamterene and spironolac-

Key Points

- **Diuretics cause natriuresis in oedematous and hypertensive states**
- **Dietary salt intake restriction is essential with diuretic use**
- **Rapid adaptation by the tubule blunts the initial response to diuretic therapy**
- **Application of pharmacokinetic and pharmacodynamic principles improves the achievement of clinical objectives**
- **Sequential nephron blockade is effective in advanced chronic renal failure and heart failure**

KEY WORDS: diuretics, heart failure, kidney, nephron, oedema, pharmacodynamics, pharmacokinetics, potassium, sodium

tone. The first two are organic cations, secreted in the proximal tubule and inhibiting the luminal epithelial sodium channels of the principal cells in the cortical collecting duct. Spironolactone inhibits the effect of aldosterone on the intracellular aldosterone receptor in these cells.

Diuretics may have actions at other sites, for example many interfere with urate absorption and secretion in the proximal tubule.

When are diuretics indicated? How are they most effectively used?[1–3]

Diuretics are primarily indicated in pathophysiological states (renal failure, cardiac failure, hepatic failure, nephrotic syndrome) in which retention of sodium is a central problem. The objective of therapy is to initiate and sustain an increased natriuresis until the patient has returned to clinical euvolaemia. It is easier to maintain homeostasis at the new desired steady state, particularly if attention has been paid to dietary salt intake.[1]

To achieve a decrease in total body salt and water requires an excess of excretion over intake. Dietary salt intake frequently exceeds 100 mmol/day (~6 g salt/day). Increased sodium avidity occurs when the diuretic is not active. For example, to lose 5 kg of excess extracellular fluid (ECF) volume requires a net sodium loss of 650 mmol *over and above* that needed to balance daily intake. It is irrational not to prescribe a reduction in dietary salt intake in those taking diuretics, but it may be difficult to achieve. Unfortunately, many patients find diets containing less than 80 mmol/day unpalatable, and most salt intake occurs because of addition in food processing.

Unexpected failure to lose weight/ECF volume in a patient on a seemingly appropriate diuretic dose should prompt enquiry into salt intake. Measurement of 24-hour sodium excretion may help. A patient passing 150 mmol/day or more but not losing weight is likely to have an excess intake.

Pharmacokinetic and pharmacodynamic considerations are the other main reasons why patients fail to respond.[1,3] Pharmacokinetics are important in *initiating* natriuresis, pharmacodynamics in *sustaining* it.

Since the natriuretic response is proportional to the rate at which diuretic is excreted in the tubular fluid, consideration should be given to the barriers present between administration and excretion. Exceeding the natriuretic threshold may be difficult in the presence of:

- *Decreased bioavailability:* furosemide has an oral bioavailability of about 60%. This may be decreased with an oedematous gastrointestinal tract. Increasing the oral dose, switching to intravenous administration or using oral bumetanide (higher bioavailability) may be chosen.
- *Increased volume of distribution:* diuretics are highly protein-bound. Secretion into the nephron is predominantly of bound drug. In patients with hypoalbuminaemia, this will lead to a decrease in tubular diuretic excretion and also allow free diuretic to pass out of the vascular space. Hypoalbuminaemia may therefore result in a smaller dose reaching the kidney for secretion into the lumen. Increasing the dose or taking the steps above may be indicated.
- *Low glomerular filtration rate (GFR):* delivery of diuretic to the kidney will be decreased in heart failure and renal failure (as will the initial filtered sodium load). Increasing the dose, taking the steps above or enhancing cardiac output by other means (eg angiotensin-converting enzyme inhibitors (ACEI)) may help.
- *Competition for secretion in the proximal tubule:* many organic ions accumulate in liver and renal failure; they compete for secretion, decreasing the amount of diuretic reaching the tubular lumen. Certain medications (eg cimetidine) also have this effect. Avoiding such agents and taking the steps above may help.

