Update on the Clinical Pharmacology of Candesartan Cilexetil

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The renin-angiotensin system plays a central role in the regulation of blood pressure through its primary effector hormone angiotensin II. Studies conducted nearly 30 years ago with peptidic angiotensin II receptor blockers (ARB) suggested that disruption of the renin-angiotensin system offered considerable promise for the treatment of hypertension as well as heart failure. This promise was initially realized with the advent of angiotensin converting enzyme inhibitors, and more recently with nonpeptidic ARB that selectively antagonize the AT1-angiotensin receptor subtype. The potent and long-acting agent candesartan cilexetil illustrates how these new ARB fulfill the promises suggested by the early studies. Candesartan cilexetil provides a clinically relevant, dose-dependent reduction in diastolic and systolic blood pressure at doses of 4 to 16 mg once daily in patients with mild to moderate hypertension. Recent studies suggest that further blood pressure lowering is obtained with a 32-mg once daily dose. In comparative clinical trials, 8 mg of candesartan cilexetil and 10 to 20 mg of enalapril provided comparable antihypertensive effects. The safety and tolerability profile of candesartan cilexetil is comparable to placebo. Notably, this agent does not produce the dry, nonproductive cough that often limits use of angiotensin converting enzyme inhibitors, nor does it cause side effects that limit other antihypertensive drug classes. On the basis of the results of initial clinical studies, ARB also possess cardioprotective and renoprotective properties that promise to expand the role that these new agents will play in treating cardiovascular disorders.


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The angiotensin II receptor blockers (ARB) are the newest drug class to be approved by the Food and Drug Administration for the treatment of hypertension.1,2 These agents, like the angiotensin converting enzyme (ACE) inhibitors, produce a number of beneficial effects as a result of disrupting the renin-angiotensin system (RAS). The ARB selectively antagonize the AT1 receptor, and thereby, they block the biological effects of angiotensin II, which are then mediated by this receptor subtype. Importantly, angiotensin II regulates blood pressure and water and electrolyte balance by the AT1 receptor by causing vasoconstriction, stimulating aldosterone and vasopressin secretion, promoting renal tubular sodium reabsorption, augmenting peripheral noradrenergic activity and central sympathetic activity, and reducing renal blood flow.3 Angiotensin II also induces vascular smooth muscle proliferation and cardiac growth through the AT1 receptor. These latter actions are believed to be important in the cardiac and vascular remodeling that occur in various cardiovascular disorders. However, angiotensin II also produces antiproliferative and vasodilatory effects through another receptor subtype, termed AT2, which...
tend to counteract some AT₁-mediated events; these beneficial AT₂ effects are not blocked by currently available ARB.³,⁴

The ARB are a more selective approach to regulating the RAS than ACE inhibitors.⁴ First, ACE not only catalyzes the conversion of angiotensin I into angiotensin II, but it also is responsible for the metabolism of the vasodilator bradykinin.⁵ As a result, ACE inhibitors reduce production of angiotensin II and also increase bradykinin levels; both effects are believed to contribute to the overall efficacy of these agents. However, the persistence of bradykinin in the airways is also believed to be responsible for the dry, nonproductive cough that often limits the use of this drug class. Approximately 5% to 20% of patients treated with ACE inhibitors develop cough, and in certain populations, such as Asian patients, the incidence may be as high as 50%.⁶ Cough generally occurs more frequently in older and female patients and in those with heart failure.⁶ Second, enzymes other than ACE, such as chymase and cathepsin G, can also produce angiotensin II. Thus, this important hormone can still be produced in the presence of ACE inhibition. Finally, by reducing angiotensin II production in general, ACE inhibitors may limit the beneficial antiproliferative and vasodilatory effects, which are mediated by AT₂ receptors.

