Thiazide Treatment of Systemic Hypertension: Effects on Serum Magnesium and Ventricular Ectopic Activity

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Clinical and investigational evidence has proved an association between thiazide-induced electrolyte imbalances and ventricular arrhythmias. It is hypothesized that this increases the potential for sudden unexplained death. Elderly hypertensive patients are at particular risk because of their tendency to have significantly depressed serum magnesium levels, which decrease even further when treated with thiazide diuretics. Potassium supplementation does not effectively restore electrolyte balance unless accompanied by magnesium. Therefore, concomitant administration of potassium and magnesium supplementation appears to be an approach to reducing the risk of arrhythmias and death in thiazide-treated hypertensive patients. (Am J Cardiol 1989;63:22G–25G)

Thiazide diuretics, alone or in combination with other agents, remain the treatment of choice for many patients with mild to moderate hypertension. A well-established record of efficacy and patient tolerability have contributed to their popularity. However, long-term use of thiazides has a documented association with the development of metabolic abnormalities, including glucose intolerance, hyperlipidemia, and such electrolyte imbalances as hyponatremia and potassium and magnesium deficiency. The link between thiazide therapy and hypokalemia, with clinical manifestations of cardiac arrhythmia, weakness, fatigue and muscle cramps, is established. It is less widely known that thiazides also cause magnesium depletion, an important contributor to ventricular ectopic arrhythmia and refractory potassium depletion (Fig. 1).1,2

MAGNESIUM DEFICIENCY

The term “magnesium deficiency” refers to less normal amounts of magnesium in body tissue, whereas “hypomagnesemia” indicates low serum levels of magnesium (normal range, 1.7 to 2.4 mEq/liter). The 2 do not always coexist: intracellular magnesium depletion can occur in the presence of normal serum magnesium levels,1 but the presence of hypomagnesemia always indicates magnesium deficiency. Magnesium deficiency can result in overt symptoms of hallucination, tetany, seizures and emotional lability. Magnesium deficiency can be found in association with alcoholism, diabetes, advanced age, other electrolyte imbalances, gastrointestinal or renal disease, and diuretic or digitalis therapy.

CLINICAL CONSEQUENCES OF MAGNESIUM AND POTASSIUM LOSS

Loss of magnesium and potassium creates a disturbing electrolyte imbalance in which the result is increased risk for arrhythmias and (it is hypothesized) sudden cardiac death. In fact, the first 20 years of thiazide use were marked by over 150 anecdotal reports suggesting a relation between thiazide use, hypokalemia and arrhythmias. More recently, results from controlled studies have strengthened the association between electrolyte de-arrangements—specifically, depletion of potassium and magnesium—and increased cardiac risk: Holland et al4 found arrhythmia in 7 of 21 patients treated with thiazides. In a study by Lown et al5 hypokalemia-induced arrhythmias were associated with diuretic therapy in 24%
FIGURE 1. Effects of long-term hydrochlorothiazide therapy on serum magnesium (Mg) and potassium levels. In a study of 38 patients, the degree of magnesium and potassium loss was directly related to the dosage of hydrochlorothiazide. An initial dosage of 25 mg daily was increased in 50-mg increments every 4 weeks to a maximum of 200 mg/day. Therapy was continued for 24 weeks (long-term segment) after the dosage increase period (short-term segment). Decreases in magnesium and potassium levels were greater with increasing diuretic doses and during long-term follow-up than during the short-term dosage adjustment period.

FIGURE 2. Association between thiazide treatment and ventricular premature complexes (VPCs). The number of VPCs is greater during thiazide therapy than it is before treatment begins. This effect is most pronounced during exercise.

of patients with sudden cardiac death. Wester and Dyckner\(^6\) correlated decreased levels of serum, skeletal muscle, and intracellular magnesium with increasing duration of thiazide therapy; magnesium depletion was also related to the onset of ventricular ectopy.

My colleagues and I also investigated the relation between potassium and magnesium levels and cardiac arrhythmias.