It was formerly speculated that diuretic excretion was increased if the drug was administered with albumin, and that proteinuria might decrease the effective tubular concentration by binding free drug within the tubule. More recent studies do not support these views.[4,5]

Table 1. Diuretic agents.

Diuretic class	Examples	Principal site of action	Comments
Loop	Furosemide Bumetanide* Torasemide Ethacrynic acid**	Thick ascending loop of Henle	*Greater oral bioavailability **Indicated if sulphonamide hypersensitivity
Thiazide	Bendroflumethiazide Hydrochlorothiazide Chlorthalidone Indapamide Metolazone	Distal convoluted tubule; connecting segment	Also used in management of urolithiasis More likely to cause hyponatraemia, hypomagnesaemia and hypercalcaemia than loop diuretics
Potassium-sparing	Triamterene Spironolactone+ Amiloride	Principal cells, cortical collecting duct	May be needed to correct hypokalaemia due to combination of loop and thiazide diuretics Consider in severe heart failure +Specific benefits in advanced heart failure

It is most important to increase the initial dose or otherwise overcome pharmacokinetic problems to initiate natriuresis. Giving an ineffective dose more frequently will not help. In difficult cases, measurement of 24-hour sodium excretion may guide dosing.

In a short time (days) after diuretic administration more distal parts of the tubule will increase reabsorption of sodium, thereby blunting the natriuretic effect. This is principally a local response to increased delivery of tubular sodium to these segments. This pharmacodynamic adaptation should be anticipated and strategies for this may include:

- *Use of adequate dose more frequently:* furosemide acts for about six hours. No enhanced natriuresis will occur for the rest of the day. Twice or thrice daily dosing, once the initial dose has been demostrated to have exceeded the 'natriuretic threshold' leading to increased sodium excretion, allows for a higher daily dose until blunting of the response begins. Studies indicate that continuous infusion may achieve a greater cumulative loss than repeated boluses.[6]
- *Sequential nephron blockade:* a structured inhibition of the distal nephron sites is indicated as the response to loop diuretics declines. Initially, thiazide diuretics should be administered, and subsequently potassium-sparing agents. The latter may in fact be required quickly. Combination therapy with the other diuretic classes markedly increases potassium loss which may be an additional limiting factor. Sequential strategies have been shown to be successful even in patients with advanced chronic renal failure or heart failure.[7] In crossover studies there appears to be little difference in the response to equipotent doses of different thiazides[8] – personal choice may be the best guide.

Careful application of these principles should achieve the treatment objectives, although in difficult cases therapy adjustments and clinical evaluation may be time-consuming and treatment prolonged.

Are there other specific indications?

The hypocalciuric effects of thiazides may be used to reduce the frequency of stone events in some hypercalciuric patients, but not all patients benefit. Other measures to achieve this should also be used. These include: increasing the fluid intake to achieve urine output greater than three litres per day, restriction of dietary salt intake, moderate restriction of dietary calcium intake, avoidance of calcium-containing supplements and restriction of dietary oxalate intake.

In some clinical circumstances, the choice of agent may be informed by other outcomes; for example, patients with heart failure, particularly with more marked left ventricular impairment and low/normal serum potassium concentrations, may have an excess mortality if potassium-sparing diuretics are not used.[9] In addition, spironolactone may have specific beneficial effects in some patients with severe heart failure.[10]

Diuretics do not alter outcomes in acute renal failure (ARF),[11] and are in fact more likely to increase the frequecy with which ARF occurs when used in protocols to diminish anticipated nephrotoxicity.

What are the side effects of diuretics?