EARLY PROMISES OF ARB

The clinical promise that ARB could offer therapeutic advantages over other antihypertensive agents can be traced to studies that were conducted in the late 1960s and early 1970s. One of the earliest ARB, the peptidic analog of angiotensin II saralasin, was used in studies that actually preceded work with ACE inhibitors by a year and a half. In the initial evaluation, saralasin was infused into patients with malignant hypertension (blood pressures 210/135 mm Hg to 225/160 mm Hg) and high or normal renin levels, in whom it produced a precipitous decrease in both systolic and diastolic blood pressure. When the infusion was discontinued, blood pressure increased, and when it was restarted, blood pressure again decreased. These early studies illustrated the promise that ARB would be effective in the treatment of hypertensive patients, including those with normal renin levels.⁷ Although this agent was found to have agonist activity, this disadvantage proved to be an important finding. Further investigations revealed that the response of patients with essential hypertension to this ARB was dependent on the sodium balance.⁸ When saralasin was infused into patients with low renin levels, it had the tendency to increase blood pressure. This agonist effect essentially disappeared in patients who were sodium depleted with a diuretic; however, blood pressure did not decrease below baseline levels. In subsequent studies, sodium was depleted to a greater extent and for longer periods by placing patients on a low sodium diet and administering a loop diuretic.⁹ Although these patients remained hypertensive in the face of sodium depletion, their blood pressure decreased into the normal range after administration of saralasin. This study offered the promise that most patients can respond to ARB if sodium levels are reduced sufficiently. In fact, this strategy is used presently to increase the number of patients who respond to drugs that effect the RAS.

Another benefit of ARB was suggested by studies of patients with heart failure.¹⁰ In these patients, infusion of saralasin lowered heart rate, mean blood pressure, and left ventricular end-diastolic pressure. Despite the decline in mean blood pressure, coronary blood flow increased. This finding prompted further investigations in experimental animals, which led to the first demonstration that angiotensin II plays a major role in coronary vasomotion.¹¹ These early studies showed that ARB had the potential to improve left ventricular function in heart failure patients, with a resulting increase in cardiac index, decline in peripheral and coronary resistance and blood pressure, and increase in coronary blood flow. Moreover, these hemodynamic improvements were seen in conjunction with less myocardial oxygen consumption.

These studies illustrate the lessons that were learned with the early peptidic ARB. Subsequent studies with the ACE inhibitors confirmed these findings, and recent studies with the current generation of nonpeptidic ARB demonstrate the same hemodynamic benefits. Although the promises of disrupting the RAS were suggested by studies with ARB, the ACE inhibitors were developed first for clinical use. One of the major hurdles faced in developing these drugs was identifying nonpeptidic compounds; this hurdle was overcome first with the ACE inhibitors by the identification of captopril, then enalapril, and finally a number of other agents. Subsequently, efforts by Dr. Pieter Timmermans and colleagues¹² led to the identification of the first nonpeptidic, orally active ARB—losartan. Newer ARB with variable pharmacokinetic properties have been developed more recently.

ARB: FULFILLING THE PROMISE IN THE TREATMENT OF HYPERTENSION

Several ARB, including losartan, valsartan, irbesartan, candesartan cilexetil, telmisartan, and eprosartan have been approved for clinical use. The antihypertensive efficacy of these ARB has been established in numerous controlled clinical trials.¹³⁻¹⁵ As a common feature, the ARB do not produce the side effects that are seen typically with other antihypertensive drug classes. This attractive safety and tolerability profile is believed to reflect the specificity of the ARB for the
AT₁ receptor, whereas other drug classes have multiple sites of action.

Candesartan cilexetil is the most potent of the currently available ARB, although potency does not necessarily imply greater clinical efficacy; its recommended daily dose in the treatment of hypertension is 4 to 16 mg once daily. In comparison, losartan is administered at daily doses of 25 to 100 mg, valsartan at 80 to 160 mg, irbesartan at 150 to 300 mg, and telmisartan at 40 to 80 mg.² Candesartan cilexetil is an ester prodrug that is converted to the active carboxylic acid form candesartan after administration (Figure 1). It lowers blood pressure in a dose-related manner, and it maintains its antihypertensive efficacy over long-term treatment.¹³,¹⁶,¹⁷

The dose-related antihypertensive efficacy of candesartan cilexetil is illustrated by a metaanalysis of six placebo-controlled, double-blind, randomized studies of up to 12 weeks duration.¹² These trials involved 1482 patients with mild to moderate hypertension. After correcting for the effect of placebo, dose-related reductions in sitting or standing diastolic and systolic blood pressure were evident at doses of 4 to 16 mg once daily (Figure 2). Moreover, the proportion of patients who responded to treatment increased in a dose-dependent manner, with 55% of patients responding at a dose of 16 mg. The effect of higher doses was evaluated recently in an 8-week, double-blind, placebo-controlled study, in which candesartan cilexetil was administered at doses ranging from 2 to 32 mg once daily to patients with mild to moderate hypertension.¹⁵ Again, candesartan cilexetil lowered blood pressure in a dose-dependent manner, with the greatest response being obtained with the highest dose. At the 16- and 32-mg doses, 54% and 64% of patients, respectively, responded to treatment. These results suggest that greater responses may be obtained by using full antihypertensive doses of candesartan cilexetil, if needed to achieve blood pressure control, relative to treatment with a lower dose.

