The role of calcium antagonists in chronic kidney disease

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Abstract

The incidence of end-stage renal disease (ESRD) secondary to diabetes and hypertension has increased and is a major worldwide public-health problem. The presence of chronic kidney disease (CKD) is an important factor to consider when selecting antihypertensive medications. Specifically, if proteinuria or albuminuria is present, agent selection to low blood pressure should ideally also lower albuminuria significantly. An increase in albuminuria is a sensitive and independent predictor of CKD progression as many post hoc analyses of clinical trials demonstrate failure to lower albuminuria even with blood pressure reduced does not provide optimal slowing of nephropathy progression. This paper reviews the effects of calcium antagonists (CAs) on hypertension, proteinuria and CKD progression. The totality of the data supports the concept that in early stage CKD with either no or low levels of microalbuminuria all CAs behaves similarly. However, in advanced proteinuric nephropathy nondihydropyridine CAs provide significantly greater reductions in albuminuria than dihydropyridine CAs. Moreover, they are preferred in that setting to assure blood pressure as well as albuminuria reduction. Achieving a blood pressure of < 130/80 mm Hg utilizing a renin angiotensin system (RAS) blocker plus nondihydropyridine CAs as part of the regimen to lower blood pressure is recommended by current CKD guidelines for treating hypertensive CKD patients with proteinuria.

Key words: dihydropyridine calcium antagonist, nondihydropyridine calcium antagonist, chronic kidney disease, proteinuria, hypertension, albuminuria.

Introduction

The overall awareness and treatment of hypertension assessed by blood pressure (BP) control in the National Health and Nutrition Examination Survey (NHANES) increased from 29% (1999-2000) to 37% in 2003-2004 [1]. More than 60 million adults in the Unites States were estimated to have hypertension in 2000 [2, 3] while update estimates of the prevalence from the NHANES data put the prevalence in 2004 at 72 million [4]. The cost to treat hypertension and its co morbid conditions has exceeded an annual amount of 55 billion dollars estimated in 2006 [5].

The prevalence of chronic kidney disease (CKD) secondary to hypertension and diabetes has become a worldwide public-health problem [6] with the disease now affecting about 14.8% of the general population [7]. The cost of health care dollars spent on CKD progression and end-stage renal disease (ESRD) spiraling out of control [8]. Therefore, slowing progression of CKD is an important factor to consider when selecting antihypertensive medications.

Presence of albuminuria or an increase over time is a sensitive and independent predictors of CKD progression and cardiovascular disease [8-

13]. Moreover, post hoc analyses of several clinical studies indicate that if high levels of albuminuria are reduced in concert with attaining blood pressure goals the rate of CKD progression is markedly slowed and cardiovascular risk reduced [8-11, 14]. Evidence is growing that blood pressure reduction without albuminuria reduction in advanced nephropathy fails to provide maximal protection against declines in kidney function [15]. This is true regardless of whether the aetiology of nephropathy is related to diabetes or other causes [16].

This paper reviews the effects of calcium antagonists (CAs) on changes in proteinuria in patients with hypertensive CKD. It focuses on differences within the CA subclasses and these affect CKD treatment outcomes.

Calcium channel distribution and blood pressure reduction

There are many different voltage-dependent calcium channels, the high voltage calcium channels including P-, P/Q-, L-, N-, and R-type channels and a low voltage-activated T-type channel. Calcium antagonists modulate various calcium-dependent functions of vascular smooth muscle in the human body including cardiac myocytes and cardiac conductive tissues.

All CAs approved for blood pressure reduction work by blocking the L-calcium channel. Moreover, each subclass binds at a uniquely different location on the L- channel [17] hence making CAs different from receptor antagonists or enzyme inhibitors. These differences account, in part for some of the observed clinical differences in dromotropy, negative inotropy and vascular selectivity [18, 19]. Verapamil was first CA synthesized in 1962 and signalled the era of an important new class of drugs, the CAs. These agents were introduced for the treatment of hypertension in the 1980s. The main classes of L-channel CA approved for blood pressure reduction are the dihydropyridines and include amlodipine, felodipine, nicardipine and nifedipine and nondihydropyridines that are comprised by the phenyalkyamine, verapamil and the benzothiazepine, diltiazem. The most common side effects of these agents are peripheral oedema, flushing and headache [20-22].

