Moexipril and left ventricular hypertrophy

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Abstract: Angiotensin-converting enzyme (ACE) inhibitors today are the standard therapy of patients with myocardial infarction and heart failure due to their proven beneficial effects in left ventricular remodeling and left ventricular function. ACE inhibitors have also been demonstrated to lead to regression of left ventricular hypertrophy (LVH). It is believed that the mechanism of action of LVH regression with ACE inhibitors arises from more than simple blood pressure reduction. LVH is an important risk factor for cardiovascular disease morbidity and mortality independent of blood pressure. Moexipril hydrochloride is a long-acting, non-sulfhydryl ACE inhibitor that can be taken once daily for the treatment of hypertension. Moexipril has now also been demonstrated to have beneficial effects on LVH and can lead to LVH regression.

Keywords: moexipril, ACE inhibitor, cardiovascular disease, left ventricular hypertropy

Background

Moexipril hydrochloride is a long acting, non-sulfhydryl angiotensin-converting enzyme (ACE) inhibitor that can be taken once daily for the treatment of hypertension (HTN) (White et al 1994; Stimpel et al 1995). It is a pro-drug that needs to be hydrolyzed in the liver into its active carboxylic metabolite, moexiprilat, in order to be effective (Stimpel et al 1995). Moexipril's synthesis has been reported previously in 1982 and 1986 (Hoefle et al 1982; Klucthko et al 1986). It is incompletely absorbed after oral administration, and its bioavailability is low, accounting for 22% of unchanged drug. This is similar in comparison with other ACE inhibitors, such as benazepril, fosinopril, and trandolapril, which have bioavailability of 37%, 32%, and 30%, respectively. Cilazapril, enalapril, quinapril, and ramipril have higher bioavailability (Table 1) (Grass and Morehead 1986; Barfour and Gos 1995; Lancaster and Todd 1998; Singhvi et al 1998; Song and White 2002).

Moexipril exerts its biological and antihypertensive effects after its metabolism in the liver into its active metabolite, moexiprilat, by blocking the conversion of angiotensin I to angiotensin II (Figure 1). Additionally, it blocks the degradation of bradykinin, which causes a hypotensive effect because of the potent vasodilation caused by the production of prostaglandin E2 and nitric oxide. Animal studies comparing moexipril to captopril have demonstrated equivalency in their antihypertensive effects. When compared with enalapril in spontaneously hypertensive rats, both moexipril and enalapril reduced the mean blood pressure by 24% at 28 days (Edling et al 1995). In clinical studies, moexipril produced significant reduction in both systolic and diastolic blood pressure with its maximum effect seen at 6 hours post-administration (Strauss et al 1994; Lucas et al 1995). When administered in a dose between 7.5 mg and 15 mg daily, the blood pressure effects have been shown to last 24 hours.

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Table 1 Pharmacokinetic characteristics of ACE inhibitors (Froshlich et al 1991; Edling et al 1995; Stimpel et al 1995)

Drug variable	Oral dose[b] (mg)	Absorption (%)	C_{max} (μg/L)	t_{max} (h)	$t_{½}$ (h)	Protein binding (%)	Elimination route
[a]Benazepril	10	37	200[c]	1.5[c]	10–11	95	B+R
Captopril	100	75	800	1.0	<2	30	R
Cilazapril[d]	2.5	78	82	0.83	9[c]	NA	R
[a]Enalapril	10	60	30–40[c]	3.5[c]	11[c]	50[c]	R+B
[a]Fosinopril	10	32	100[c]	3.0[c]	12[c]	95[c]	R+B
Lisinopril	10	25	38	7.0	12	10	R
[a]Moexipril	15	23	25[c]	2.0[c]	10[c]	72[c]	B+R
[a]Perindopril	8	75	12	3–7[c]	3–10[c]	60[c]	R+B
[a]Quinapril	40	60	1456[c]	1.38[c]	2	97[c]	R+B
[a]Ramipril	10	60	33.6[c]	2.1[c]	2–4[c]	56[c]	R+B
[a]Trandolapril	2	10	2.8[c]	4–10[c]	10[a]	60[c]	B+R

[a]ACE inhibitors existing as pro-drugs
[b]These were the doses given for the study of pharmacokinetics of the drug and do not represent necessarily, therapeutic doses.
[c]parent drug
[d]Cilazapril is not yet marketed in the USA.
Abbreviations: B, bile; R, renal; C_{max}, maximal drug concentration; t_{max}, time to maximal drug concentration; NA, not available.

