Diuretics: a review for the pharmacist

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Introduction

Diuretics or “water pills” are medicines that aid in the elimination of sodium (salt) and water from the body. They act by increasing the excretion of sodium in the urine. When the kidneys excrete sodium, they excrete water along with it. This decreases the blood volume and reduces pressure of the blood on the walls of the arteries. Diuretics are used to treat several conditions, such as high blood pressure, heart failure, liver disease and certain types of kidney disease.1-8

Renal handling of sodium and water

To understand the action of diuretics, it is important to review the general mechanism by which sodium is reabsorbed and how the kidney filters fluid and forms urine (Figure 1).3,6

Table I provides an overview of how the kidneys regulate and maintain water and electrolyte balance in the body.9-11

Management

Diuretics cause an increase in urine output. It is important to note that, except for the osmotic diuretics, these drugs typically enhance the excretion of solute and water. Therefore, the net effect of most diuretics is to decrease plasma volume.11 Most diuretics produce diuresis by inhibiting the reabsorption of sodium at different segments of the renal tubular system. Sometimes a combination of two diuretics is given because this can be significantly more effective than either compound alone, e.g. a synergistic effect. The reason for this is that one nephron segment can compensate for altered sodium reabsorption at another nephron segment.

Figure 1: Effects of diuretics on renal handling of sodium, potassium and water


Therefore, blocking multiple nephron sites significantly enhances efficacy.1 Diuretics have different clinical uses depending on their mechanism of action.4

Five classes of diuretics and their major sites of action include:11

- Thiazide diuretics: Distal tubule
- Loop diuretics: Ascending limb of the Loop of Henle
- Potassium-sparing diuretics: Cortical-collecting duct

Abstract

Diuretics are among the most commonly prescribed medications. They inhibit electrolyte reabsorption from the lumen of the nephron, increasing osmolarity and enhancing water and electrolyte excretion. It is important to note that there is a delicate balance between dietary sodium intake and sodium loss. If the balance is compromised and there is a greater intake of sodium into the body, but not enough sodium removal, complications of fluid overload occur, such as oedema, pulmonary oedema or high blood pressure. When there is greater removal of sodium, but not enough sodium intake, complications of fluid depletion take place, such as renal failure or reduced output of blood from the heart. The ability to induce a negative fluid balance has made diuretics useful in the treatment of a variety of conditions, particularly in hypertension and oedematous states.

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Thiazide diuretics

Thiazide or low-ceiling diuretics

Thiazide diuretics are the most commonly used. The thiazide diuretics are sulphonamide derivatives which act through the inhibition of sodium and chloride reabsorption at proximal sites of the distal kidney tubules. Because this sodium-chloride transporter normally only reabsorbs approximately 5% of filtered sodium, these diuretics are less efficacious than loop diuretics in producing diuresis and natriuresis. Nevertheless, they are sufficiently powerful to satisfy most therapeutic needs when a diuretic is required. Their mechanism depends on renal prostaglandin production. The excretion of potassium, magnesium and zinc is also enhanced, while calcium excretion is diminished. Thiazides, e.g. hydrochlorothiazide, and the thiazide-like diuretic, indapamide, are used mainly in low doses in the treatment of hypertension, for the management of oedema associated with nephrotic syndrome, liver cirrhosis, heart failure, idiopathic hypercalciuria and nephrogenic diabetes insipidus. High doses are not recommended because of biochemical repercussions, such as hypokalaemia.

Loop or high-ceiling diuretics

Loop diuretics, e.g. furosemide, bumetanide, torasemide and piretanide, are widely used for the symptomatic treatment of heart failure and fluid retention in chronic kidney disease. Loop diuretics act primarily by inhibiting chloride and sodium reabsorption over the entire length of the thick ascending limb of the loop of Henle. The sodium-potassium-chloride co-transporter in the thick ascending limb normally reabsorbs approximately 25% of the sodium load. Inhibition of this pump leads to a significant increase in the distal tubular concentration of sodium, reduced hypertonicity of the surrounding interstitium, and less water reabsorption in the collecting duct. This altered handling of sodium and water leads to both diuresis and increased loss in sodium. By acting on the thick ascending limb, which handles a significant fraction of sodium reabsorption, loop diuretics are powerful. These drugs also induce the renal synthesis of prostaglandins and this contributes to their renal action, including an increase in renal blood flow and the redistribution of renal cortical blood flow. The effect of the loop diuretics is dose dependent, and is largely determined by the rate at which the diuretic is delivered to its site of action. Diuresis is not seen with very low doses.

