



# The Ins & Outs of Diuretic Therapy

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Diuretics have become frequently prescribed drugs for the treatment of edematous disorders and arterial hypertension since oral agents became available in the 1950s and 1960s. One must understand their mechanisms of action to anticipate the potential complications associated with their use.

## Sites of action of diuretics

There are four major classes of diuretics and all of them inhibit sodium (and water) reabsorption in different segments of the nephron (Table 1),<sup>1-7</sup> therefore increasing urinary excretion of sodium and urine volume.

**Carbonic anhydrase inhibitors**, the first diuretics made available in the late 1940s,<sup>8</sup> induce only a mild alkaline diuresis in the proximal tubule. Acetazolamide, though, can be used to reduce the intraocular pressure in glaucoma or to alkalinize urine.

**Loop diuretics** (*i.e.*, furosemide, bumetanide) are the most potent diuretics and can induce significant volume depletion. These diuretics are organic anions that are secreted in the lumen of the proximal tubule. They bind to the chloride site of the Na-K-2Cl co-transporter in the luminal membrane located in the thick ascending limb of Henle.

### In this article:

1. Sites of action of diuretics.
2. Clinical uses of diuretics.
3. Adverse effects of diuretics.
4. Management of diuretic resistance.

**Thiazides** (*i.e.*, hydrochlorothiazide, indapamide) are organic anions secreted by the proximal tubule that bind to the chloride site of the Na-Cl co-transporter in the luminal membrane of the distal convoluted tubule. Thiazides can induce hyponatremia because they inhibit urine dilution.

**Potassium-sparing diuretics** are weak because not much sodium is reabsorbed in their site of action, the cortical collecting duct. Spironolactone is an aldosterone antagonist useful in the treatment of congestive heart failure and hepatic cirrhosis.<sup>3,9</sup> Triamterene and amiloride are organic cations secreted by the proximal tubule that bind to the sodium epithelial channel in the luminal membrane in the collecting duct.

These three potassium-sparing diuretics decrease sodium reabsorption and potassium secretion and, therefore, tend to increase kalemia. They are mostly used in combination with thiazides. However, one must be very careful when using potassium-sparing diuretics in the presence of significant renal failure or with the utilization of other drugs that increase kalemia (*i.e.*, potassium supplements, angiotensin-converting enzyme [ACE] inhibitors, angiotensin II receptor antagonists, nonsteroidal anti-inflammatory drugs [NSAIDs]).

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Table 1

## Sites of Action of Diuretics

Carbonic anhydrase inhibitors (*i.e.*, acetazolamide): proximal tubule

Loop diuretics (*i.e.*, furosemide, bumetanide): thick ascending limb of Henle

Thiazides (*i.e.*, hydrochlorothiazide, indapamide): distal convoluted tubule

Potassium-sparing diuretics (*i.e.*, spironolactone, triamterene, amiloride): cortical collecting duct

Finally, there are also osmotic diuretics, such as glucose (in uncontrolled diabetes) and mannitol, that are not part of the four major classes, but do decrease salt and water reabsorption in the proximal tubule and in the loop of Henle.

## Clinical uses of diuretics

These drugs are mostly used for the treatment of edema-forming states and arterial hypertension (Table 2).<sup>3,10</sup> Edema is detected when the accumulation of fluid within the extracellular space exceeds 3 L to 4 L. Urinary retention of salt and water is responsible for this and can be observed in congestive heart failure, hepatic cirrhosis with ascites, nephrotic syndrome, and acute or chronic renal failure. Diuretics are given to reduce the increased extracellular fluid volume to its normal value.

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Table 2

## Clinical Uses of Diuretics

### Generalized edema

Congestive heart failure  
Hepatic cirrhosis  
Nephrotic syndrome  
Acute or chronic renal failure

### Arterial hypertension

Thiazides remain very useful in the treatment of arterial hypertension because of their efficacy, their low cost and the long-term experience we have with these drugs.<sup>10</sup> With the lower dosage of 25 mg of hydrochlorothiazide daily, very few side effects are observed.

## Adverse effects of diuretic therapy

Fluid and electrolyte disorders resulting from the utilization of diuretics are usually observed within the first few weeks of treatment (Table 3).<sup>11</sup> Plasma electrolytes, therefore, should be monitored during this period. The following is a brief description of some adverse effects of diuretic therapy.

