Managing Diuretic-Induced Hypokalemia in Ambulatory Hypertensive Patients

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The majority of hypertensive patients receiving diuretics will not develop hypokalemia, and routine potassium supplementation is superfluous in many cases. In patients presenting with hypokalemia, predisposing factors should be considered before commencing therapy. Many treatment alternatives exist for managing hypokalemia, and physicians aware of all the options will be able to control patients effectively and many times at a much lower cost.

In today's era of cost containment and cost effectiveness in the health care field, many suggestions are found to help reduce costs of both diagnostic procedures and drug therapy. One area of the ambulatory setting in which many health dollars are spent each year is in the prevention and management of diuretic-induced hypokalemia in hypertensive patients.

Potassium salts are among the most widely prescribed drugs in the United States, with a conservative estimate of 20 to 30 billion milliequivalents prescribed annually.[1] A vast amount of these electrolyte supplements are prescribed to hypertensive patients receiving diuretics. Potassium-sparing diuretics are also popular, especially in combination formulations, with Dyazide being the most frequently prescribed drug in 1980.[2]

Guidelines for managing diuretic-induced hypokalemia have changed considerably over the past decade. The following review discusses the incidence, causes, and current treatment alternatives in the management of hypokalemia in essential hypertensive patients on diuretic therapy.

Incidence of Hypokalemia

The incidence of diuretic-induced hypokalemia in the ambulatory hypertensive population is difficult to quantify because of problems with measuring body potassium stores, lack of suitable control data in most studies, and potassium deficits resulting from causes other than diuretic therapy.[1] In an excellent review on diuretics and potassium metabolism, Kassirer and Harrington[1] state that typical serum concentrations of potassium average 3.3 to 3.8 mEq/L in patients on diuretics, and values

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below 3.0 mEq/L are encountered rarely. The majority of studies reporting total body potassium stores are also in agreement that little or no potassium deficiency occurs in hypertensive patients prescribed diuretics.[3-7] Diuretic-induced hypokalemia is more common and serious in edematous patients with cardiac or hepatic disease, and these patients are more likely to need potassium correction.

A Veterans Administration cooperative study in 1962[8] reported an 8.7 percent incidence of hypokalemia, defined as a serum potassium below 3.5 mEq/L, in diuretic-treated hypertensive patients. Other studies have reported an incidence of 15 to 48 percent.[9] Several of these studies included patients with various disease states. Recently Lemieux et al[10] reported a 6 percent incidence of serum potassium less than 3.5 mEq/L in 50 ambulatory patients treated for uncomplicated hypertension who were administered 50 to 100 mg of hydrochlorothiazide daily. The low serum potassium values were transient, occurring during the first few weeks of treatment, and not associated with symptoms sufficient enough to justify potassium supplementation. Serum potassium levels of less than 3.0 mEq/L occur in 2 to 4 percent of diuretic-treated hypertensive patients.[9,11] Unfortunately, the reality is that 30 to 78 percent of all diuretic-treated hypertensive patients are given potassium supplements or potassium-sparing diuretics early in their management in spite of some having completely normal serum potassium values.[7,11-13]

Guidelines for managing hypokalemia have varied tremendously over the past decade. The 1968 *Textbook of Medicine*[14] states that it is "usually necessary to give potassium chloride" in thiazide-treated hypertensive patients. Twelve years later another major medicine text states, "hypokalemia need only be treated when it is severe (less than 3.0 mEq/L), symptomatic, or when seen in patients with diabetes mellitus or heart disease requiring digitalis therapy."[15] Recommendations between these two extremes abound in the medical literature. Some currently accepted guidelines for administering potassium supplementation or one of the potassium-sparing diuretics are listed in Table 1.[15-17] The importance of adequately determining the need for potassium supplementation cannot be overemphasized, since in routine practice potassium supplements, once started, are rarely stopped.[13] The widespread routine use of potassium supplements and potassium-sparing diuretics may indeed do more harm than good because of the risk of hyperkalemia.[18]

Causes of Hypokalemia

Managing hypertensive patients with diuretic-induced hypokalemia is an area where individualization of treatment and seeking out secondary factors can be cost effective. Before opting to treat the hypokalemic patient, causes other than or in addition to the diuretic should be considered.