Progressively increasing diuresis is achieved at higher doses. A plateau is reached, at which even higher doses produce no further diuresis. This dose is called the maximum effective dose, which increases with worsening renal function. Furosemide is chemically similar to the thiazide diuretics. It has a fast onset of diuretic action. The oral form is used for hypertension, either alone or in combination with other antihypertensive agents, but the thiazide-type diuretics are preferred, unless there is renal impairment or cardiac failure. The intravenous route is fast acting in emergency situations, such as pulmonary oedema. Furosemide has an acute haemodynamic effect in such circumstances.

Loop diuretics also have an important effect on renal calcium handling. The reabsorption of calcium in the loop of Henle is primarily passive, being driven by the electrochemical gradient created by NaCl transport. As a result, inhibiting the reabsorption of NaCl leads to a parallel reduction in that of calcium, thereby increasing calcium excretion. A concern is that the calcuiarc
response can lead to kidney stones and/or nephrocalcinosis.6 (Nephrocalcinosis is a disorder in which too much calcium is deposited in the kidneys).13

Potassium-sparing diuretics

Unlike loop and thiazide diuretics, some potassium-sparing diuretics do not act directly on sodium transport. They also antagonise the actions of aldosterone (aldosterone receptor antagonists, e.g. spironolactone) at the distal segment of the distal tubule. This causes more sodium (and water) to pass into the collecting duct and to be excreted in the urine. They are called potassium-sparing diuretics because they do not produce hypokalaemia, like the loop and thiazide diuretics. The reason for this is that by inhibiting aldosterone-sensitive sodium reabsorption, less potassium and hydrogen ions are exchanged for sodium by this transporter, and therefore less potassium and hydrogen are lost to the urine.3 Spironolactone is a competitive inhibitor of aldosterone. It is an effective antihypertensive, which may be particularly useful in patients with resistant hypertension. It has the advantage of not affecting glucose metabolism or uric acid elimination. It is the drug of choice for hypertension due to primary aldosteronism. Eplerenone is an important alternative to spironolactone in patients experiencing oestrogenic side-effects.5 Spironolactone and eplerenone are used in the treatment of hypertension, heart failure and oedema in liver failure. Spironolactone and eplerenone are also known as aldosterone antagonists.4

Amiloride and triamterene inhibit sodium reabsorption in the distal tubule. They are weak diuretics1 when administered alone. Amiloride also has some antihypertensive activity. These agents should be used with caution in patients at risk of hyperkalaemia, such as in patients with renal impairment and those taking angiotensin-converting enzyme inhibitors or potassium supplements.5

Carbonic anhydrase inhibitors

Carbonic anhydrase inhibitors inhibit the transportation of bicarbonate out of the proximal convoluted tubule into the interstitium, which leads to less sodium reabsorption at this site, and therefore greater sodium, bicarbonate and water loss in the urine. These are the weakest of the diuretics, and are seldom used in cardiovascular disease. Their main use is in the treatment of glaucoma.1 Carbonic anhydrase inhibitors, such as acetazolamide, are used for the prophylaxis of mountain sickness, which is an unlicensed indication.4

Osmotic diuretics

Osmotic diuretics, e.g. mannitol, are used in a hospital setting for the treatment of cerebral oedema.2 Mannitol is a non-reabsorbable sugar alcohol that acts as an osmotic diuretic, inhibiting sodium and water reabsorption in the proximal tubule, and more importantly, the loop of Henle. As with loop diuretics, mannitol produces relative water diuresis in which water is lost in excess of sodium and potassium. Mannitol is not generally used in oedematous states since initial retention of the hypertonic mannitol can induce further volume expansion, which precipitates pulmonary oedema in heart failure.6