**Volume contraction** resulting from an excessive diuresis can induce a pre-renal failure because of a marked rise in the ratio of blood urea to plasma creatinine. This complication is most often observed with the potent loop diuretics.

**Hyponatremia** is more often observed with thiazides because they decrease the urinary excretion of free water.<sup>12</sup>

**Hypokalemia** occurs very frequently with loop diuretics or thiazides, especially when sodium intake has not been reduced. In fact, these diuretics are by far the most common cause of

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## Practice Pointer

Hyperkalemia is a life-threatening electrolyte abnormality, which is induced by potassium-sparing diuretics — especially in the presence of significant renal failure or with the concomitant use of other drugs that increase kalemia.

hypokalemia.<sup>13-14</sup> The increased delivery of sodium to the collecting duct accelerates potassium secretion at this level and its excretion into the urine.<sup>13</sup> Potassium-sparing diuretics or potassium supplements are added if hypokalemia cannot be prevented, or if it represents a serious threat.

**Hyperkalemia** is a life-threatening electrolyte abnormality induced by potassium-sparing diuretics, especially in the presence of significant renal failure or with the concomitant use of other drugs that increase kalemia.<sup>15</sup>

**Hypomagnesemia** occurs mostly with loop diuretics since most of the filtered magnesium is reabsorbed in the thick ascending loop of Henle. This electrolyte disorder can induce cardiac arrhythmias.

**Metabolic alkalosis** with volume contraction occurs frequently with the use of thiazides and loop diuretics.

**Metabolic acidosis** can be observed with carbonic anhydrase inhibitors and potassium-sparing diuretics.

**Hyperuricemia** is observed with most diuretics and may precipitate an acute gout attack.

## Management of diuretic resistance

Several therapeutic manoeuvres can be tried in order to overcome diuretic resistance in patients, including the following (Table 4):<sup>3,16</sup>

Table 3

### Adverse Effects of Diuretic Therapy

-Volume contraction	-Hypomagnesemia
-Hyponatremia	-Metabolic alkalosis
-Hypokalemia	-Metabolic acidosis
-Hyperkalemia	-Hyperuricemia

**Rule out diuretic noncompliance**, which is observed quite frequently.

**Reduce salt and water intake.** A patient can easily decrease his daily sodium chloride intake by 50% by reducing the amount of salt in his diet. Diuretic efficacy is greatly improved by this salt restriction.

**Bedrest** helps to mobilize refractory edema.

**Stop the use of NSAIDs**, which decrease the synthesis of prostaglandins and the diuretic-induced natriuresis.

**Optimize the treatment of the underlying disorder** by a more specific therapy. For example, a patient with congestive heart failure may benefit from digitalis or an angiotensin II receptor antagonist, whereas corticotherapy may improve a patient with glomerulonephritis and nephrotic syndrome.

**Increase the diuretic dosage** if renal failure is reducing the amount of diuretic in the tubular lumen and its corresponding effect on sodium reabsorption.

**A combination of diuretics** inhibiting different nephron sites of sodium reabsorption is usually more effective than a single agent.<sup>17</sup> For example, a thiazide diuretic can be added to a loop diuretic, increasing diuresis even when there is severe renal failure.<sup>18-19</sup>

**Intravenous administration of the diuretic.** Because massive edema may be accompanied by swelling of the intestinal mucosa and impaired absorption of the oral diuretic, a patient may be

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Table 4

## Management of Diuretic Resistance

Rule out diuretic noncompliance  
Reduce salt and water intake  
Bedrest  
Stop the use of nonsteroidal anti-inflammatory drugs  
Optimize the treatment of the underlying disorder  
Increase the diuretic dosage if renal failure occurs  
A combination of diuretics  
Intravenous administration of the diuretic  
Intravenous salt-poor albumin

switched to the intravenous administration of the diuretic.

**Intravenous salt-poor albumin** temporarily increases the plasma volume, the amount of diuretic in the intravascular space and the diuretic effect.<sup>20</sup>

## Conclusion

In summary, the following three points must be emphasized. First, when diuretics are prescribed, salt intake must always be reduced for two reasons: to improve the efficacy of the diuretics, and to prevent important losses of potassium caused by thiazides and loop diuretics. Second, thiazides are very useful to treat arterial hypertension. And third, always remember that when dealing with diuretic therapy, widely used potassium-sparing diuretics become very dangerous when severe renal failure is present. Hyperkalemia is a silent killer. [CME](#)

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