Excessive Sodium Ingestion

Hypokalemia is greater in those patients who have a high intake of sodium. The more sodium ingested, the greater the exchange at the distal tubule for potassium. Ram and Kaplan[19] compared potassium wastage in hypertensive patients on diuretics while they received either a normal sodium dietary intake (175 to 200 mEq/d) or one that was moderately sodium restricted (75 mEq/d). Potassium wastage was about one half as much on the lower sodium diet. However, patients on diuretics and consuming a very low sodium intake (44 mEq/d or less) may actually have an increase in potassium wasting due to marked secondary aldosteronism.[20]

It is a good idea to review periodically dietary sodium intake in all patients who are hypokalemic. Excessive sodium intake secondary to drugs must not be overlooked either. Alka-Seltzer and baking soda are two common home remedies high in sodium that are often consumed on a regular basis by patients. One of the easiest ways to reduce the incidence of hypokalemia associated with diuretic therapy is to limit salt intake to at least 4 to 6 g per day. This may also permit the use of a lower diuretic dose and makes antihypertensive effect maximal.[21]

Duplication of Diuretics

It is important to obtain a careful medication history in all hypertensive patients presenting with

Table 1. Indications for Potassium Replacement

Therapeutic
Serum potassium less than or equal to 3.0 mEq/L (some prefer treating between 3.2 to 3.5 mEq/L)
Symptoms of hypokalemia develop; many minor symptoms reported by patients (ie, cramps, tiredness, and lethargy) are due to volume changes associated with diuretic administration and are not always corrected by restoring serum potassium to normal
Patients on digitalis with a serum potassium less than or equal to 3.5 mEq/L
Patients with arrhythmias or heart disease
Prophylactic
Patients receiving digitalis preparations or corticosteroids with diuretics
Diabetic patients (use potassium supplements or potassium-sparing agents with caution, since there is an increased propensity of diabetic patients to develop hyperkalemia)
Edematous states (cardiac, hepatic, nephrotic)
Poor dietary intake (elderly, ill, eating poorly, or dieting)
Excessive sodium intake
Diuretic-treated patients who may become refractory because of secondary hyperaldosteronism
Patients performing hard physical labor in hot climates, and patients with a high degree of physical activity

hypokalemia. It is not unusual to find patients receiving several different diuretics from different physicians and pharmacies. Unstandardized labeling practices often lead to confusion where generic substitution is allowed. Patients may have prescriptions for Oretic, Esidrix, and hydrochlorothiazide, unaware that each is the same medication. They may also be receiving diuretics from friends or neighbors, most commonly to help lose weight caused by swelling, bloating, or premenstrual edema.

Drugs and Foods Causing Hypokalemia

Concomitant ingestion of certain foods or drugs with diuretics may be the precipitating factor in causing hypokalemia (Table 2). Corticosteroids and laxatives deserve special attention because of their frequency of use and their notoriety in causing hypokalemia when used in conjunction with diuretics.

Corticosteroids cause hypokalemia by several mechanisms. The mineralocorticoid activity of steroids leads to an aldosterone-like effect at the distal tubule, thereby promoting sodium and potassium exchange. The glucocorticoid activity of the steroids improves glomerular filtration rate and also increases catabolic activity, both predisposing factors to hypokalemia.[22] Patients tapering off high doses of steroid should be re-evaluated periodically to assess the necessity for potassium supplementation.

Stimulant and osmotic cathartics or enema abuse may frequently induce hypokalemia.[22,23]

Table 2. Foods and Drugs Implicated In Causing Hypokalemia

ACTH
Corticosteroids
Carbenoxolone
Carbenicillin
Laxatives
Polymyxin B sulfate
Penicillin
Amphotericin B
Tetracycline (outdated)
Licorice and licorice-containing products
Carbonic anhydrase inhibitors
Kayexalate
Alkali ingestion
Barium
Diuretics
Glucose
Mannitol
Insulin