Calcium channel distribution in the kidney

The L-type calcium channels had a substantial distribution within the renal vascular bed and they are located primarily on the afferent (preglomerular) arteriole. When antagonised results in impairment of renal autoregulation. In animal models this impairment in auto regulatory function is associated with a relative lack of renal protection compared with the observed blood pressure reduction [23-25]. As a result these agents fail to maximally protect against renal parenchymal changes unless systolic BP is lowered bellow the range of 100-105 mm Hg [24, 26].

T-type calcium channels are located in both the afferent (pre-glomerular) and the efferent (post-glomerular) arterioles [27] and as both arterioles would be dilated in the additional presence of renin-angiotensin (RAS) blockade, their inhibition may overcome the effect of increased glomerular pressure transmission.

Efonidipine, a dihydropyridine T-type CAs demonstrated significant greater reduction in intraglomerular pressure and proteinuria than L-type dihydropyridine despite similar lowering effects in BP [27-29] This hemodynamic effect of T-type calcium channels is further supported with non hemodynamic effects, including inhibition of Rho-kinase activity in response to transforming growth factor-β, reduced tubulointerstitial fibrosis and epithelial-mesenchymal transition [30].

The L-channel dihydropyridine CAs have been studied in humans with regard to proteinuric kidney disease progression, and they failed to show comparable outcomes benefit with blockers of RAS system [31, 32].

Differential effects of calcium antagonists on albuminuria

Given these differences in calcium channel properties and distribution as well as differential vascular effects it is not hard to imagine how they could differentially affect changes in glomerular hemodynamics and flow. In this regard a possible explanation for the differential effect of dihydropyridine and non-dihydropyridine CAs on proteinuria is their action on renal autoregulation. Animal studies clearly demonstrate that dihydropyridine CAs, through their action on the afferent arteriole abolish the inherent ability of the kidney to regulate flow and pressure transmitted to the glomerulus over a wide range of pressures [24-26, 33-35]. This results in the linear transmission of the systemic blood pressure into the glomerular capillary. Glomerular hypertension results in increased protein filtration (proteinuria) and endothelial damage ensues. If systolic pressure is not substantially reduced to levels below 120 mm Hg, increased shear stress has been shown to result in release of soluble mediators that, promote replacement of normal kidney tissue by fibrosis [33, 34, 36]. As a result, the potentially beneficial effects of blood pressure reductions are balanced or outweighed by the increased transmission of pressure to the glomerulus due to the afferent vasodilation [11]. Non-dihydropyridine CAs also impair renal autoregulation, although to a lesser degree and thus, allows for some regulation by the kidney [33, 36].

A differential effect also has been observed between dihydropyridine CAs and nondihydropyridine CAs in their ability to affect glomerular membrane permeability. In patients with impaired renal autoregulation, dihydropyridine CAs have no effect on glomerular membrane permeability [37]. Conversely, nondihydropyridine CAs when tested in the same subjects reduced glomerular membrane permeability [37]. This permeability effect was especially pronounced with large molecules. These differences in membrane permeability are independent of the effects on BP [38]. These differences between subclasses of CAs are summarized in Table I.

Kidney protection with calcium antagonists in clinical trials

Reductions in BP are associated with decreases in both urine protein excretion and progression of nephropathy in patients with advanced CKD [10, 39]. However, not all antihypertensive medications that reduce BP achieve similar reductions in proteinuria and the progression of nephropathy [11, 38]. This suggests that some antihypertensive medications virtue of their mechanism of action may result in production of other cytokines or mediators that aid in their protective effect apart from BP reduction.

Antihypertensive agents that reduce both BP and proteinuria have been shown to reduce the progression of nephropathy. Both ACE inhibitors and ARBs have been shown to have such effects in advanced nephropathy [40-44]. The question is do CAs have such effects?

In the most randomized clinical trials of advanced proteinuric nephropathy statistically powered to compare dihydropyridine CAs to ACE inhibitors or ARBs, dihydropyridine CAs, the CAs fail to show comparable slowing in CKD progression [40, 42, 44]. Despite this a few studies have shown that CAs are effective agents for long-term maintenance of kidney function as assessed by GFR compared with a diuretic and an ACE inhibitor [45, 46].

In two separate systematic reviews, CAs were found effective in reducing BP in patients in patients with advanced CKD. Both dihydropyridine CAs and nondihydro-pyridine CAs equally reduced BP, but their effects on CKD progression in patients with proteinuric kidney disease were divergent [11, 31].

Several studies document that dihydropyridine CAs do not reduce proteinuria or slow CKD progression in advanced proteinuric kidney disease [40, 47-65]. In a limited number of studies, data suggest that nondihydropyridine CAs might have beneficial effects on slowing nephropathy progression [33, 38, 66-69].