Side-effects

The most common side-effect associated with diuretics is the increased elimination of potassium, resulting in a dangerously low level of potassium in the body. With the exception of potassium-sparing diuretics, diuretics cause loss of potassium, which, if left untreated, can increase the risk of serious heart rhythm disturbances. Taking a potassium supplement or eating high-potassium foods, such as bananas and orange juice, helps to maintain healthy potassium levels. A potential side-effect of potassium-sparing diuretics is a dangerously high level of potassium in people who already have a high potassium level or in those who have kidney disease.5

Diuretics cause the patient to pass more urine than usual, and therefore should not be taken at night before bedtime.2,4 Increased urination occurs most frequently in people taking loop diuretics. This side-effect improves within a couple of weeks of taking the diuretic in most people.1 When taking diuretics, the patient will need to have regular check-ups to monitor potassium levels and kidney function.2

Other potential side-effects of diuretics include:1-3

- Increased thirst
- Urinary incontinence
- Heart palpitations
- Muscle cramps, fatigue or weakness from low potassium levels
- Dizziness or light-headedness
- Numbness or tingling sensations
- Headaches
- A rash
- Impotence
- Menstrual irregularities
- Depression
- Irritability

Allergic reactions: Thiazide diuretics should not be used if the patient is allergic to sulphonamides.

Table II provides a comparison of the classes of diuretics with respect to side-effects and drug interactions.3

Conclusion

Each class of the diuretics works by affecting a different part of the kidney, and have different uses and side-effects, and for which there are different precautions. The efficacy of a diuretic relates to a number of factors, including its site of action, duration of action and dietary salt intake. The choice of diuretic depends on the condition for which it is being prescribed, and on the health of the patient being treated.
Table II: A comparison of the classes of diuretics with respect to side-effects and drug interactions3

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<thead>
<tr>
<th>Class</th>
<th>Side-effects</th>
<th>Drug interactions</th>
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<tr>
<td>Thiazide diuretics</td>
<td>• Hypokalaemia</td>
<td>• Hypokalaemia potentiates digitalis toxicity</td>
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<td></td>
<td>• Metabolic alkalosis</td>
<td>• Beta blockers potentiates hyperglycaemia and hyperlipidaemia</td>
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<tr>
<td></td>
<td>• Hyperuricaemia (at low doses)</td>
<td>• NSAIDs reduce diuretic efficacy</td>
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<td></td>
<td>• Hypovolaemia (dehydration), leading to hypotension</td>
<td>• Corticosteroids enhance hypokalaemia</td>
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<td></td>
<td>• Hyperglycaemia in diabetics</td>
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<td></td>
<td>• Hyponatraemia</td>
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<td>• Hypercholesterolaemia and hypertriglyceridaemia</td>
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<td></td>
<td>• Hypomagnesaemia</td>
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<td></td>
<td>• Hypovolaemia, leading to hypotension</td>
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<td></td>
<td>• Dose-related hearing loss (ototoxicity)</td>
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<td>Potassium-sparing diuretics</td>
<td>• Hyperkalaemia</td>
<td>• ACE inhibitors potentiate hyperkalaemia</td>
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<td></td>
<td>• Metabolic acidosis</td>
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<tr>
<td></td>
<td>• Gynaecomastia (due to aldosterone antagonists)</td>
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<td></td>
<td>• Gastric problems, including peptic ulcers</td>
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<tr>
<td>Carbonic anhydrase inhibitors</td>
<td>• Hypokalaemia</td>
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<tr>
<td></td>
<td>• Metabolic acidosis</td>
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ACE: angiotensin-converting enzyme, NSAIDs: nonsteroidal anti-inflammatory drugs

References
5. South African medicines formulary.11th ed. Cape Town: Division of Clinical Pharmacology, Faculty of Health Sciences, University of Cape Town; 2014.