During candesartan cilexetil treatment, systemic and renal hemodynamics improved in patients with hypertension.¹⁸ After administration of a 16-mg dose, the onset of blood pressure lowering occurred smoothly and reached a maximal level by 3 to 4 h. The reduction in blood pressure corresponded to a reduction in total peripheral resistance without a change in cardiac output. Despite the reduction in blood pressure, the glomerular filtration rate and renal plasma flow increased in association with a pronounced decrease in renal vascular resistance. Moreover, during long-term treatment, the fractional excretion of sodium also improves, which is another very interesting feature of ARB. These findings demonstrate that ARB produce renal vasodilation, which fulfills the promise suggested in early studies with saralasin and later shown with ACE inhibitors.

The antihypertensive effects of ARB appear comparable to those of other drug classes. In most comparative studies, an ARB and ACE inhibitor were assessed. For example, several doses of candesartan cilexetil were compared with 10 mg of enalapril in a double-blind, placebo-controlled study involving 364 patients with mild to moderate essential hypertension.¹⁹ In this study, 8 mg of candesartan cilexetil and 10 mg of enalapril had comparable efficacy; they lowered sitting diastolic blood pressure from baseline by approximately 10.5 mm Hg, with 69% of patients responding to each treatment. In a placebo-controlled titration study involving 227 patients with mild to moderate hypertension, 4 to 8 mg of candesartan cilexetil and 10 to 20 mg of enalapril similarly reduced diastolic and systolic blood pressure, with both active treatments being significantly superior to placebo.²⁰ Moreover, a similar percentage of patients responded to treatment with candesartan cilexetil and enalapril. Notably, twice as many patients in the enalapril group experienced at least one adverse event, with cough...
being reported in 4% of enalapril-treated patients, but none of those treated with candesartan cilexetil.

In patients with mild to moderate hypertension, losartan, valsartan, and irbesartan also provide antihypertensive effects that are comparable to those of enalapril and other ACE inhibitors. Similarly, the ARB are comparable in efficacy to other drug classes as well. For example, 80 mg of valsartan was as effective as the long-acting calcium channel blocker amlo-dipine (5 mg) in patients with mild to moderate hypertension, and 75 to 150 mg of irbesartan was as effective as 50 to 100 mg of the β-blocker atenolol. In hypertensive patients who remain above treatment goals, the addition of hydrochlorothiazide to an ARB regimen provides further blood pressure lowering that is comparable to that obtained by adding hydrochlorothiazide to antihypertensive drugs from other classes.

The ARB are distinguished from ACE inhibitors and other antihypertensive drug classes by an adverse event profile that is comparable to placebo. This improved safety and tolerability profile make ARB an attractive choice as first-line therapy for hypertension. In 8-week controlled trials in patients with mild to moderate hypertension, the proportion of patients who experienced at least one adverse event (regardless of relationship to study treatment) was comparable for candesartan cilexetil (35%) and placebo (34%). The most common adverse events were headache, upper respiratory tract infection, back pain, and dizziness. Whereas back pain occurred at a slightly higher incidence in the candesartan cilexetil group, there was no significant difference between candesartan cilexetil and placebo in the incidence of any other adverse event (Figure 3). Moreover, there was no evidence for dose-dependency over the clinically relevant dose range of 4 to 16 mg once daily. Notably, the incidence of cough was indistinguishable between candesartan cilexetil and placebo (1.6% vs. 1.1%). In these clinical trials, only 2.4% of candesartan cilexetil-treated patients and 2.6% of those given placebo discontinued prematurely due to an adverse event. The safety and tolerability of candesartan cilexetil as well as other ARB were comparable in older (≥65 years) and younger (<65 years) patients as well as in men and women. Thus, the potential of improved tolerability has been realized with the new ARB. This may be expected to translate into better patient adherence to treatment as fewer patients discontinue taking their medications due to negative side effects.