Cardiovascular effects

Moexipril has been demonstrated in in vitro and in vivo studies to possess cardioprotective properties. In rats, administration of 10 mg moexipril either alone or in combination with losartan, one week prior to induction of myocardial infarction, decreased the infarct size. These beneficial effects of moexipril were negated by the bradykinin b_2 receptor antagonist icatibant. Administration of losartan alone did not demonstrate any significant effect on infarct size (Rosendorff 1996). Although these findings suggest that these beneficial effects of moexipril were mediated exclusively through inhibition of the breakdown of bradykinin, other studies have shown that the cardioprotective effects of ACE inhibitors are mediated through a combination of inhibition of angiotensin II production and bradykinin degradation (Froshlich and Horinak 1991; Brilla et al 1996; Rumble et al 1996; Grohe et al 1997; Chrysant 1998a). Angiotensin II exerts its remodeling effects on the cardiovascular system through its direct proliferative actions and also indirectly through its stimulation of the production of endothelin 1 and 3 (ET_1, ET_3) and the transforming growth factor b_1 (TGF-b_1), all of which have tissue proliferative effects (Figure 2). Bradykinin itself, and through its stimulation in the production of prostaglandin E_2 (PGE_2) and nitric oxide (NO), exerts antiproliferative effects (Chrysant 1998a). In addition, angiotensin II stimulates the production of various protooncogenes, such as c-fos, c-jum and c-myc which all have cellular proliferative actions (Froshlich and Horinak 1991). The antiproliferative effects of moexipril have been demonstrated in vitro studies where moexipril inhibited the estrogen-stimulated growth of neonatal cardiac fibroblasts in rats (Pfeffer et al 1992). It should be stated here that these effects of moexipril on cardiovascular remodeling have been demonstrated with other ACE inhibitors and they appear to be a class effect (Grohe et al 1997).

ACE inhibitors today are the standard therapy of patients with myocardial infarction and heart failure due to their proven beneficial effects in left ventricular remodeling and left ventricular function (SOLVD 1991; Dahlof et al 2002).

Clinical experience with moexipril in hypertension

Moexipril has been extensively studied in patients with mild, moderate, or severe hypertension, compared with placebo and other antihypertensive drugs. It was also studied in fixed combinations with low dose hydrochlorothiazide (HTZ). Most of the studies were double-blind, randomized, multicenter short-term and a few were open label long-term studies. They were based on sitting diastolic blood pressure (SDBP) of 95–120 mmHg, of 8–24 weeks' or 2 years' duration. In all these studies, moexipril was dispensed once daily due to its long elimination half-life of 10 hours, in doses ranging from 7.5–30 mg. The results of the most pertinent studies are listed in Table 2.

Placebo-controlled studies

In placebo-controlled multicenter trials in Europe and the United States of 8–12 weeks' duration in patients with mild to moderate essential hypertension (SDBP 95–114 mmHg), moexipril was more effective than placebo. Given in single daily doses of 7.5–30 mg, moexipril produced a sustained blood-pressure control over 24 hours and decreased the SDBP from 4 to 11 mmHg over placebo with a response rate of 48%–61% for those receiving moexipril 7.5 and

