Diuretics, Potassium, and Ventricular Ectopy

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In November 1985, we reviewed the then current status of experimental and clinical evidence and opinion on diuretic-associated hypokalemia with particular attention to its potential for inducing ventricular ectopy. Nearly a decade later we had the opportunity to revisit this topic in preparation for the Third Dahl Symposium; nearly 12 years later, we have reviewed the current literature in preparation of this paper. What has changed? Not much in the way of solid data, but there does appear to be some alteration of the paradigm. This paper is a review of work by ourselves and others, but the reader must keep firmly in mind that, in the final analysis, it is an expression of my personal opinion.

WHAT ARE THE ISSUES?

I see the issues as follows. First, there is the concern over why cardiovascular mortality has not been reduced by antihypertensive therapy over time to the degree predicted when the reduction of cerebrovascular mortality has met expectations. Second, there was considerable concern over the promotion of potassium supplements and potassium-sparing diuretics because they were expensive and thought to be unnecessary. Third, there was considerable controversy about whether or not diuretics alone or associated with hypokalemia could cause lethal or potentially lethal ventricular ectopy. Finally, the fact that there is a current trend toward using non-diuretic antihypertensive drugs and using only low-dose diuretics, could render most of the above discussion moot.

Cardiovascular Mortality That the era of more intense antihypertensive therapy has been accompanied by a reduction in cardiovascular mortality is indisputable. The questions are whether blood pressure reduction alone accounted for this and whether the reduction would have been greater had the diuretics not caused a “backlash” of cardiotoxicity. Certainly, the introduction of orally available thiazide diuretics in 1957–8 revolutionized the treatment of hypertension. Earlier oral drug regimens caused such significant deterioration of the quality of life of patients with otherwise asymptomatic hypertension that convincing patients to be miserable in order to live longer was a difficult sales pitch. To paraphrase the late Herbert Langford, how can one expect a patient to take medications that make them unable to cerebrate, defecate, or fornicate in the hope of living longer? Of course, one could add the visual and urinary sphincter changes plus orthostatic hypotension and depression to that short list. Oral diuretics changed all of that by providing single-drug control for patients with milder hypertension and by permitting lower doses of other drugs when combined with them.

In my opinion, none of the hypertension studies designed, completed, and published to date can be interpreted to show true cardiotoxicity of diuretics. First, the patient population was middle-aged and patients with cardiac risk factors were not excluded. Indeed, patients with known coronary heart disease manifested by an old myocardial infarction or angina pectoris were specifically included. Second, very large doses of diuretics were generally used. A recent case-controlled study suggests that the use of 25 mg or less of hydrochlorothiazide may actually be cardioprotective. Third, many trials were not really designed to test a specific hypothesis regarding cardiac mortality. Fourth, some of the diuretics used were combined with potassium-sparing agents and some were not. The major clinical trial, Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), is designed to detect differences in cardiovascular mortality between different classes of drugs, including diuretics, but it will not be completed until after the turn of the century. In conclusion, I do not believe that anyone knows whether the use of diuretics limited the reduction of cardiovascular mortality. Furthermore, even...
if the data had so indicated, the modern shift to the use of lower doses may have rendered those studies irrelevant.

**Potassium Supplements** As the use of thiazide diuretics for both edematous states and hypertension became widespread, the issue of hypokalemia became important. A large commercial market for various potassium supplements and potassium-sparing drugs evolved and promotion of these drugs was feverish. Despite some clever methods for disguising the unpleasant taste of potassium salts, none were problem-free. Those not based on potassium chloride were not very effective and those that bypassed gustatory exposure often created gastrointestinal problems such as strictures or were not adsorbed at all.³ Kassirer⁴ in particular brought the case against what he considered to be a national obsession with potassium, but others kept arguing that hypokalemia was frequent and potentially lethal.⁵ Again, the paradigm has shifted to the use of low-dose diuretics so that the issue is much less volatile; in fact, it is nearly invisible.⁷

**VENTRICULAR ECTOPY**

The late John Hollifield,⁸ Brian Holland⁹ and others generated studies that suggested that diuretics were associated with increased ventricular ectopic activity. Messerli¹⁰ and many others have demonstrated the relationship of left ventricular hypertrophy to increased risk for both ventricular ectopic activity (VEA) and cardiac death. It was argued that many patients with hypertension had organic heart disease, often silent, and that diuretic use would place them at an increased risk for death. On the other hand, Edward D. Freis, who really brought thiazide diuretics to clinical practice, Papademetriou,¹¹ Madias,¹² Caralis¹³,¹⁴ and many others published studies that cast doubt on any specificity of diuretics for increasing VEA. Indeed, the basic message was that, unless there was underlying organic heart disease, even rather marked hypokalemia would not trigger a significant increase in VEA.

