CALCIUM ANTAGONISTS: A MORE EXPANSIVE ROLE IN TREATING PERSONS WITH REDUCED KIDNEY FUNCTION?

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INTRODUCTION

Several recent studies have highlighted the benefits of inhibition of the renin-angiotensin-aldosterone system (RAAS) in reducing adverse clinical outcomes in many patients with chronic kidney disease (CKD). In patients with hypertensive and diabetic nephropathy, the African American Study of Kidney Disease and Hypertension (AASK) and the Irbesartan Diabetic Nephropathy Trial (IDNT), respectively, have not only demonstrated improved composite renal outcomes with renin-angiotensin-aldosterone-system (RAAS) inhibition, but have raised concerns about the role of dihydropyridine calcium channel blockers (DHPCCBs) in patients with CKD. Prospective studies of renal outcomes suggest that DHPCCBs may be less advantageous than other anti-hypertensive drugs in patients with proteinuric CKD, thus arguing against the use of DHPCCBs as first-line drugs in this setting. Despite these findings, a comprehensive assessment of the multiple end organ risks in CKD patients and difficulties in achieving recommended blood pressure control may support a more expanded role for DHPCCBs and/or non-DHPCCBs in patients with CKD.

CALCIUM CHANNEL BLOCKERS IN HYPERTENSION

Historical evidence strongly supports the use of CCBs for reducing adverse hypertension-related events. For example, the use of a DHPCCB in combination with a diuretic has yielded comparable significant reductions in cardiovascular disease (CVD) events and stroke in both the Hypertension Optimal Treatment trial and the Systolic Hypertension in Europe trial. In addition, in meta-analyses of 5 positive controlled trials, there were trends that favored CCB-based therapy for stroke over traditional treatment for coronary heart disease (CHD), with no difference for all-cause mortality.

The recently completed Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) reported no difference in overall cardiovascular mortality among high-risk patients with hypertension randomized to either diuretic (chlorthalidone), DHPCCB (amlodipine), or angiotensin converting enzyme inhibitor (ACEI; lisinopril). However, the alpha-blocker arm (doxazosin) was terminated early due to increased rates of congestive heart failure (CHF). Of note, all cause mortality did not differ between groups, nor was there an increase in non-cardiovascular deaths in the amloaspine group. Among cardiovascular (CV) outcomes, only CHF was more prevalent in the amlodipine group in comparison to chlorthalidone. This was not totally unexpected as the study design specified a preference for diuretic to be reserved until the third line agent in the non-chlorthalidone arms. Stroke, a major complication of hypertension and CKD, did not differ between amlospine and diuretic (RR 0.93; 95% CI 0.82–1.06, P=.28), whereas stroke was higher in the ACEI group compared to diuretic, (RR 1.15; 95% CI 1.02–1.30, P=.02). Thus, DHPCCBs, either alone or in combination, may be of benefit in the prevention and management of hypertension-related CV events.
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CALCIUM CHANNEL BLOCKERS IN CKD

So far, several studies indicate that DHPCCBs appear to be less effective than ACEI or angiotensin receptor blocker (ARB) in reducing composite renal endpoints (defined as a doubling of serum creatinine, end stage renal disease, or death) in patients with type 2 diabetic nephropathy or hypertensive nephropathy, respectively. However, no difference has been observed between inhibition of the RAAS and DHPCCB use for death alone or secondary CV outcomes.

The effects of DHPCCB on proteinuria and glomerular filtration rate (GFR) have been prospectively evaluated in the Ramipril Efficacy In Nephropathy (REIN) study in which 117 non-diabetic patients with chronic proteinuric nephropathies were randomized to ACEI or placebo plus conventional antihypertensive therapy. Sixty-three percent of the patients were treated with DHPCCB. Within the placebo group, DHPCCB-treated patients had higher levels of proteinuria (5.1±0.2 g/24 h vs 4.3±0.3 g/24 h, P=.02), but not in the ACEI group (4.4±0.2 g/24 h vs 4.1±0.2 g/24 h). Overall, DHPCCB-treated patients in the ACEI group had significantly less proteinuria compared with placebo (P=.028). DHPCCB-treated patients also had a more rapid decline in GFR than non-DHPCCB-treated patients in the placebo group, but not in the ACEI group, reinforcing the clinical utility and safety of DHPCCB in combination with ACEI. Moreover, no differences between groups in urinary protein excretion at mean arterial pressure levels equal or below 100 mm Hg were demonstrated, suggesting an attenuation of class-specific differences at lower blood pressure levels.

In the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) Trial where the angiotensin receptor blocker (ARB), losartan, was shown to be superior to non-RAAS inhibition, it was remarkable that in order to achieve goal blood pressure, 83.8% of the ARB arm received diuretic and 77.9% of the ARB received CCB (80% DHPCCB). Given the background of these and related clinical trials the role of CCB as part of a combination approach in CKD patients deserves close attention.

Combination ACEI and ARB not only lowered both blood pressure and urinary protein excretion in diabetic subjects, but improved composite renal outcomes (doubling of serum creatinine or ESRD) for non-diabetic proteinuric patients in comparison to either alone. Although DHPCCBs have not been shown to lower proteinuria despite a reduction of blood pressure, non-DHPCCBs have been shown to reduce both arterial pressure and proteinuria. Bakris et al reported that the combination of an ACEI with a non-DHPCCB produced a greater reduction in proteinuria over either agent alone at one year, suggesting the sustained added anti-proteinuric effect may assist in slowing CKD progression and attenuating CVD risk. A recent systematic review was performed of these and other studies to assess the differential effects on the progression of nephropathy when using DHPCCBs and non-DHPCCBs in patients with or without diabetes but with hypertension and proteinuria. The report demonstrated that despite similar antihypertensive effects, only non-DHPCCBs achieved a consistent reduction in proteinuria. Thus, the available data suggests that non-DHPCCB agents may be particularly advantageous in patients with CKD. However, further prospective studies are needed.

SUMMARY

It is now well known that multiple antihypertensive agents are needed to reach goal BP in patients with CKD. Most large randomized CKD trials have reported that more than 3 medications per patient are needed to achieve a BP goal in the range of 130/80 mm Hg. The available evidence
sponsors the use of ACEI or ARB in combination with a diuretic as first line therapy. While several studies have shown promising outcomes with combined ACEI/ARB, in most prospective CKD trials designed to compare RAAS inhibition with placebo, more than half of the participants randomized to the RAAS inhibition arm received CCB therapy to achieve BP control: again supporting the role of CCBs as effective adjuncts for effective BP control in patients with CKD (Figure 1). While significant intra-class variations of CCBs on urinary protein excretion have been reported, the CCBs including DHPCCBs appear to be safe and effective when used in combination with RAAS inhibitors, particularly at the recommended lower BP levels where the class differences in antihypertensive agents appear to be attenuated. In addition, the antiproteinuric properties of non-DHPCCBs are likely to provide additional reno-protection, more similar to RAAS inhibition. While combination ARB and ACEI have been shown to be safe and effective in CKD patients, the addition of a beta-blocker should be used with caution as a recent report suggested the combination of these three agents may be deleterious in patients with CHF, a common co-existing medical condition in CKD patients. Therefore, CCBs should be strongly considered as the third drug in a multi-drug regimen to achieve recommended goal blood pressure (130/80 mm Hg) in CKD patients.

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