Table 3. Nondrug Causes of Hypokalemia

Poor Intake
Dieting
Elderly
Alcoholism
Hypomagnesemia
Gastrointestinal Wasting
Diarrhea
Villous adenoma of colon
Vomiting
Nasogastric suction
Gastrocolic duodenal colic fistula
Pancreatic islet non-beta cell tumors
Ureterosigmoidostomy
Kidney
Primary or secondary aldosteronism (hyperglycemia, adrenal adenoma, bilateral adrenal hyperplasia, malignant hypertension, renal artery stenosis, adrenogenital syndrome)
Renal tubular acidosis
Diabetic ketoacidosis
Skin
Excessive sweating
Potassium Redistribution
Familial periodic paralysis

Patients do not need to develop diarrhea to become hypokalemic. A difficult aspect of the management of these patients includes confirming the surreptitious use of these agents.

The potential for licorice or licorice-flavored products to cause hypokalemia, owing to their aldosterone-like activity should also be re-emphasized because of several case reports implicating these as a major cause of hypokalemia.[24-26]

Diseases or Clinical States Causing Hypokalemia

Before incriminating diuretic therapy as the sole cause for hypokalemia, diseases or clinical states in which electrolyte imbalance is common must be considered (Table 3).

Sudden increases in potassium loss, such as during intercurrent episodes of anorexia, vomiting, diarrhea, or excessive sweating, that may acutely disturb potassium homeostasis should be reported by the patient. Hypokalemia presenting during an acute illness will usually not require continual potassium supplementation after resolution of the problem.

Managing Hypokalemia

Once precipitating factors of hypokalemia, other than diuretic therapy, have been ruled out, the options available to manage specific patients include use of the smallest effective dose of diuretic that will produce the necessary result, a short-acting diuretic, food supplementation, liquid potassium supplementation, potassium supplements in tablet formulations, salt substitutes, and potassium-conserving diuretics. These are all viable management alternatives in selected patients, with differences in efficacy, compliance, and cost.

Decreasing the Dose of Diuretic

The larger the dose of diuretic, the greater the chance of hypokalemia.[27] The dose of diuretic may be lowered successfully in some patients with established hypertension while still maintaining adequate control. Success rate may be higher in patients who have lost weight, stopped smoking, and decreased their sodium intake and are now exercising. In some hypertensive patients, lower doses of a diuretic may be effective, and prescribing more will not produce better results but will increase the chances of hypokalemia.[27,28]

Use of a Short-Acting Diuretic

Switching from a long-acting diuretic (eg, chlorthalidone) to a short-acting diuretic (eg, hydrochlorothiazide) administered as a single morning dose may reduce the incidence of hypokalemia.[27,29] The long-acting diuretics have a greater potential to produce protracted diuresis and volume contraction with secondary hyperreninism and hyperaldosteronism, leading to the loss of potassium. Switching diuretics may be a viable alternative in selected patients.

Food Supplementation

Ingesting potassium-rich foods is an easy and acceptable way to make up for potassium loss.[30] A diet providing 100 mEq of potassium per day is a reasonable goal in the treatment of most adults.[31] Unfortunately, dietary potassium is often deficient in situations for individuals who are elderly, ill, eating poorly, or are dieting for weight reduction.[32] Lists of potassium content in foods are readily available in most dietary pamphlets.

Increasing potassium intake through food supplementation has its advantages and disadvantages. Most patients can find a food they like that is also fairly high in potassium and may not think of this as an added medical expense, since they work the cost into their food budget. However, many of the foods high in potassium are expensive. A disadvantage of food supplementation is that the ratio of potassium is rarely lower than 1 mEq of potassium per 20 calories.[33] A supplement of 40 mEq of potassium per day would therefore necessitate adding 800 more calories to the diet. This is obviously unacceptable in obese and diabetic patients. Variation in soil, climate, ripeness, food processing, and preparation methods all lead to a high variability of potassium content in food supplements.[33] Some foods high in potassium may also be high in sodium, and many are deficient in chloride.[34]

Increasing the dietary intake of potassium for some patients is well worth the effort, since it may prevent problems. The routine dictum, "take your diuretic with orange juice or a banana," however, may not only provide false insurance but may also be dangerous in obese, diabetic, and hypokalemic patients. This method of potassium supplementation should not be relied upon when maintaining a serum potassium greater than 3.5 mEq/L is mandatory, as in patients receiving a digitalis preparation.