**SELECTED INFORMATION SINCE 1985**

Hollifield¹⁵ was interested in the effects of diuretics on both potassium and magnesium. He studied 35 patients to whom he gave 12.5 to 50 mg of hydrochlorothiazide, increasing the dose every 4 weeks until the blood pressure was controlled. They were treated for 24 weeks. Each increase in diuretic dose further decreased the blood pressure but also serum potassium and magnesium levels. Lumme and Jounela¹⁶ used 24-h electrocardiogram (ECG) monitoring to study 24 hypertensive patients who were treated with either hydrochlorothiazide up to 50 mg / day or indacrinone, with or without amiloride. Mean serum potassium was reduced with both diuretics, but magnesium was not. Four of the patients had increased VEA, but this had no correlation with the serum potassium or magnesium levels.

Emara and Saaded¹⁷ reported three cases of atrial fibrillation related to thiazide therapy and hypokalemia. Correction of the hypokalemia returned the rhythm to normal sinus. No underlying cardiac disease was found.

Dyckner and Wester,¹⁸ who had made earlier contributions to this area in regard to magnesium, pointed out that muscle magnesium levels were frequently low in patients with congestive heart failure who were treated with diuretics. They argued for the use of potassium-sparing diuretics because they spare magnesium as well. Of course, serum magnesium does not reflect intracellular magnesium accurately. Ragnarsson et al¹⁹ were unable to show a correlation of serum magnesium in diuretic-treated older patients, but they did find a higher rate of ventricular ectopy in the diuretic group than a group treated with a β-blocker. Hypokalemia was associated with the increase in VEA in these older men. In contrast, Myers²⁰ studied 37 elderly patients whose mean age was 81 years. Patients were given 50 mg hydrochlorothiazide alone or in combination with amiloride 5 mg. There was a placebo control group. Hydrochlorothiazide alone reduced serum potassium significantly from 4.1 to 3.5 mmol/L compared to the combination and placebo group. The placebo group had a higher incidence of serious ventricular arrhythmias (15/37; 41%) than those receiving thiazide alone (13/37; 35%) or the combination (9/37; 24%). The conclusion was that this dose of hydrochlorothiazide did not affect the frequency or severity of VEA in that elderly population.

Poole-Wilson²¹ took the position that most physicians were already aware (1987) of the basic issues so that, even if they were not fully understood, the physicians knew what to do about it and that “it was no longer a major therapeutic issue.” I suspect that this is where we are today!

Animal experiments generally suggest that hypokalemia induced by diuretics is harmful. For example, Alexander²² found that Wistar rats injected with various diuretics had reduced intracerebral magnesium and were more susceptible to arrhythmias induced by digoxin. He could reverse this effect by giving intracerebral magnesium. Garan et al²³ used an acute myocardial infarction model in dogs. They depleted potassium with an extremely low potassium diet and hydrochlorothiazide. They found that both the total potassium deficit and serum potassium levels correlated significantly with spontaneous ventricular fibrillation after the infarct. Note that members of this group had earlier objected to the routine use of potas-
sium supplementation in humans.\textsuperscript{4,5} A related study in humans by Szlachcic et al\textsuperscript{24} did show an increase of VEA associated with hydrochlorothiazide but not nitrendipine in men with documented ischemic heart disease.

Holland and colleagues\textsuperscript{25} used a high dose (100 mg) of hydrochlorothiazide in a group of patients with previously documented diuretic-associated hypokalemia who did not have cardiac disease by ambulatory ECG monitoring or exercise stress tests. Amiloride was used in a second group of patients to maintain normal potassium levels. The diuretic treated patients developed hypokalemia with associated increased VEA; this was reversed by giving amiloride. One patient died an arrhythmic death while hypokalemic. They again concluded that diuretics induce increased VEA by virtue of the electrolyte abnormalities that they effect. Papademetriou and his colleagues\textsuperscript{26} held their prior position as well. In a study of 44 uncomplicated hypertensive patients who were given 100 mg hydrochlorothiazide, they found no evidence that the diuretic or diuretic-associated hypokalemia resulted in increased ventricular ectopy. This was true even for the patients with left ventricular hypertrophy who had increased VEA at baseline. Peters et al\textsuperscript{27} published results similar to that of Papademetriou. They randomly allocated 19 men to treatment with hydrochlorothiazide 25 mg, 50 mg, or 25 mg plus 50 mg triamterene for 6 months. Serum potassium levels fell to <3.5 mmol/L in about half of the patients, regardless of treatment group and there was no relationship between serum potassium level and VEA by 24-h ambulatory monitoring. They concluded that low-dose diuretic therapy for hypertension is not arrhythmogenic. Messerli and coworkers\textsuperscript{28} studied patients with left ventricular hypertrophy. Patients were given either a calcium channel blocker, which reduced VEA, or hydrochlorothiazide, which did not change the rate of VEA even in this group with LVH. Papademetriou, Notargiacomo, and Freis\textsuperscript{29} extended their studies to exercise stress testing of patients treated with either hydrochlorothiazide or placebo. They did not find any difference between the two groups in frequency or complexity of arrhythmias.

