Serum Potassium, Thiazides, Aldosterone, and Mineralocorticoid Receptors

To the Editor:

I read with interest the article by Alderman et al1 on the clinical significance of hypokalemia and hyperkalemia in the antihypertensive treatment and prevention of cardiovascular complications. The conclusion was that, in most patients, concerns about potassium levels should not influence the clinician’s decision about initiating hypertension treatment with low-moderate doses of thiazides. Chlorothalidone reduces the risk of congestive heart failure, in comparison with lisinopril and amldipine,1 but it also activates the renin-angiotensin-aldosterone system. We address the issue that, beyond plasma potassium levels, during thiazides, the activation of the renin-angiotensin-aldosterone system and, in particular, the stimulation of mineralocorticoid receptors (MRs) are key determinants in the inflammatory process and the progression of cardiovascular disease.

The Randomized Aldactone Evaluation Study and Eplerenone Post-AMI Heart Failure Efficacy and Survival Study2 have shown that low doses of spironolactone (SP) or eplerenone, added to the standard therapy including thiazides for treatment of severe heart failure, improve survival by 30%. An interesting demonstration that the positive effect of SP is not attributed to amelioration of serum potassium but to the blocking of MRs comes from the study by Ma et al.3 These authors showed that, in hypertensive patients, SP could reduce plasminogen activator inhibitor 1 concentration in serum, whereas triamterene was ineffective; hydrochlorothiazide indeed worsened plasminogen activator inhibitor 1 concentration, which is a known marker of inflammation. The conclusion was that the principal effect of SP in the reduction of cardiovascular risk is the blocking of MR and not the increase of potassium. We also found that canrenone is able to protect MRs from the inflammatory action of aldosterone in mononuclear leukocytes in vitro, whereas amiloride is not.4

From all of these considerations, it can be concluded that thiazides can reduce blood pressure and ameliorate congestive heart failure but can only partially protect from cardiovascular risk because of an increase of aldosterone, leading to inflammatory reaction at the level of the kidney, heart, and lymphocytes, independent from the sodium intake. SP or its derivatives improve serum potassium, reduce insulin resistance, and prevent the inflammatory effect of aldosterone. SP activates all of the components of the renin-angiotensin-aldosterone system, but MRs are blocked, neutralizing the proinflammatory effect of aldosterone. These discrepancies point out the fundamental role of MR even in situations of volume depletion and activation of the renin-angiotensin-aldosterone system.5 Previous studies have ascribed to angiotensin II a key role in the onset and progression of cardiovascular damage, but it is more likely that the increase of aldosterone and MR-mediated effect is the principal factor involved in the inflammatory reaction at the level of the target tissues.

From all of these considerations it follows that the treatment of hypertension with MR antagonists should not only regulate plasma volume, potassium concentration, and blood pressure but also reduce cardiovascular risk by inactivating MRs, which are the principal mechanisms involved in heart fibrosis and hypertrophy. Our point of view is that MR blockers alone or combined with thiazides or other drugs could be considered for treatment of hypertension because they can regulate blood pressure, further reduce cardiovascular complications, and avoid the risk of hyperkalemia or hypokalemia.

Disclosures

None.

Decio Armanini
Department of Medicine-Endocrinology
University of Padua
Padua, Italy

Luciana Bordin
Giulio Clari
Department of Molecular Medicine-Biological Chemistry
University of Padua
Padua, Italy


