
Controversy in Hypertension: Are Diuretics Harmful?

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Currently the trend is away from thiazide diuretics as a primary treatment for hypertension. Elimination of these agents from the therapeutic armamentarium—or a decrease to very low dosage levels—could make control of hypertension much more difficult. In at least 50% of mild hypertension cases, thiazide diuretics in adequate doses are effective in lowering blood pressure. In addition, they are the most efficacious agents now available for use in combination with other antihypertensive drugs.

■ Should the treatment of hypertension always be initiated with a thiazide diuretic, a beta blocker, or some other antihypertensive drug? Today, there is a trend away from thiazide diuretics as primary or step-one treatment, particularly in Europe. In Scandinavia especially, some physicians use diuretics only as adjuncts to other drugs and in very small doses; for example, hydrochlorothiazide is prescribed in doses of 6.25 or 12.5 mg per day.¹

Reluctance to employ standard doses of diuretics in the routine treatment of uncomplicated hypertension is based primarily on two presumed adverse effects. The first, and most important, is the concern that diuretic-induced hypokalemia may predispose to potentially fatal ventricular arrhythmias. The second is that the elevation of serum cholesterol resulting from diuretic treatment might increase the long-term risk of developing coronary artery disease.



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Eliminating thiazide diuretics from the therapeutic armamentarium or reducing their dosage to very low levels could make effective control of hypertension considerably more difficult than it is at present. The mode of action of the diuretics is unique: they are the only therapeutic agents that reduce blood pressure by lowering extracellular and plasma volume. In adequate doses, they are effective in controlling blood pressure in at least 50% of patients with mild hypertension. Also, they are the most effective agents for use in combination with other antihypertensive drugs. Therefore, it is extremely important that the charges against these agents be examined carefully.

Misconceptions About Thiazides

The case against diuretic-induced hypokalemia as a cause of fatal ventricular arrhythmias remains unproven. It is, we believe, based on several commonly held misconceptions.

1. *The hypokalemia is associated with a physiologically significant depletion of intracellular potassium stores.* A review of the various studies of changes in total body potassium following thiazide administration indicates a near consensus that the losses of total body potassium are only 5% to 7%.² This is far below a level that could be considered biologically important. In contrast, extracellular potassium is reduced by about 20% in thiazide-

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induced hypokalemia. The intracellular concentration of potassium is unrelated to the extracellular concentration since the former is maintained against a concentration gradient by metabolic pump activity. Therefore, intracellular concentration can be maintained despite extracellular hypokalemia.

2. *Hypokalemia results in increased irritability of the heart and produces earlier depolarization.* The susceptibility of the heart to depolarization is said to depend, at least in part, on the ratio of the concentration of potassium inside the cells to that of potassium outside the cells.³ The ratio of intracellular to extracellular potassium increases with thiazide-induced hypokalemia because the fall in extracellular potassium is greater than the fall in intracellular potassium. Thus, the changes in the ratio should increase the depolarization threshold, which should make the heart less, rather than more, susceptible to the development of arrhythmias. However, a relative increase in intracellular to extracellular potassium also is said to raise conduction velocity, which may increase reentry phenomena and thereby possibly influence the induction of arrhythmias.

Which of these opposing mechanisms dominates in the presence of thiazide-induced hypokalemia is not known. Indeed, the pathophysiologic consequences of thiazide-induced hypokalemia on the heart are unknown at present and certainly cannot be assumed to be harmful as some authors believe.

The dangers of thiazide-induced hypokalemia, if any, probably are quite different in patients with overt heart disease compared to asymptomatic patients with mild or moderate hypertension. In congestive heart failure there may be considerable intracellular depletion due to various complicating factors.² In myocardial infarction (MI), the sodium-potassium pump functions inadequately in the ischemic zone and intracellular potassium leaks from the cells, causing a local increase in extracellular potassium that results in increased arrhythmogenic activity.⁴ Such hearts are susceptible to ventricular arrhythmias, and any further reduction in intracellular potassium, however small, may tip the balance.

