

two available classes of drugs mechanistically speaking, the antisodium volume drugs and the antirenin-angiotensin system drugs. All of the six major classes of antihypertensive drug fit into one of these two categories. The plasma renin test identifies which type of patient you have and it guides your starting choice of either a “V” (sodium volume drug) or an “R” (antirenin drug) the response to which verifies your drug choice for correcting both the pathophysiologic lesion and the blood pressure. Thus, if you are willing to enjoy and use a little physiology you can dig your way out of this chaos and find a solution that works.

For this review course I will draw heavily on the experiences of my long-time colleagues, and working partners, Michael Alderman, Jon Blumenfeld, Daniel Catanzaro, and of course my wife, and longest colleague, Jean Sealey, all of whom directly or indirectly, have contributed vitally to our research work and to these lessons. Many others as trainees from all parts of the world also have contributed importantly. Altogether, this has been synergism at its best. When I use the word we instead of I in these lessons, this is what I am expressing.

In this course we describe the pathophysiology of hypertension through the eyes of the renin system because the renin system is our blood pressure control system. It constantly reacts to and corrects deviations in blood pressure and flow by responding to central and autonomic nervous signals and by also constantly reacting to postural changes in blood pressure as well as to changes in dietary sodium and potassium intake. Getting a feel for the cybernetics of these interactions and how to recognize them will make the treatment of hypertension a joy and a source of gratification.

Readers of these lessons and our accompanying clinical pearls in following issues of the *Journal* are invited to communicate with us by e-mail or by fax. We will try to answer all of your questions promptly. As we proceed, we will also provide a number of simple review questions, to reinforce your learning.

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Clinical Pearl #1: Diuretic-Induced-K⁺ Depletion May be Hazardous: The Miracle of Low-Dose Spironolactone

Since 1960, sulfonamide thiazide diuretic therapy has been a cornerstone of long-term antihypertensive therapy and also for the treatment of patients with congestive heart failure (CHF). Since the beginning it was recognized that such natriuretic–diuretic therapy is regularly accompanied by demonstrable body potassium and magnesium deficiencies, often reflected by significant, albeit generally mild, observed decrements in plasma K⁺ and Mg²⁺ levels.

Because no particular problems were recognized with broad usage of these diuretics, over the years physicians became increasingly sanguine about their occurrence. Accordingly, thiazide diuretics and then, the similar, but more powerful, loop diuretics (eg, furosemide) became broadly used as primary treatment for high blood pressure and also for treating the edematous state of congestive heart failure, cirrhosis with ascites, and nephrotic syndrome.

The first selective aldosterone receptor antagonist spironolactone (Aldactone) was introduced into clinical medicine in about 1972. By blocking aldosterone action it proved to be a potent natriuretic and K^+ -retaining agent. Thus, it produced diuresis and weight loss with no loss of K^+ or Mg^{2+} , something I for one viewed as a great conceptual advantage over thiazides. However, the lack of any demonstrable morbidity from thiazide-induced K^+ depletion and the impressive prompt diuresis that these drugs produced at low cost carried the thiazides into a leadership position in the treatment marketplace for hypertension and for edematous states that continues presently.

Notwithstanding, my attraction to the aldosterone antagonist approach was enhanced by two facts. First, in outpatient trials, in more than 20 reports of head-to-head trials comparing spironolactone to thiazide diuretic, spironolactone proved to be at least as effective as thiazides for correcting hypertension¹ and second, spironolactone treatment was actually considerably more potent than were thiazides or furosemide for fully diuresising patients with congestive heart failure, or cirrhosis with ascites often working after a failed thiazide/lasix trial. Therefore, its power in these latter two situations was literally amazing. Moreover, these results correctly implicated a large role for aldosterone excess in their pathogenesis.

But, besides cost, there were two other problems with spironolactone that stalled its acceptance. First was its very gradual action, which made it apparently less effective and therefore, less attractive to impatient physicians and patients. It takes 3 to 5 weeks of daily therapy to express its full effect. This is because spironolactone blocks only that 2% of the daily renal sodium reabsorption that is governed by aldosterone. However, at this rate cumulative sodium loss becomes large; therefore after 4 weeks or so it can easily exceed what could be achieved over that time with a loop diuretic. This scenario resembles what happens after total adrenalectomy in animals. These animals die of salt loss or hyperkalemia (the counterpart of an Addisonian crisis), but this takes 6 weeks to develop, and, of course, the process can be avoided by feeding NaCl. The second problem with spironolactone was that it causes unpleasant dose-related antiandrogenic side effects, especially in the 50- to 100-mg daily dose used at first. These are gynecomastia in men, menstrual disturbances in women. But then we learned this could be largely avoided by giving only 12.5 to 25 mg daily.