Liquid Potassium Supplementation

Various liquid preparations of potassium are safe and effective for prevention and treatment of hypokalemia. The chief advantage of these preparations is their low cost. However, the newer, more palatable preparations (flavored powders and effervescent tablets) are expensive.

Potassium chloride is the drug of choice for replacement of potassium. Potassium depletion may be accompanied by metabolic alkalosis and hypochloremia. None of the alkaline salts (ie, potassium bicarbonate, potassium citrate, or potassium gluconate) will reverse the hypokalemic metabolic alkalosis. Even though these preparations taste better and are therefore better accepted by patients, they should be the drugs of choice only in certain circumstances, such as renal tubular acidosis, in which extra chloride is not advised.

The most notable disadvantage of liquid potassium supplements is poor patient compliance due to unpalatability.[35,36] Abdominal cramps, nausea, diarrhea, and vomiting may also occur.[36] These problems can sometimes be controlled by recommending various liquids for diluting the preparations. Patients are frequently told to use orange juice or water for dilution, and they do not con-

sider other alternatives such as apple juice, cranberry juice, grapefruit juice, pineapple juice, lemonade, and limeade. Storing the liquid potassium solutions in the refrigerator may also improve patient acceptability. It is important to ensure that the potassium preparations are being adequately diluted in at least 6 to 8 oz of liquid. Inadequate dilution may be the cause of nausea or vomiting. Another disadvantage of the liquid is inconvenience, since some measuring and mixing is necessary.

Unflavored potassium chloride should be tried initially because of its low cost. When adequately diluted, taken with meals, and slowly sipped over 5 to 10 minutes, these preparations should be acceptable to the majority of patients.

Potassium Supplementation with Tablet Formulations

Several wax-matrix, slow-release potassium chloride tablets are currently available. These preparations contain between 8 and 10 mEq of potassium per tablet. The package inserts recommend these products be reserved for patients who cannot tolerate or refuse to take liquid or effervescent preparations or for patients noncompliant with these preparations; gastrointestinal ulceration, bleeding obstruction, perforation, and poisoning (in children) occur, though rarely, with the tablets but have not been reported with liquid potassium chloride.

Most of the reports of ulceration with the tablet formulations appear in association with predisposing conditions. Esophageal ulcerations are most common in patients with left atrial hypertrophy with subsequent compression of the esophagus. Patients with esophageal compression resulting from other causes, dysphagia, phrenic nerve paralysis, or delayed esophageal motility should not be given potassium tablet formulations. This may include patients with goiters, polymyositis, scleroderma, Sjögren's syndrome, and severe diabetic autonomic neuropathy. Small-bowel ulcerations appear most frequently in patients with delayed intestinal transit time.[37] Patients predisposed to a delayed intestinal transit include the elderly or immobile and also patients on medications with high anticholinergic activity. Slow-release tablets should also not be used in patients with partial bowel obstruction, strictures, diverticula, bowel atony, or ulcerative bowel disease.[37] Mouth ulceration may occur if these preparations are retained in the mouth.[38]

Slow-release potassium tablets have a definite place in the treatment of hypokalemia. They are considered effective and especially beneficial in patients getting gastrointestinal upset, nausea, vomiting, bad taste, anorexia, or diarrhea from the solutions. Selected disease states predispose patients to problems with these preparations.

Salt Substitutes

Interest in the use of salt substitutes as a source of potassium was revived by Sopko and Freeman several years ago.[39] They analyzed common brands of commercially obtained salt substitutes and reported a potassium content of 50 to 65 mEq per teaspoonful, predominately the chloride salt. A blind taste preference study was also done in 28 patients. Neocurtasal and Morton Salt Substitute had the highest overall preference scores. Morton Salt Substitute is recommended because it is less expensive and readily available.

Minor problems in using salt substitutes have been encountered, the most frequent of which is alteration in the taste of certain foods. Most patients accept this and after several weeks seem to develop a tolerance. For others another brand of salt substitute may be tried. Selected patients may ultimately reject this form of potassium replacement; however, good patient communication appears to improve success. Another problem frequently encountered when salt substitutes are recommended is that patients go to the grocery store and buy onion salt, garlic salt, or seasoned salt in the belief that they are salt substitutes. These products contain as much sodium as regular salt. Be specific with patients when recommending a salt substitute, and write the product on a piece of paper so they can refer to it when they go shopping. Mortons Lite Salt, basically a 50/50 mixture of sodium chloride and potassium chloride, is often acceptable to patients not tolerating a salt substitute.