FAST TAKE

Resistance to thiazides: Physicians, particularly in Europe, are moving away from thiazides as primary treatment for hypertension. This trend is based on two presumed adverse effects of these agents:

- (1) potentially fatal ventricular arrhythmias may be more likely in diuretic-induced hypokalemia and
- (2) elevated cholesterol caused by diuretic therapy might increase the risk of heart disease.

The situation is quite different in patients with uncomplicated hypertension, in whom intracellular potassium concentrations are essentially normal. However, it should be emphasized that the evidence for an association between hypokalemia secondary to diuretics and ventricular fibrillation in acute MI is based on retrospective studies,⁵ and conclusive evidence of a correlation has not been documented. The only proven relationship between thiazide-induced hypokalemia and increased susceptibility to cardiac arrhythmias is the association with digitalis.⁶

3. *Catecholamines aggravate hypokalemia, which may trigger arrhythmias.* Further concern has been generated by the recent finding that catecholamines, by causing a movement of extracellular potassium into cells, further aggravate the hypokalemia secondary to thiazides.⁷ This movement is mostly into skeletal muscles with only minimal changes in the myocardial cell potassium concentration. Theoretically, this change in the equilibrium between intracellular and extracellular potassium, if it occurs in the myocardium, should make it less rather than more susceptible to arrhythmias.

More importantly, it has not been demonstrated that the reduction in serum potassium from the combined effects of diuretics and catecholamines increases either the frequency or severity of arrhythmias. While high local catecholamine concentrations undoubtedly increase the frequency of serious cardiac arrhythmias, the latter are probably caused by other actions of these adrenergic agents on the myocardium.

4. *An increased incidence of cardiac arrhythmias has been objectively documented with diuretic-induced hypokalemia.* Most of the evidence implicating diuretics has been generated by electrocardiographic (ECG) monitoring.^{8,9} This evidence has been challenged, however, by several recent studies. Papademetriou and co-workers in our laboratory failed to find any evidence of increased cardiac arrhythmias during hypokalemia secondary to thiazides.¹⁰ Using 24-hour continuous ECG monitoring, they found that normalization of the hypokalemia with potassium supplements and/or potassium-sparing diuretics failed to change either the frequency or type of arrhythmias significantly.

Papademetriou and associates then carried out 48-hour monitoring before and after thiazide-induced hypokalemia. Again, there was no significant difference in the incidence or type of arrhythmia before or after treatment with diuretic.¹¹ All of the patients had asymptomatic hypertension and no overt heart disease. Using 48-hour monitoring, Lief and colleagues also found no increase in cardiac arrhythmias during thiazide-induced hypokalemia.¹²

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FAST TAKE

Hypokalemia: While some authors have reported that diuretic-induced hypokalemia causes increased cardiac arrhythmias, the findings have been challenged by several investigators. In one study, for example, when potassium or potassium-sparing diuretics normalized thiazide-induced hypokalemia, there were no significant changes in the frequency or type of arrhythmia.

A report that hypokalemia secondary to diuretic treatment produces increased cardiac arrhythmias is frequently cited.⁹ This study used 24-hour ECG monitoring before and after inducing hypokalemia with thiazide diuretics. These results differ from those of Papademetriou and Lief probably because of their method of case selection. Papademetriou and Lief did not select their patients on the basis of the amount of ectopic activity displayed during the pretreatment period.

The other study, however, rejected any patients who had displayed more than five premature ventricular beats per hour. Since the frequency of ectopic beats varies widely from one 24-hour period to another, their study design greatly increased the likelihood of finding increased arrhythmic activity on the posttreatment recording. Thus, because monitoring lasted for only 24 hours and patients were selected with recordings taken at the low end of their range of spontaneous variability, their results may have been biased.

The Medical Research Council of Great Britain studied a subgroup of their patients. An increased incidence of ventricular ectopy was observed in the long-term thiazide-treated group compared to the placebo-treated patients using only one posttreatment and no pretreatment ECG monitoring.¹³ In a larger series, however, they monitored patients both before and after treatment with thiazides and found no difference in arrhythmia. Furthermore, there was no correlation between plasma potassium levels and ventricular arrhythmia frequency.