**STUDY DESIGN**

We evaluated 38 patients with mild to moderate hypertension who had hypokalemia, palpitations or cardiac arrhythmia. Study participants received 50 to 100 mg of thiazide for 1 to 3 months; blood pressure and serum potassium were measured at regular intervals throughout the study. All patients were evaluated for arrhythmia twice, before and after initiation of thiazide treatment. Cardiac rhythm was monitored by way of electrocardiography standing at rest and during Bruce stage 1 treadmill exercise that continued for at least 5 minutes. The frequency of ventricular premature complexes (VPCs) during control periods (at rest) was compared with those during exercise. The paired t test was used to determine the significance of findings.

**RESULTS**

Results showed a correlation between thiazide therapy, hypokalemia and increased incidence of VPCs. At standing rest before initiation of therapy, VPCs averaged 0.60 beats/min. This increased to 1.40 beats/min during treatment with thiazides. During exercise, the biggest change in ventricular ectopic activity occurred. Data obtained during 5 minutes of Bruce stage 1 exercise (1.7 mph at a 10% grade) from patients receiving thiazide therapy showed a VPC frequency of 5.70 beats/min, an increase from the exercise baseline frequency of 0.50 beats/min (Fig. 2). There was no significant increase in the frequency of ventricular ectopic beats during the control period when no thiazides were given, indicating that exercise itself was not responsible for the increase in VPCs. The correlation between serum potassium during thiazide therapy and the incidence of VPCs showed that more ectopic activity occurred at lower levels of serum potassium. There was also a distinct association between the serum magnesium, the change in magnesium that occurred between baseline and treatment periods, and the incidence of ventricular ectopic beats (Fig. 3). These findings present strong circumstantial evidence that magnesium and potassium deficiency resulting from thiazide therapy directly contribute to ventricular ectopy, ultimately increasing the potential risk for sudden death. They also present a strong clinical rationale for the use of potassium and magnesium supplementation in patients taking thiazide diuretics.

**INCIDENCE OF MAGNESIUM DEPLETION IN ELDERLY HYPERTENSIVE PATIENTS**

All hypertensive patients receiving thiazide therapy
are at risk of having potassium and magnesium deficiencies, with the concomitant potential for arrhythmias. This sequence of events is particularly dangerous for the elderly, in whom cardiac function is likely to be compromised and subclinical or overt coronary heart disease is present. Routine checks of serum magnesium revealed a high incidence of hypomagnesemia in older hypertensive patients. This prompted a study to determine whether magnesium deficiency occurs often in the elderly.7

The study population was derived from 3 local retirement facilities. Of 118 patients evaluated, 57 were normotensive and 61 were classified as hypertensive. The mean level of serum magnesium for the entire group, 1.6 mg/dl, was less than the reference range observed in ordinary normotensive or hypertensive persons. A significant proportion of the study population was receiving diuretic treatment for hypertension, edema or congestive heart failure, and showed a lower serum magnesium value than comparable patients who were not taking diuretics. For example, the average serum magnesium for normotensive elderly patients (aged 60 to 69 years) not taking diuretics was 2.0 mg/dl, compared with 1.7 mg/dl for the patients who were taking diuretics. Among the hypertensive patients in the same age group, serum magnesium averaged 1.8 mg/dl, compared with 1.6 mg/dl for hypertensives who were taking diuretics.

MAGNESIUM/POTASSIUM SUPPLEMENTATION

Although there is no conclusive proof that thiazide therapy directly results in malignant arrhythmias and sudden death, our evidence—along with that from other investigations—suggests an increasingly strong association. This brings with it the issue of magnesium and potassium supplementation for patients receiving thiazide diuretics—especially those who are elderly. It also raises the question of how to optimally replenish stores of these electrolytes.