Salt substitutes can be used on a supplemental basis, or a specific dose can be prescribed. This can be done by telling the patient to measure out one-fourth to one teaspoonful of the salt substitute in the morning, put it in an empty salt shaker, and during the day use this on their food. Compliance may be improved by advising patients to consume the total dose at one main meal instead of throughout the day.

Although potassium chloride is readily available as a salt substitute, it must be considered more as a drug than as a food-flavoring agent, since it is capable of producing severe harm and even death. Adequate potassium supplementation can be achieved inexpensively in patients who tolerate the slight taste alteration in their food. Salt substitutes should not be used in patients with impaired renal function or patients who are also taking a potassium-sparing diuretic.[17]

Potassium-Sparing Diuretics

Spironolactone and triamterene, usually in combination with a thiazide diuretic, are frequently used in treating or preventing hypokalemia in diuretic-treated hypertensive patients.[2] Amiloride, a recently released potassium-conserving diuretic, is also an effective alternative. If serum potassium does not increase with 60 to 100 mEq of an oral potassium supplement, substitution of one of these drugs may prove of benefit. In most nonedematous thiazide-treated patients with mild to moderate hypertension, potassium-sparing diuretics should not be the first drugs of choice because of their expense and side effects. Their chief indication is in the management of edematous conditions in which hypokalemia is likely to exist because of secondary hyperaldosteronism.[17,30] This criterion most commonly includes those hypertensive patients who also suffer from congestive heart failure, cirrhosis with ascites and edema, idiopathic edema, or nephrotic syndrome.

The Boston Collaborative Study reported a 20.8 percent incidence of adverse reactions in hospitalized patients receiving spironolactone of which 8.6 percent consisted of hyperkalemia.[40] An important finding of this report was that the frequency of hyperkalemia increased with the blood urea nitrogen (BUN), a 20.3 percent incidence in patients with BUN greater than or equal to 50 mg/ 100 mL. In nonazotemic patients not receiving supplemental potassium, a 2.6 percent incidence of hyperkalemia has been reported.[40] Spironolactone can also cause gynecomastia in men and various endocrine effects in women.[41-43]

Hansen and Bender[44] reported triamterene-induced hyperkalemia in 14 percent of 839 patients when used alone and in 7 percent of patients treated with a triamterene-hydrochlorothiazide combination. Up to 26 percent of diabetic patients treated with triamterene have developed hyperkalemia.[45] Triamterene is less expensive than spironolactone but may be less effective.[1]

Amiloride has been widely used abroad for many years and is pharmacologically similar to triamterene. It is as effective as spironolactone and triamterene as a potassium-sparing agent and appears to have an antihypertensive effect similar to spironolactone.[46] Side effects are minimal; however, it can cause hyperkalemia, which may be fatal.[46,47] Risk of hyperkalemia is greater in patients with renal impairment, diabetes mellitus, and in the elderly. Amiloride is effective when administered once a day, but it probably offers no great advantage over spironolactone, which has also been reported effective when prescribed in a single daily dose regimen.[48,49]

The use of potassium-sparing diuretics for the management of hypokalemia is fairly safe overall, but patients must be monitored carefully, since hyperkalemia may be severe and can be fatal. These agents are fairly similar in their ability to conserve potassium,[50] and spironolactone and amiloride may add to the antihypertensive efficacy of the thiazide diuretics. Do not give these medications to patients receiving supplemental potassium or salt substitutes, since this combination is associated with a high incidence of hyperkalemia.

Conclusion

Potassium supplementation is not routinely needed in the majority of patients with mild to moderate hypertension treated with diuretics. In patients presenting with hypokalemia, predisposing factors should be ruled out before commencing

treatment. Many treatment alternatives exist for managing hypokalemia, and each may be the method or drug of choice in selected patients. Physicians aware of all the options will be able to manage patients effectively and often at a much lower cost.

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