5. *An increased incidence of sudden death associated with diuretic-induced hypokalemia has been demonstrated in large intervention trials.* The evidence usually cited to implicate thiazide diuretics as a cause of fatal arrhythmias is provided by the Multiple Risk Factor Intervention Trial (MRFIT).¹⁴ A subgroup of patients with ECG abnormalities at baseline showed an increased incidence of sudden death. These patients received hydrochlorothiazide, 50 mg twice daily. It is not known how the control group was treated, since they were referred to other treatment sources.

The MRFIT data may be challenged on several points.

First, the evidence is the result of an analysis of many patient subsets chosen by a number of criteria after the study was completed. The correlation was not an objective of the original trial. The more subsets that are examined, the greater the possibility of a positive correlation by chance alone. Therefore, such a finding can only be regarded as a lead that requires further investigation to provide substantive corroboration. It is interesting that the sister study to the MRFIT, the Hypertension Detection and Follow-up Program (HDFP), failed to confirm the MRFIT observation.

Attempts have been made to explain the difference on the basis of the dosages of diuretics used in the two studies, since HDFP used a dose of 50 mg chlorthalidone once daily. It is questionable, however, whether 50 mg chlorthalidone results in less hypokalemia than the 50 mg hydrochlorothiazide bid dose used in MRFIT. Chlorthalidone is a more potent diuretic than hydrochlorothiazide, and its duration of action is considerably longer. In fact, in 50 to 100 mg doses, the former agent is known to produce hypokalemia more frequently than most of the other known diuretics. Also, there was no correlation between serum potassium levels and the incidence of arrhythmias in the MRFIT. Therefore, it is difficult to ascribe the results in the MRFIT to thiazide-induced hypokalemia.

Do Diuretics Increase Plasma Cholesterol?

Plasma cholesterol usually rises slightly when thiazide treatment is initiated.¹⁵ The concern is that even though the elevation is modest, it might increase the risk of atherosclerosis over a long period. This fear probably is unfounded, however, because the rise in plasma cholesterol apparently does not persist over the long term. After one or two years of continuous treatment, plasma cholesterol levels are no higher than they were prior to treatment.¹⁶

Three studies demonstrated both the early increase and the later normalization of plasma cholesterol levels during thiazide treatment. The Veterans Administration trial of hydrochlorothiazide versus propranolol treated 343 patients with diuretic alone with no other drug or dietary interventions.¹⁷ Plasma cholesterol rose during the first three months of treatment but at 12 months it had fallen to slightly below baseline. Alcazar and associates¹⁸ also found that the increase in plasma cholesterol did not persist beyond the first few months of treatment with thiazides and afterward remained at pretreatment values during two years of observation. Williams and colleagues, using data from the HDFP, also found a short-term increase followed by a long-term return to baseline.¹⁹

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Because the thiazide-induced modest elevation of cholesterol appears to be short-lived, it cannot be considered an aggravating factor in the long-term development of atherosclerosis.

Low-Dose Treatment with Diuretics

Because of the concerns about hypokalemia and hypercholesterolemia, there is at present a tendency to prescribe very small doses of diuretics, such as 6.25, 12.5, or 25 mg of hydrochlorothiazide, once daily. Some recent European studies have indicated that such small doses are as effective as the standard therapeutic doses in reducing blood pressure, particularly when the diuretic is given in combination with a step-two drug.^{1,20} This has led to the impression that the dose-response curve is flat between 6.25 and 25 mg per day of hydrochlorothiazide.

FAST TAKE

Cholesterol levels: Concern that diuretics cause elevated plasma cholesterol and thus increase the risk of atherosclerosis is largely unfounded. While thiazides do cause an initial slight increase in plasma cholesterol, over the long term, plasma cholesterol levels are normalized.

It is difficult to understand how such small doses could exert as great an antihypertensive effect as standard doses. Thiazides lower blood pressure by reducing extracellular and plasma volume.²¹ Body weight reflects the reduction in extracellular volume which is manifested in a loss of three to four pounds. In the European studies cited above, the small doses had no effect on body weight, and only the highest dose of 50 mg per day of hydrochlorothiazide used by MacGregor and associates²⁰ caused any significant reduction in body weight. Thus, the lowering of blood pressure that occurred with the low doses of hydrochlorothiazide was not due to a decrease in volume and, therefore, may not have been caused by the diuretic.