In subsequent randomized blinded outcomes studies of patients with advance nephropathy was noted progressive increases in proteinuria and a more rapid decline in kidney function in patients treated with dihydropyridine CAs compared with those treated with ACE inhibitors or ARBs [42, 70]. In these studies a dihydropyridine CAs, amlodipine failed to reduce proteinuria, an effect that correlated with a faster decline in kidney function, despite substantial reductions in BP.

The Ibesartan Diabetic Nephropathy Trial (IDNT) was a randomized, double-blind study conducted in 1715 patients with type 2 diabetes. The objective of the trial was to compare the effectiveness of an ARB, irbesartan, a dihydropyridine CAs, amlodipine, and placebo on the progression of nephropathy. Blood pressure changes were comparable between all of the treatment groups. However, proteinuria levels decreased by 33% in the ARB treatment group compared with a reduction of 6% in the dihydropyridine CAs treatment group and 10% in the placebo treatment group. Patients taking an ARB had better renal outcomes compared with the dihydropyridine CAs and placebo treatment groups, despite equal control of BP [71].

The African-American Study of Kidney Disease and Hypertension (AASK) study was a randomized, double-blind trial conducted in 1094 African Americans with hypertensive renal disease. The objective of the study was to determine an effective strategy to treat hypertension and to prevent ESRD, using 3 antihypertensive drug classes: an ACE inhibitor ramipril, a dihydropyridine CAs, amlodipine, and a β-blocker, metoprolol. Data obtained 3 years into the study for the ACE inhibitor and dihydropyridine CAs groups showed a similar lowering of BP for both groups. However, proteinuria levels increased in the dihydropyridine CAs group and decreased in the ACE inhibitor group [72]. This difference between the treatment groups was significant and persisted throughout the follow-up period. There was a similar difference between

Table I. Factors that help explain the differential effects of calcium channel blockers on renal morphology and function

Parameter	CCB effect	
	DHPCCBs (Amlodipine-like)	Non-DHPCCBs (Verapamil, Diltiazem)
Albuminuria/ proteinuria	→	→↓[#]
Mesangial volume	→	↓ Expansion (diabetes)**
Glomerular scarring**	→	↓
Renal autoregulation[†]	Abolished	Partially abolished

→ no effect; ↓ decrease

[#] Decreased only if blood pressure reduced and on low salt diet

[†] Data from both animal and human experiments

*** Data from animal models. Note, however, that renal autoregulatory mechanisms are not affected by ACE inhibitors*

the treatment groups on renal events. In subjects with mild-to-moderate chronic renal insufficiency associated with hypertensive nephrosclerosis, there was a greater slowing in the deterioration of renal function in the ACE inhibitor treatment group than in the dihydropyridine CAs treatment group.

In both of these long term CKD outcome trials, dihydropyridine CAs failed to reduce proteinuria levels and slow CKD progression despite achieving reductions in BP comparable to an ACE inhibitor or ARB. Conversely, controlled clinical trials with nondihydropyridine CAs consistently shown reductions in both BP and proteinuria, and nondihydropyridine CAs in small but long term studies demonstrate slowed CKD progression [31, 73].

A systematic review of 28 randomized trials evaluated the effects of CAs and other antihypertensive agents on the progression of renal disease in hypertensive patients with or without diabetes found similar blood pressure-lowering with differential antiproteinuric effects between dihydropyridine CAs and nondihydropyridine CAs [31]. The primary end point assessed was percentage change in proteinuria, compared with baseline values, in patients treated with one of the CAs subclasses. Blood pressure parameters and kidney function data were analyzed for 1338 patients and 510 patients respectively. A 32% difference in proteinuria values was observed between the 2 subclasses. There was +2% change in proteinuria for dihydropyridine CAs and –30% change for nondihydropyridine CAs (95% confidence interval, 10 to 54%, $p = 0.01$) (Figure 1).