Side effects are common and include:

- *ECF volume depletion and raised urea concentrations* because of renal hypoperfusion. Typically, serum creatinine concentrations (a more sensitive marker of GFR) are unchanged or do not increase by more than 10–20% of baseline values. Urea concentrations may rise dramatically. (GFR is relatively preserved due to autoregulation, but impaired renal blood flow causes enhanced tubular urea reabsorption.)
- *Electrolyte disturbances*, for example:
  - hyponatraemia (commoner with thiazides)
  - hypomagnesaemia (similarly)
  - hypokalaemia (most common with combinations of loop and thiazide diuretics), usually manifest within 5–7 days of establishing therapy; 'routine screening' is not indicated in the absence of changes in clinical circumstances, dose or other medications
  - hyponatraemia (more common in the elderly), the incidence of which may be reduced by avoiding a high water intake (>1.5 l/day)
- *Metabolic alkalosis* due to chloride loss and ECF volume contraction
- *Hyperuricaemia* – tubular handling of uric acid is complex, with both reabsorption and secretion occurring in the proximal tubule. Diuretics (particularly thiazides) can interfere with either of these processes, the usual consequence being hyperuricaemia. This effect is usually dose-dependent and frequently asymptomatic. Combination therapy with ACEIs or angiotensin-receptor blockers may blunt the effect. Clinical gout is more likely if the patient is also ECF volume depleted.
- *Hypersensitivity reactions* such as skin rashes and interstitial nephritis.
- *Ototoxicity* is a major, but uncommon, potential side effect. It occurs with high dose loop diuretic therapy. It has been reported with high-dose (>2 g/day) infusion therapy in patients with renal failure. The mechanism is believed to be mediated via the Na-K-2Cl transporter in the inner ear.

Diuretics should be avoided in pregnancy. They can cross the placenta and may cause fetal electrolyte disturbances. Placental perfusion may be compromised, and diuretics enter breast milk.

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When should atheromatous renal artery stenosis be considered?

A guide for the general physician

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Atheromatous renal artery stenosis (ARAS) is common – it is present in 15–30% of otherwise unselected patients with coronary, peripheral or cerebral vascular disease.[1] It is easy to find; in our unit, about 75% of cases selected only on clinical clues and basic ultrasonography have some degree of ARAS at angiography. However, it is much more difficult to identify patients in whom ARAS is contributing to morbidity because all the possible clinical manifestations of ARAS can also be caused by other complications of atheromatous disease (Table 1).

This article will discuss clinical scenarios in which ARAS should be considered with a view to revascularisation. The increasing refinement and availability of computed tomography (CT) and magnetic resonance (MR) angiography make definitive investigation simpler and safer than traditional angiography. Duplex scanning of the renal artery may have a role, but it is highly operator-dependent and can be impossible in obese subjects even in skilled hands.

The introduction of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor antagonists (AIIRA) has both unearthed previously silent cases of ARAS and made the diagnosis more important. Drugs of both classes abolish AII mediated glomerular efferent arteriolar constriction which is vital to maintain glomerular filtration rate (GFR) when renal perfusion pressure is reduced. This loss of GFR is independent of the cause of reduced renal blood flow and is also seen in the presence of hypotension or hypovolaemia of any cause as well as in renal artery stenosis. The effect of these drugs is dose dependent to some extent, and their effect on renal function in ARAS may also be masked by intravascular volume overload and/or hypertension. If the

Key Points

- **Atheromatous renal artery stenosis (ARAS) is common in arteriopaths**
- **All the clinical manifestations of ARAS have more common causes in arteriopaths**
- **ARAS and chronic renal failure (CRF) often co-exist, but the CRF is not usually due to the ARAS (and therefore not improved by revascularisation)**
- **The role of intervention in preventing end-stage renal failure remains unclear**
- **The response to intervention in hypertension is usually no better than mild improvement**
- **When pulmonary oedema is due to ARAS, the response to intervention can be dramatic**
- **When acute oliguric renal failure occurs as a consequence of renal artery occlusion, excellent renal recovery can occur after intervention**

KEY WORDS: atheromatous renal artery stenosis, ischaemic nephropathy, athero-embolic nephropathy, renovascular hypertension