MacGregor and associates used a crossover design in which patients received a beta blocker plus a different dose of hydrochlorothiazide every four weeks—12.5, 25, and 50 mg once daily. The blood pressure response was the same with all three doses of hydrochlorothiazide. However, it was not possible from this experimental design to determine how much of the blood pressure reduction was due to the beta blocker alone. Furthermore, in crossover trials there is always the possibility of carry-over antihypertensive effects that may persist for weeks or months after the treatment is withdrawn. Also, with

repeated clinic visits, blood pressure usually drifts down even with a placebo.²²

Andren's trial, which used once-daily doses of 6.25, 12.5, and 25 mg of hydrochlorothiazide with enalapril did not employ a control of enalapril alone.¹ Thus, the blood pressure reductions observed could have been due to the converting enzyme blocker alone.

If the toxicity of thiazide diuretics is not as great as some authorities believe, the important issue becomes whether the dose-response curve of hydrochlorothiazide is indeed flat between 6.25 and 100 mg per day. If it is not flat, many patients are receiving inadequate doses of the drug. This is unfortunate because the most important goal of treatment is effective blood pressure control.

Recent evidence from the Veterans Administration study on propranolol versus hydrochlorothiazide²³ indicates that the dose-response curve is not flat even at doses well above 25 mg per day. Hydrochlorothiazide alone was titrated upward from 25 mg twice daily to 50 mg, and then to 100 mg twice daily at monthly intervals until the blood pressure was controlled.

Of the patients controlled below 90 mm Hg, 50% responded to the smallest dose of 25 mg bid but 30% required the intermediate dose and the remaining 20% needed 100 mg bid. While it might have been more practical to have added a step-two drug rather than to proceed to the highest dose, this study at least indicates that evidence is lacking for a flat dose response even at high doses and that there is great variation in the dose requirement among different patients. Other investigators also have found that the dose-response curve is not flat with a daily dose of hydrochlorothiazide above 25 mg.²⁴⁻²⁶

Because of the present "obsession with potassium,"²⁵ physicians tend to administer doses of diuretics that are inadequate to reduce volume and, therefore, probably blood pressure as well. Clinicians may confuse spontaneous falls in blood pressure that occur even with placebo with the therapeutic action of the diuretic,²² and thus become convinced of the efficacy of small doses. They may ascribe the spontaneous fall to normotensive levels to the diuretic. Unfortunately, other patients who do not show such a spontaneous drop are considered treatment failures and never receive the benefit of more effective doses of the diuretic.

Conclusion

In the absence of congestive heart failure and digitalis, there is inadequate evidence to implicate thiazide-induced hypokalemia as a cause of cardiac arrhythmias. Also, the small rise in serum cholesterol that occurs with thiazide treatment is short-lived and reverts back to pretreatment values during long-term treatment. Undue

concern over these side effects has led to the use of small doses of diuretics, which may be subtherapeutic in many patients even when given as an adjunct to step-two drugs. If therapy is begun with a small dose of diuretic such as 25 mg of hydrochlorothiazide once daily, either alone or with a step-two drug, the dose should be doubled at least or given twice daily before concluding that the diuretic is ineffective.

It is not possible to have a reduction in volume without some decrease in serum potassium. Indeed, the drop in serum potassium is due primarily to an equilibrium shift secondary to volume loss. Since the blood pressure decrease following diuretic treatment is also volume-dependent, a drug-related reduction in blood pressure is probably impossible without at least some reduction in serum potassium.

The primary aim of treatment is to control the hypertension. Inadequate doses of diuretics or any other drug will not accomplish this aim. It is better to control the blood pressure than to be guided by unjustified fears of adverse drug effects. □

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Practice Procedures

Efficacy Testing of Hydrochlorothiazide

If hypertensive therapy is begun with a small dose of diuretic, such as 25 mg of hydrochlorothiazide once daily, either alone or with a step-two drug

- The dose should be doubled

or

- The dose should be given twice daily

Before concluding that the diuretic is ineffective.

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