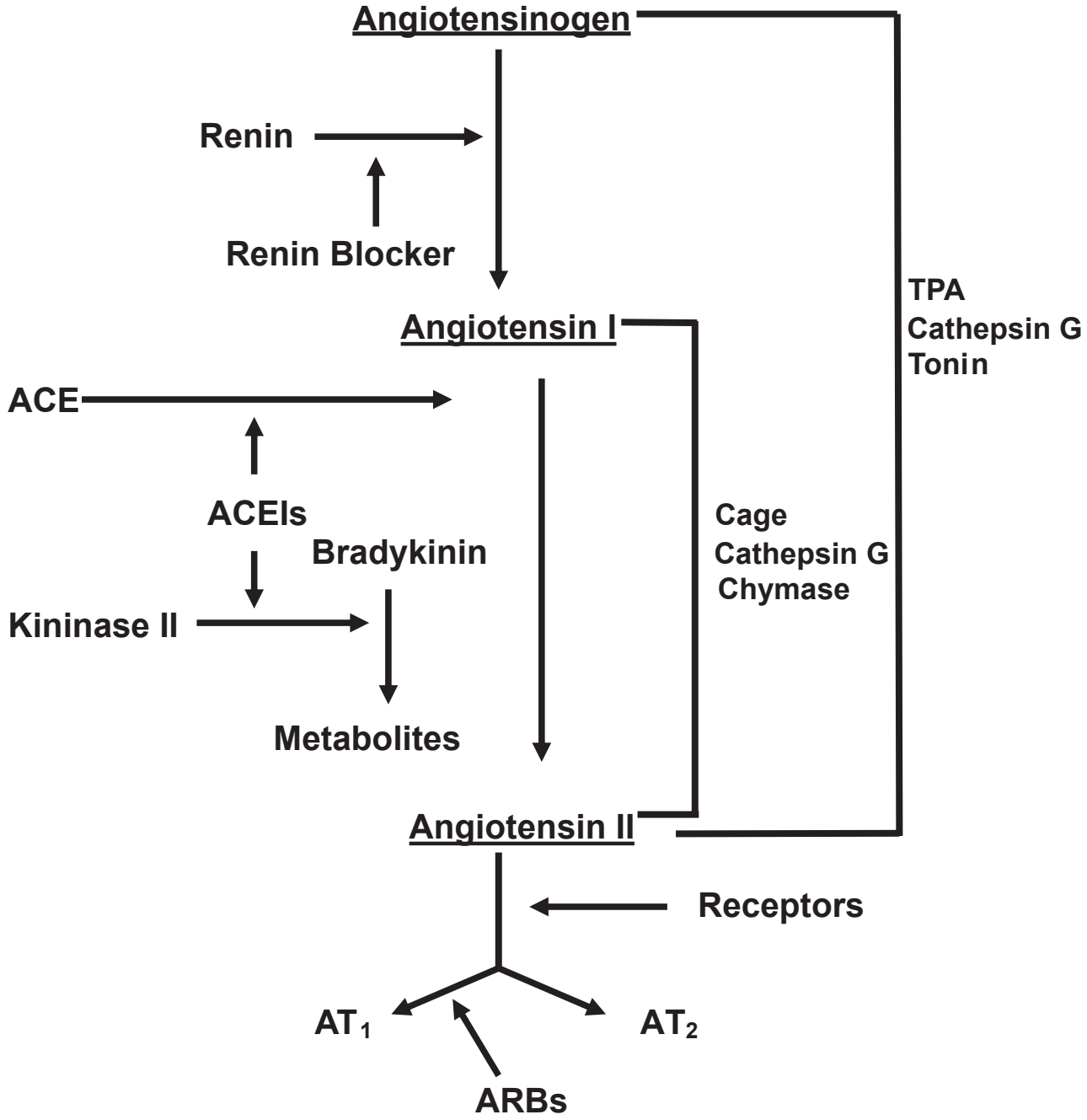

Figure 1 Classical and alternative pathways of angiotensin II production.

15 mg/day, vs 29% and 34% for those receiving placebo, respectively (Strauss et al 1994; Lucas et al 1995; Stimpel and Koch 1996, 1997).

Comparative studies

The antihypertensive effectiveness and safety of moexipril has also been compared with other antihypetensive drugs in patients with mild to moderately severe hypertension (SDBP 95–114 mmHg). In comparison with HTZ 25 mg once daily, atenolol 25–50 mg once daily, metoprolol 100 mg once daily, verapamil-SR 120–240 mg once daily, nitrendipine 20 mg once daily, and captopril 25–50 mg twice daily, moexipril given in single daily doses of 7.5–15 mg was as effective in lowering the blood pressure as the other antihypertensive drugs (Dickstein et al 1994; Abernethy et al 1995; Chrysant et al 1995; Stimpel et al 1996a, b; White et al 1997).