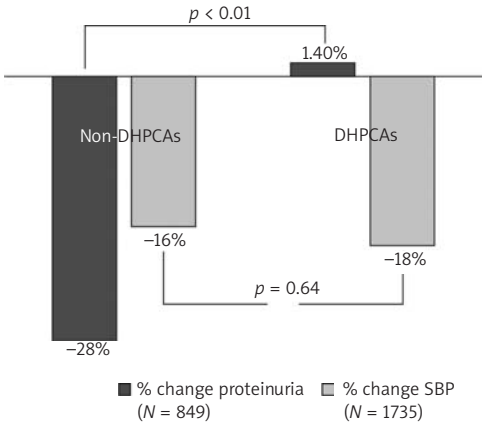

Figure 1. The percentage change in proteinuria after adjustment for sample size and study length for dihydropyridine CAs and nondihydropyride CAs

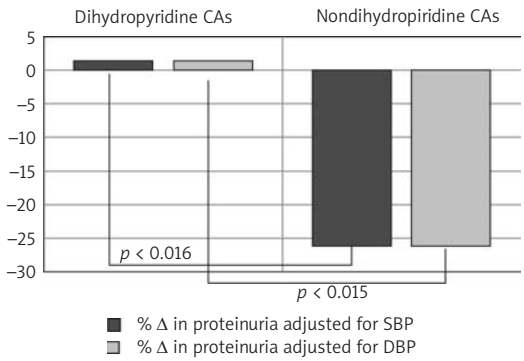

Figure 2. The percentage change in proteinuria among patients treated with dihydropyridine CAs or nondihydropyride CAs adjusted for change in SBP and DBP

After adjustment for BP, sample size and study duration, a trend persisted in favor of proteinuria for nondihydropyridine CAs (Figure 2). A secondary analyses supported the benefit of nondihydropyridine CAs with or without concurrent ACE inhibitor or ARB therapy and showed the mean change in proteinuria was 2% for dihydropyridine CAs and –39% for nondihydropyridine CAs (95% confidence interval for a 41% difference, 19 to 63%, $p = 0.002$). These findings are important and suggest that a differential effect exists between dihydropyridine CAs and nondihydropyridine CAs on proteinuria, despite equal reductions in systemic BP [31].

These findings are further supported by data from recent studies. The Clinidipine vs. Amlodipine Randomized Trial for Evaluation in Renal Disease (CARTER) study, where cilnidipine, a dual L-/N-type CA that dilates both efferent and afferent arterioles, exerted a greater antiproteinuric effect over amlodipine in a group of 339 patients already receiving treatment with a RAS blockade. In this study the urinary protein/Cr ratio decreased in the cilnidiline group (–14.4 ±5.6%) but not in the amlodipine group (+13.9 ±7.7%) ($p < 0.01$). Cilnidipine compared to amlodipine group prevent the progression of proteinuria even in the subgroup of patients whose BP felt below the target level when coupled with a RAS blockade [74]. Similarly combination therapy with clinidipine and an ARB, valsartan reduced albuminuria by 44% in diabetic patients with albuminuria [75].

In the Amlodipine to Benidipine Changeover (ABC) study, in 58 poorly controlled hypertensive patients was evaluated BP and proteinuria after changeover from amlodipine, an L-type dominant CAs, to benidipine, an L- and T-type CAs. According to the results BP and urinary protein excretion adjusted for urinary creatinine reduced significantly (from 151/90 to 140/81 mm Hg, $p < 0.0001$ and from 0.35 ±0.82 to 0.22 ±0.55 g/g creatinine, $p < 0.0119$ respectively). It is noteworthy that also in this study the urinary protein reduction was observed only in patients with RAS blockade [76].

Dihydropyridine CAs have not demonstrated a beneficial effect on the progression of advanced proteinuric CKD and are specifically prohibited as first line agents in such patients by guidelines [77]. Nondihydropyridine CAs are superior to dihydropyridine CAs for reducing proteinuria and while

there are no head to head comparisons, if proteinuria is a marker of CKD progression, nephropathy as well. This suggests that nondihydropyridine CAs in combination with an ACE inhibitor or an ARB, should be preferred for treating hypertensive patients with proteinuric renal disease or renal insufficiency.

These differences between CAs on proteinuric kidney disease are not seen in the context of microalbuminuria, primarily because of the mechanisms that portend microalbuminuria relate more to inflammatory states and stimuli than major podocyte problems [16]. No significant differences were seen in microalbuminuria levels between those patients treated with the ACE inhibitor or an L-type CAs [78-80].

Conclusions

This review supports the following conclusions:

(1) in patients without proteinuric CKD the reduction of BP with any agents available, regardless of CA subclass is approproiate and may be used;
(2) in patients with proteinuric CKD the anti-proteinuric superiority of nondihydropyridine CAs is evident, and is the preferred class between these 2 subclasses of CAs;
(3) nondihydropyridine CAs in combination with an ACE inhibitor or an ARB, should be preferred for treating hypertensive patients with high levels of proteinuria and CKD.

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