Lumme and Journela\textsuperscript{30} extended their studies with 11 hypertensives with known increased VEA at baseline. They gave 50 mg hydrochlorothiazide daily plus either potassium or a combination of potassium and magnesium. The potassium supplementation did help to control the VEA, but the addition of magnesium offered no additional benefit.

Ed Freis\textsuperscript{31} reviewed this topic carefully in 1990 and concluded once again that further evidence from ambulatory ECG monitoring “does not support the hypothesis that thiazide diuretics, either in the presence or absence of hypokalemia, increase the frequency or severity of ventricular arrhythmias.”

A more recent, careful study by Siegel et al\textsuperscript{32} appears to support the position of Dr. Freis. They performed a randomized, double-blind controlled clinical trial of 233 hypertensive men aged 35 to 70 years. They were randomly allocated to treatment for 2 months in one of six groups: hydrochlorothiazide, hydrochlorothiazide plus potassium, hydrochlorothiazide plus potassium and magnesium, hydrochlorothiazide plus triamterene, chlorthalidone, or placebo. The serum potassium levels in the hydrochlorothiazide alone group were 0.4 mmol/L lower than the placebo group and this difference was not affected by any of the three supplementation regimens. Nevertheless, the supplements did prevent the development of serum potassium levels of 3.0 mmol/L or less which occurred in 12/90 (13%) of the men who were treated with diuretic alone. This latter group also had a 2-fold increase in ventricular arrhythmias. The majority of patients had no difference in ventricular arrhythmias. The authors concluded that in most patients “treatment with 50 mg/ day of hydrochlorothiazide does not cause marked hypokalemia or ventricular arrhythmias.” They do go on to caution that potassium levels should be monitored and potassium-sparing strategies used when indicated.

Two studies\textsuperscript{33,34} compared an angiotensin-converting enzyme inhibitor to hydrochlorothiazide in regard to cardiac arrhythmias and other factors. Although they focused on the beneficial effects of the ACE inhibitors, hydrochlorothiazide did not increase VEA in either study. Papademetriou et al\textsuperscript{35} did a similar comparison of hydrochlorothiazide with an ACE inhibitor, calcium channel blocker and \(\beta\)-blocker in 31 patients with documented LVH. Although diltiazem and metoprolol significantly decreased ventricular ectopy, both enalapril and hydrochlorothiazide were neutral.

In his most recent and very careful review of this topic,\textsuperscript{36} Dr. Freis again supported the continuing use of diuretics for the treatment of hypertension. He particularly endorsed the use of small doses as being prudent. Even this position elicited a pointed rebuttal to which his measured answer is a typical masterpiece from a master.\textsuperscript{37}

**WHO BENEFITS?**

One of the key questions in sociology research is: who benefits? The question often generates some interesting perspectives that might otherwise be missed. It is clear that either a successful stepped-care algorithm or a Joint National Committee recommendation that suggests use of a diuretic as a first step will eliminate about 50% of the potential market for more recent and generally more profitable antihypertensive drugs. By creating fear of diuretics, those that market nondi-
uretic antihypertensives can increase their market share considerably.

I believe that in the long run the patients benefit from this controversy. It has created a more careful examination of the issues and led to the use of much lower doses of diuretics and of combinations of non-diuretics with low-dose diuretics. When a diuretic is indicated, we now routinely begin therapy of stage I hypertension with 12.5 mg hydrochlorothiazide, 15 mg chlorthalidone, 1.25 mg indapamide, or 0.5 mg micronized metolazone. Patients with congestive heart failure or ischemic heart disease are more likely to have other drugs used that benefit both their hypertension and the concomitant problem. We do remain aware of serum potassium levels to the extent that serum potassium below 3.5 mmol/L should generally be avoided. We do not worry about serum magnesium or magnesium replacement therapy.

**FUTURE DECISIONS**

As noted earlier, the results of the ALLHAT study may or may not provide definitive answers to the relationship between the use of diuretics and cardiac morbidity and mortality. That patient population has been selected deliberately to represent hypertensives who have underlying cardiovascular risk factors and are, therefore, particularly susceptible to any additional risk imposed by the drug. It is fascinating that there is now more focus on the results of ALLHAT as they will pertain to the calcium channel blockers than to the diuretics.

In the meantime, the members of JNC-VI will have to reexamine their position on the recommendation for diuretics or β-blockers as first line choices for the treatment of uncomplicated hypertension when a specific indication for another drug class is absent. There should be some lively debate on this issue, but the final recommendations will be supported by the best evidence currently available.

**SUMMARY AND CONCLUSIONS**

Diuretics remain an important part of the therapy of hypertension. When used in low doses, they appear to be remarkably safe. Like any other antihypertensive drug, they should be selected or deselected based on the characteristics of the individual patient.

**REFERENCES**


34. Lumme JA, Jounela AJ: Left ventricular mass, serum electrolyte levels and cardiac arrhythmias in patients with mild hypertension treated with cilazapril or hydrochlorothiazide. Intern J Cardiol 1993;42:71–78.