To investigate this, we induced hypokalemia and hypomagnesemia in 21 patients given a 6-week course of thiazide therapy. Patients then received potassium alone (40 mEq), magnesium alone (20 mEq), a combination of potassium (40 mEq) and magnesium (20 mEq), or hydrochlorothiazide (100 mg) plus a potassium-sparing diuretic (triamterene, 200 mg). Potassium and magnesium, given alone, proved ineffective in correcting the electrolyte imbalance, as was the drug triamterene. The combination of potassium and magnesium proved to be the most effective form of supplementation, although at 6 weeks levels were not as high as we would have liked. This indicates that electrolyte repletion is a problem that cannot be resolved quickly; long-term supplementation is necessary to achieve appreciable results.8

The finding that concomitant potassium and magnesium supplementation is more effective than either supplement alone is consistent with observations by Whang et al, who observed the phenomenon of refractory potassium repletion in magnesium-deficient patients. A possible cause for this may be diminished activation of membrane sodium-potassium adenosine triphosphatase—as exists in magnesium deficiency—leading to loss of cell potassium and accumulation of intracellular sodium.9

PROPHYLACTIC ELECTROLYTE SUPPLEMENTATION

The relation between potassium and magnesium deficiency and ventricular ectopy raises questions about the safety of thiazides as antihypertensive agents, particularly among the elderly. Such factors as dosage and duration of therapy, cardiovascular status and concomitant medications help to shape the risk/benefit profile for each individual patient. Whether prophylactic therapy with potassium and magnesium supplementation offsets the potential for electrolyte depletion and its consequences is also considered. Current experience identifies certain groups of diuretic-treated hypertensive patients in whom

FIGURE 3. Serum magnesium/potassium and onset of ventricular premature complexes (VPCCs). Changes in serum potassium (K) and magnesium (Mg) that result from treatment with thiazides are directly correlated with the incidence of VPCCs. This suggests that changes in the internal cationic balance of the body directly impact on cardiac performance.

FIGURE 4. A strategy for magnesium repletion with entericoated magnesium chloride (MgCl₂).
supplementation with magnesium and potassium appears to be prudent; patients taking digitalis, those with a history of hypokalemia and arrhythmia, patients having left ventricular hypertrophy or coronary heart disease, and the elderly. Patients receiving digitalis therapy are a cause for concern because of the documented association between magnesium deficiency and potentiation of digitalis toxicity. Left ventricular hypertrophy and coronary heart disease constitute conditions for magnesium/potassium supplementation because of their association with arrhythmias. The elderly are candidates for prophylaxis because of their tendency toward magnesium deficiency.

CONCLUSIONS

Based on available data, the following conclusions apply to thiazide-treated hypertensive patients: Thiazide diuretics contribute to loss of potassium and magnesium, which in turn may predispose the patient to the development of arrhythmias and sudden death. Routine monitoring of potassium and magnesium can help in early detection—and prevention—of electrolyte imbalance, before it becomes manifest clinically as ventricular ectopy. Elderly hypertensive patients receiving thiazide therapy are at special risk for cardiac arrhythmias because they are likely to be magnesium deficient. Concomitant magnesium and potassium supplementation or potassium/magnesium-sparing agents are necessary to correct underlying potassium deficiency. Supplementation with potassium and magnesium (Fig. 4) or co-treatment with sparging agents to impede the development of electrolyte imbalance appears to be prudent in patients at special risk, i.e., those receiving diuretic or digitalis therapy, or those with conditions that predispose to arrhythmia such as hypokalemia, left ventricular hypertrophy or coronary heart disease.

Of the available magnesium formulations, magnesium chloride (MgCl₂) is particularly suitable for patients taking diuretics. Diuretics, in addition to causing magnesium loss, can also cause loss of chloride. The resulting alkalosis interferes with potassium repletion unless the chloride deficit is also corrected. MgCl₂ is a highly soluble preparation that readily releases the magnesium ion for absorption into the small intestine. Other magnesium salts are highly insoluble in an alkaline environment and must be converted to the chloride form before they can be absorbed from the gut. Because the solubility of MgCl₂ does not depend on the acid environment, MgCl₂ supplementation can be given to a variety of patients who have an altered stomach pH, such as the elderly with achlorhydria or those who are taking H₂-receptor antagonists.

REFERENCES