With this information at my disposal, over the years I

rang up success after success as a consultant for treating desperate cardiac patients (already on full doses of Lasix and a CEI) by adding small daily doses of spironolactone and then observing, time and time again, dramatic diuresis with clearing of all edema fluid plus an obvious improvement in total cardiovascular performance that sometimes added years to the lives of these patients.

Some years ago I shared my experiences and views about spironolactone with Dr. John Alexander, whom I had worked with on captopril when he was at Squibb. He had moved to Searle and he set out to revive interest in their spironolactone product (Aldactone). He planned a clinical trial in heart failure. First, in a test run they confirmed my experiences, that 12.5 to 25 mg daily would be enough to do the job. Then, with Bert Pitt's leadership, they designed and performed the now famous RALES trial reported late in 1999.² Their trial of 1665 patients with severe congestive heart failure (CHF) was planned for 3 years but had to be discontinued after 24 months because the death rate from cardiac causes was already reduced by an amazing 30% in the group that received spironolactone superimposed on their full drug regimen.

These spectacular results teach us that sulfonamide diuretic-induced K^+ and Mg^{2+} deficiencies may not be benign. This could per se create serious dysfunction in cardiac and skeletal muscle performances that in CHF could hasten progression of heart failure. This possibility is strongly supported by large measured deficiencies in muscle K^+ and Mg^{2+} with increased Na^+ content in muscle biopsies of either diuretic-treated CHF or diuretic-treated hypertensive patients in many studies by Dyckner and associates.³⁻⁵ They also demonstrated impressive correction of those muscle disturbances by superimposed spironolactone therapy, which blocks endogenous aldosterone's kaliuretic and magnesiuric actions. These results teach us anew that the K^+ and Mg^{2+} loss in these patients is caused or amplified by the diuretic-induced high aldosterone levels that occur in CHF, which in turn are caused by their higher plasma renin angiotensin levels, created in the first place in CHF patients by poor blood flow to the kidneys from poor cardiac function⁶ and also are created in hypertensive patients by their renin aldosterone response to the thiazide-induced sodium volume loss.⁷ Accordingly, the kidney renin response in CHF can be turned off by feeding NaCl to improve volume and flow after which renin and aldosterone decrease dramatically, but this is not appropriate or safe to do in most CHF patients.⁶

Thus, in CHF, heart failure begins in the heart with its failure as a pump,⁷ leading to poor renal perfusion that causes the kidneys to release renin, causing plasma renin angiotensin to increase, which in turn stimulates aldosterone release, which causes Na^+ retention (and edema), and if aldosterone is too high, K^+ loss. In this setting, the volume depletion of thiazide diuretics makes renin and especially aldosterone⁸ go even higher causing aldosterone to produce kaliuresis, which is then correctable by spironolactone blockade of the aldosterone action. Long

ago, my friend Jim Davis showed that experimental massive edema of dog heart failure is dramatically corrected by total adrenalectomy, because this removes all aldosterone from the circulation.⁷ Spironolactone does the same job in patients, albeit much less dramatically, or completely than does surgical adrenalectomy.

Often great clinical discoveries, like this one from the RALES trial, revealing a striking and discrete pathogenic role for endogenous aldosterone excess in the progression of CHF, and in the kaliuresis of its attendant diuretic therapy are first made in the most egregious forms of a disease. However, by extrapolating from these findings, one can often recognize the signs of the same long-term thiazide-induced biochemical pathopathology (ie, high aldosterone and low K^+ levels), not only in milder forms of heart failure, but also in that vast population of diuretic-treated hypertensive patients, which are there for the plucking. Thus, practically all thiazide-treated hypertensive patients do exhibit lower plasma K^+ levels than before their thiazide therapy. Even when using low-dose chlorthalidone, a significant fraction of hypertensive patients exhibits at least a relative hypokalemia and in 7.2% the K^+ values are clearly <3.5 .⁹ In such low-dose diuretic-treated hypokalemic patients in the SHEPS trial,⁹ all the potential protection from morbid cardiovascular sequelae was lost.⁹ These findings closely resemble earlier findings in the MRFT trial of a 2.4-fold greater risk of sudden death associated with higher dose diuretic therapy.^{10,11} These relationships are entirely in keeping with our earlier studies by Paul Cannon in which he showed that urinary K^+ loss in diuretic-treated patients with either hypertension or heart failure is consistently closely related to the height of their endogenous aldosterone secretion rates.^{12,13} Cannon also showed that the kaliuresis of diuretic therapy does not occur after adrenalectomy, thereby proving that it is the aldosterone response to diuretic-induced sodium volume depletion, not the diuretic itself that cause the kaliuresis.¹³ Moreover, we know that a high aldosterone level in response to diuretic treatment can reverse its antihypertensive effect.⁸

We also know that body K^+ depletion can occur without a reduced plasma level. Therefore what we are seeing in hypokalemic patients could be a tip of the iceberg situation. In this regard, thiazide diuretic treatment of hypertensives is associated with more ventricular arrhythmias^{14,15} and higher sudden death rates,¹⁶ and these events are avoided by spironolactone treatment. In this context, it should not escape your notice too that most diuretic-based long-term trials of hypertensive patients have failed to show significant protection from myocardial infarction and that this protection also disappeared in the hypokalemic subgroup of the SHEPS trial.⁹ Thus fully 6% at least are suffering from a second thiazide-induced disorder that at least cancels out its primary purpose, to protect from later morbidity. If 50 million hypertensive took thiazides, then this iatrogenic disorder might afflict 3 million ambulatory hypertensives.