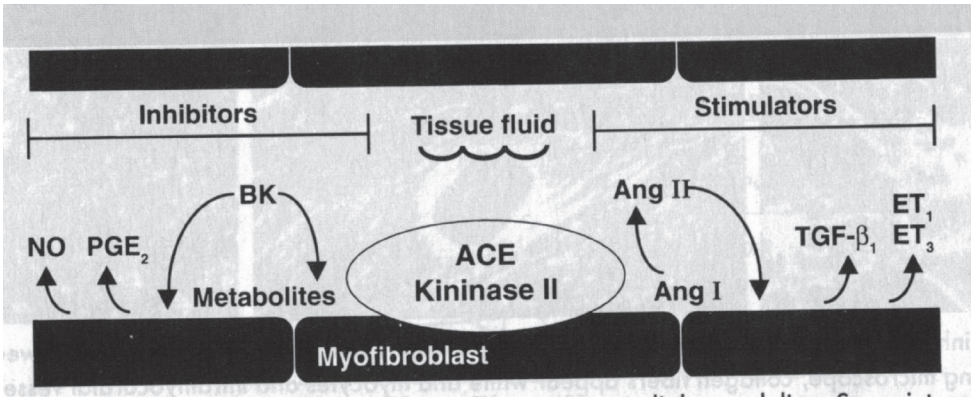

Figure 2 Tissue level stimulation and inhibition of angiotensin II.

Add-on studies

Moexipril was also studied in patients with moderate to severe hypertension as add-on therapy to pre-existing drugs. In one study, moexipril 7.5 once daily, or verapamil-SR 180 mg once daily, were added to pretreatment with HCTZ 25 mg once daily if the SDBP was 100–114 mmHg inclusive (Chrysant and Simpel 1998). If after 4 weeks of treatment the SDBP was ≥90 mmHg, the dose of moexipril was increased to 15 mg once daily and that of verapamil-SR to 240 mg once daily. This resulted in further, but similar decrease of SDBP by week 8. Similar results were reported by other investigators when moexipril 7.5 or 15 mg once daily were added to HCTZ 25 mg once daily, or to nifedipine sustained release 20 mg twice daily (Chrysant 1994; Chrysant et al 1996).

Fixed combination studies

Moexipril has been thoroughly investigated in the treatment of hypertension as a low-dose combination with HCTZ. In multi-factorial design studies, the combination of moexipril 3.75 mg to 30 mg with HCTZ 3.125 to 50 mg were more efficacious in lowering the blood pressure than the individual components alone (Chrysant 1997). In another study, 223 patients with SDBP of 95–114 mmHg and SSBP ≤200 mmHg, were treated with a fixed very low dose combination of moexipril/HCTZ 3.75/6.25 mg once daily, and demonstrated a reduction of their SSDP/SDBP by –7.6/–7.6 mmHg compared with placebo of +0.2/–3.9 mmHg (Chrysant 1998b). The fixed combinations of HCTZ 12.5 mg with moexipril 7.5 mg or with metoprolol 100 mg given once daily were studied in 140 hypertensive patients (SDBP 95–114 mmHg), for 12 weeks (Chrysant et al 1983). In this study both combination treatments reduced the SSBP/SDBP by 17.6/12.8 and 17.2/13.9 mmHg for the moexirpil-HCTZ and metoprolol-HCTZ combinations, respectively (Table 2).

Left ventricular hypertrophy (LVH)

LVH, determined by echocardiography, is a left ventricular mas (LVM) or LVM index (LVMI); LVM/ body surface area in the upper 2.5%–5.0% of the adult population (Levy et al 1988; Phillips and Diamond 1999). An LVMI of ≥25 g/m^2 is considered to be approximately at the 95th percentile. A direct and progressive relationship exists between LVM and cardiovascular disease (CVD) risk, including risk of coronary heart disease (CHD), heart failure (HF), stroke, and sudden death (Frolich et al 1992; Devereux and Roman 1993; Haider et al 1998). Increased LVM has been shown to predict the risk of CV events, especially fatal events, independent of BP or CHD (Koren et al 1991; Ghali et al 1992; Levy et al 1994). Conversely, in persons with CHD, the relative risk of mortality is increased two-fold by LVH (Phillips and Diamond 1999). In the Framingham cohort, each increase in LVM of 50 g/m^2 was associated with an increase in relative risk of CVD to 1.49 in men, and 1.57 in women (Levy et al 1988).