**FUTURE PROMISES—CARDIOPROTECTION AND RENOPROTECTION WITH ARB**

The ARB are expected to provide long-term cardioprotective and renoprotective effects that are similar to those of ACE inhibitors. Nevertheless, the exact mechanism by which ACE inhibitors protect cardiac and renal function has not been fully established. Although the effects of ACE inhibitors are likely due to a reduction in angiotensin II production, it remains plausible that the potentiation of bradykinin may also contribute. As described earlier, the ARB disrupt the RAS in a different, more selective manner.

ACE inhibitors are believed to protect renal function by reducing both systemic and intraglomerular pressure, which leads to a profound decrease in proteinuria. The decrease in intraglomerular pressure may be due to an ability of ACE inhibitors to reduce angiotensin-II-induced constriction of efferent glomerular arterioles. In most experimental and clinical studies, the effects of ARB and ACE inhibitors on renal hemodynamics appear comparable. As described previously, acute administration of candesartan cilexetil to hypertensive patients produced a pronounced decrease in renal vascular resistance. In a recent study, the effects of irbesartan and enalapril on renal hemodynamics were compared after acute and chronic administration to patients with mild to moderate hypertension and normal renal function. Both agents similarly reduced systemic blood pressure and caused renal vasodilation; however, the time course for the renal effects differed. Enalapril, but not irbesartan, significantly increased effective renal plasma flow and decreased filtration fraction at 4 h after administration of the first dose. However, after 6 weeks of treatment, irbesartan had a longer lasting effect on renal hemodynamics. At 24 h after the last dose, irbesartan still provided an increase in effective renal plasma flow and decrease in renal vascular resistance, whereas the effect of enalapril had returned to baseline. These results suggest that long-acting ARB maintain their...
effects on renal hemodynamics through the end of the dosing interval, which may be important for providing long-term renoprotection.

The ability of ACE inhibitors to reduce urinary albumin excretion has been confirmed with ARB. Candesartan cilexetil (8 to 16 mg once daily) was evaluated in hypertensive patients with type II diabetes in a 12-week randomized controlled study. In a subset of 35 patients who had microalbuminuria, candesartan cilexetil reduced urinary albumin excretion by 57%, whereas it increased slightly with placebo. In another study, losartan and enalapril significantly reduced albuminuria to a similar extent in 93 patients with essential hypertension. This finding suggests that glomerular leakage of albumin is an AT1 receptor-mediated event.

Angiotensin II is believed to play an important role in the cardiac fibrosis and remodeling that is seen in heart failure and after myocardial infarction. In patients with chronic heart failure, ACE inhibitors significantly reduce mortality, improve symptoms, and delay progression. Similarly, in patients suffering an acute myocardial infarction, early treatment with ACE inhibitors reduces cardiovascular morbidity and mortality. It remains to be determined whether ARB provide similar benefits. In the Evaluation of Losartan in the Elderly (ELITE) study, the effect of losartan and captopril were compared in 722 elderly patients with New York Heart Association class II to IV heart failure. Although these treatments did not differ in terms of their effects on the primary end point, renal dysfunction, the ARB provided a significant 46% reduction in risk for all-cause mortality relative to the ACE inhibitor (P = .035). Other studies with ARB in heart failure indicate that these agents provide symptomatic improvement in exercise time and left ventricular ejection fraction. These studies suggest that ARB represent attractive therapies for the treatment of heart failure as well as hypertension. In reality, these two conditions represent the same disorder, except that in heart failure, the heart is unable to sustain the elevated blood pressures. Given the benefits of both ARB and ACE inhibitors, the ongoing Candesartan Cilexetil in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) study is evaluating whether candesartan, compared to placebo, reduces the combined end point of cardiovascular mortality or hospitalization for the management of chronic heart failure (unpublished data).

In summary, inhibition of the RAS is an attractive approach for treatment of hypertension and heart failure. The promises seen in early experiments with agents such as saralasin have largely been fulfilled, initially with ACE inhibitors and more recently with selective ARB. The results of ongoing long-term studies, which are evaluating cardiovascular outcomes in patients with hypertension, are expected to show that these agents also have favorable effects on cardiovascular morbidity and mortality.

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