There is a good possibility that this lack of cardioprotection as reflected by premature morbid cardiac events is related to an attendant induced myocardial K^+ or Mg^{2+} depletion.³⁻⁵ Recent studies reinforce these possibilities.^{17,18} It's too bad that someone 20 years ago did not have the perspicacity to propose an outcome trial comparing spironolactone head-to-head with thiazide. Many cardiovascular deaths might have been avoided. But now at last we do have the evidence from the RALES trial² and from the subgroup analysis of SHEPS.⁹

In this context, it should also be noted that dietary K^+ depletion appears to be a *sine qua non* for expressing various rat forms of genetic hypertension, all of which are accordingly corrected or prevented by increasing dietary K^+ intake or even better by treating with spironolactone.¹⁹ The converse of these relationships is also true. In a human trial²⁰ and in our studies of stroke-prone hypertensive animals,²¹ high K^+ diets were associated with stroke protection in humans, and in the animals a lowered renin activity with arrest of vascular pathology along with the stroke protection.

Finally, there could be other hazards of K^+ depletion in thiazide-treated patients. Thus, the original MRC trial reported a 12% incidence of glucose intolerance after 5 years of thiazide treatment. Glucose intolerance and insulin secretion are impaired by K^+ depletion and improved by its correction. This relationship too needs further consideration.

In summary, first, thiazide-induced K^+ or Mg^{2+} depletion in hypertension and in CHF is probably not benign and may increase the risk of morbid cardiac events. Second, increasing dietary K^+ without also blocking high aldosterone levels probably has little corrective value because, unless aldosterone is also blocked, the fed K^+ is directed into the urine by the endogenous excess aldosterone¹³ caused by the thiazide diuretic activation of the renin system. Third, the future for developing better aldosterone antagonists to produce an ideal natriuresis, ie, one with no K^+ and Mg^{2+} loss, has never been brighter. This is because the renal intracellular mineralocorticoid receptor has been purified and cloned, and it could be used in binding studies to search for better and better antagonists without any endocrine side effects. One such candidate, eplerenone, is now in clinical trial. Such a pharmacologic resource would enable physicians to more broadly or selectively contain renin system activity in cardiovascular disorders.

Meanwhile, right now generic spironolactone is already in the drugstore waiting for thoughtful clinicians to give it a try at just 25 mg/day or even 25 mg every other day. You could stop the thiazide drug when starting this or shortly thereafter. Just remember, for the reasons I have given, do not expect anything much to happen before 3 or 4 weeks. By then, your patient will be dry, and his or her heart and skeletal muscles will work better. He or she will feel better, and will live longer, and the good news is you do

not need anybody's permission (except your patient's) to proceed. Good luck!

Editor's Note re: Clinical Pearls #1

This first discussion of a clinical dilemma fits our criteria for a "clinical pearl" because it offers rational, but widely unrecognized solution to broad everyday clinical problem. Clinical pearls can surface anytime in the minds of clinicians or basic scientists provided they are already tuned in to the pathophysiologic factors in play. This first example involves the impact of daily diuretic therapy to reduce body salt and water content in either hypertensive or heart failure patients. The cost of this therapy in both situations is the same, unwanted K^+ loss. The desired sodium volume depletion invariably induces a commensurate reactive increase in kidney renin release, to increase plasma angiotensin and aldosterone levels to support the falling blood pressure. However, when aldosterone is increased it continuously diverts more of the dietary K^+ and Mg^{2+} into the tubular urine and it becomes more efficient at doing this when your patient ingests more K^+ .^{12,13} Thus, you cannot easily eat your way out of this with high K^+ foods or with K^+ tablets.²² The solution is, either live without the thiazide (renin and aldosterone levels would decrease), or better yet add or substitute spironolactone to block aldosterone action. This will restore cardiac muscle K^+ and Mg^{2+} and cardiac performance^{23,24} and well being, and more than likely it will reduce the risk of later cardiovascular morbid events and prolong useful life.

JOHN LARAGH
Editor-in-Chief
American Journal of Hypertension
515 Madison Avenue, Suite 1212
New York, NY 10022

Address correspondence and reprint requests to: Dr. John Laragh, American Journal of Hypertension, 515 Madison Avenue, Suite 1212, New York, NY 10022; e-mail: jsealey@mail.med.cornell.edu. © 2001 American Journal of Hypertension, Ltd.

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