

THIAZIDE DIURETIC-INDUCED HYPOKALEMIA: PREVENTION AND TREATMENT

Thiazide diuretics are frequently used in the treatment of hypertension. Expert committees and health organizations from several countries continue to recommend them as one of the initial therapies. These agents have been recognized to lower serum potassium in a dose-dependent manner, and this reduction has been an ongoing concern due to the fear that hypokalemia could provoke cardiac arrhythmias. These concerns have prompted clinicians to add a potassium supplement or combine the diuretic with a potassium-sparing agent. The following is a brief review of the relative advantages and respective roles of K supplements and K-sparing agents in the prevention and management of diuretic-induced hypokalemia.

Who is at risk from diuretic-induced hypokalemia?

Hypokalemia ($K < 3.5$ mmol/L) should be avoided and aggressively treated in certain patients who are vulnerable to cardiac arrhythmias and other consequences of hypokalemia. Those at risk include:

- the elderly
- patients receiving digoxin
- patients with myocardial disease (CHF, LVH, history of MI, antiarrhythmic therapy)
- diabetics, where the degree of hypokalemia may affect insulin action
- patients who develop signs or symptoms attributable to hypokalemia

In such patients, measures designed to prevent hypokalemia should be instituted when therapy with a diuretic is initiated. In other patients requiring a diuretic, the general approach has been to use a K supplement or K-sparing agent only if the initial pretreatment serum potassium is low (< 3.5 mmol/L) or if this low level is reached after the diuretic is started. However, cumulative evidence from hypertension trials and several case-controlled studies strongly suggests that thiazide diuretics increase the risk of sudden death even in patients without clinical evidence of heart disease or predisposition to arrhythmias. Moreover, the two case-controlled studies were consistent in their finding that thiazides were associated with a two-fold risk of sudden death compared to the combination of thiazide plus a K-sparing agent. These results suggest that even patients without evidence of heart disease may be at risk from thiazide therapy, and that the addition of a K-sparing agent (not a K supplement) may lower the risk.

Prevention of Diuretic-Induced Hypokalemia: K-supplement vs. K-sparing agent

At low doses (i.e., HCTZ ≤ 25 mg/d), thiazides do not produce depletion of total body potassium stores. Although K supplements are commonly used with thiazide diuretics to prevent hypokalemia, they may be of little benefit because they exert little effect on serum K when potassium stores are not depleted. As more potassium is ingested, more is excreted in the urine, with only a slight increase or no change in the serum level. In contrast, K-sparing agents correct the alkalosis and reduce urinary potassium losses by inhibiting the secretion of K^+ and H^+ ions in the distal tubule. In addition, results from several intervention trials in the elderly and the two observational studies cited above suggest that combined therapy with a low-dose thiazide and a K-sparing agent may further reduce mortality from coronary heart disease in patients with hypertension. Thus, K-sparing agent are preferred over K supplements for the prevention of diuretic-induced hypokalemia, and their routine use should be considered in all diuretic-treated hypertensive patients (excluding those with renal dysfunction, diabetic nephropathy or receiving ACE inhibitors). (Personal Communication: Dr. M. Myers)

Treatment of Non-Urgent, Mild to Moderate Diuretic-Induced Hypokalemia

The majority of these patients have a plasma potassium concentration of 3 to 3.5 mmol/L and are usually asymptomatic. Treatment in this setting is directed toward replacing the lost potassium. Low doses of K supplements are usually ineffective, since at least 40 to 60 mmol per day of K supplement is usually required to correct the deficit and maintain serum K within the normal range in patients in whom potassium losses are continuing. However, the persistence of urinary K losses, hypomagnesemia, and systemic

alkalosis often prevents complete correction of hypokalemia despite use of large doses of K supplements. Because K-sparing agents reduce renal excretion of potassium, magnesium, and hydrogen ions, they are generally more effective for treatment of diuretic-induced hypokalemia than K supplements.

Treatment of Urgent, Severe Hypokalemia

When oral potassium supplementation is used to treat severe hypokalemia, the liquid dosage form of potassium chloride should be used. Solid oral dosage forms (e.g., K-Dur[®], Micro-K[®]) are sustained-release formulations designed to release potassium slowly over time. The liquid dosage form is absorbed more rapidly, achieving peak K levels in 1.5 h compared with 4 h for the SR products. This difference in T_{\max} should be considered when interpreting a K level following a dose of supplement.

Potassium-sparing agents are less effective for the urgent treatment of severe hypokalemia for at least two reasons. First, unless they are combined with a K supplement (which can lead to serious hyperkalemia and should only be considered when renal K losses are very high), they cause a net gain only as large as the dietary potassium intake (~40 to 50 mmol/d), which may delay repletion of potassium stores and correction of hypokalemia. Second, in the setting of acute hypokalemia and potassium depletion, the kidney attempts to conserve potassium, reducing the rate of excretion (~2 to 3 mmol/hr). With such minimal urinary losses, a K-sparing agent would not be expected to significantly and rapidly increase serum potassium. Therefore, in this setting, K supplements are more effective than K-sparing agents.

Potassium Supplements

When a potassium supplement is indicated, potassium chloride is the preferred salt. The Formulary currently lists two sustained-release products, K-Dur[®] 20 mmol tablets and Micro-K[®] 10 mmol capsules, as well as a liquid containing 20 mmol per 15 mL. **To avoid confusion, orders for oral KCl should be written generically and should specify the dose in mmol (not number of tablets); use of trade names is discouraged.** Alkaline salts of potassium (e.g., potassium citrate; K-Lyte[®], Polycitra-K[®]) should be reserved for patients with renal tubular acidosis or renal stones.

Potassium-sparing agents

- Spironolactone is probably the most effective potassium-sparing agent, especially in patients with elevated aldosterone levels. However, its onset of effect is delayed several days and its chronic use is associated with gynecomastia. Spironolactone use may increase due to the favourable results from the recently published RALES study.
- Amiloride is almost as effective in conserving potassium as spironolactone. Unlike spironolactone, it has a negligible effect on blood pressure when given as monotherapy. Long-term studies suggest that it is well tolerated. Amiloride is the preferred agent for the prevention of diuretic-induced hypokalemia. Amiloride doses of 2.5 mg are approximately equivalent to 20 mmol of potassium supplement; 5 mg = 40 mmol; and 10 mg = 60 mmol.
- Triamterene is less effective than either amiloride or spironolactone and is generally considered to be equivalent to potassium supplements. Long-term use of triamterene has been associated with nephrotoxicity manifested by abnormalities at a microscopic level.

Cost of Therapy

Potassium supplements are not covered by the Ontario Drug Benefit (ODB) Program. The cost of 40 mmol per day ranges from \$6 to \$16 per month. Thiazides combined with K-sparing agents are covered by ODB. Amiloride 5 mg plus HCTZ 50 mg at a dose of one-half tablet daily, or spironolactone 25 mg plus HCTZ 25 mg at a dose of one tablet daily, each cost approximately \$3 per month.