LVH is an important risk factor for CVD morbidity and mortality independent of BP. The prognostic importance of LVH has been shown in population studies such as the Framingham Heart Study and the Honolulu Heart Program, as well as in clinical studies of patients with essential HTN, secondary HTN and CHD (Koren et al 1991; Ghali et al 1992; Levy et al 1994). LVH found on resting ECG has been associated with the highest risk of fatal CHD, conferring a relative risk of 11.4 in one cohort of 7682 men followed for 12 years (Knutsen et al 1988). In the Framingham cohort, follow-up was extended until a subject developed CVD, died or attended clinic two years later. The increased risk of CV events was related to baseline electrocardiogram (ECG) voltage by quartile (sum of R wave in lead AVL and the S wave in lead V3 ≥1.3 mV [25th percentile], 1.8 mV [50th percentile], and 2.3 mV [75th percentile]) and repolarization abnormalities (classified as normal, mildly abnormal [ST-T flattening, isolated

Table 2 Summary of clinical trails with moexipril

Author (n = no. pts)	Drug (mg)	Change in SDBP from baseline (mmHg)	Duration (weeks)
Comparative studies			
Persson (n = 201)	MO 7.5 od	–8.7	8
(1996)	MO 15 od	–10.1	8
	HCTZ 25 od	–10.5	8
Stimpel, Oparil (n = 97)	MO 15 od	–10.0	12
(1998)	HCTZ 25 od	–11.8	12
Stimpel, Weber[a] (n = 116)	MO 15 od	–10.0	8
(1998)	ATE 50 od	–8.4	8
Abernethy (n = 178)	MO 75–15 od	–10.0	24
(1995)	VER-SR 180–240 od	–11.0	24
Stimpel (n = 159)	MO 7.5–15 od	–9.8	12
(1996a)	CAP 25–50 BID	–8.7	12
Agabiti-Rosei (n = 93)	MO 15 od	–15.2	8
(1999)	NIT 20 od	–13.6	8
Add-on studies			
Chrysant[b] (n = 147)	MO 7.5–15 od	–11.0	12
(1995)	VER-SR 180–240 od	–12.0	12
Dickstein[b] (n = 200)	MO 3.75 od	–8.4	8
(1994)	MO 7.5 od	–8.8	8
	MO 15 od	–8.9	8
	PL od	–4.6	8
Persson[c] (n = 203)	MO 3.75 od	–6.0	8
(1996)	MO 7.5 od	–9.0	8
	MO 15 od	–9.0	8
	PL od	–5.0	8
Fixed combination studies			
White (n = 272)	MO 15 od	–8.0	12
(1997)	MO 30 od	–9.7	12
	HCTZ 25 od	–8.1	12
	HCTZ 50 od	–11.0	12
	MO/HCTZ 15/25 od	–16.0	12
	MO/HCTZ 30/50 od	–17.9	12
Chrysant (n = 223)	MO/HCTZ 3.75/6.25 od	–7.6	12
(1998)	PL od	–3.9	12
Stimpel (n = 140)	MO/HCTZ 7.5/12.5 od	–12.8	12
(1997)	MET/HCTZ 100/12.5 od	–13.9	12
Open label long-term studies			
White (n = 172)	MO 7.5–15 od	–14.0	52
(1995)	MO/HCTZ 7.5–15/25 od	–17.0	52
White (n = 281)	MO 7.5–30 od	–14.0	52
(1994)	MO/HCTZ 7.5–30/12.5 od	–15.0	52

[a]HCTZ 25 mg od was added if necessary.
[b]HCTZ 25 mg background-therapy.
[c]Nifedipine 20 mg background-therapy.
Abbreviations: ATE, atenolol; CAP, captopril; HCTZ, hydrochlorothiazide; MET, metoprolol; MO, moexipril; NIT, nitrendipine; VER-SR, verapamil SR.

ST depression, T-wave inversion], or severely abnormal [ST depression in association with inverted or biphasic T waves]). Persons in the highest quartile of voltage (sum of R wave in lead AVL and the S wave in lead V3 ≥2.3 mV) were at highest risk. When voltage decreased or repolarization abnormalities improved (in men only), risk declined and prognosis improved by as much as 50%. Conversely, if voltage increased serially over two years of follow-up, risk doubled (Levy et al 1994). The prevalence of ECG evidence of LVH declined from 4.5% to 2.5% in men and 3.6% to 1.1% in women over 38 years of follow-up. Mean BP reduction was greater in women than in men (–15/–8 mmHg vs –4/–3 mmHg) and the prevalence of

severe HTN (SBP ≥160 mmHg or DBP ≥100 mmHg) declined to a greater extent in women than men (28% and 18.5% to 7.7% and 9.2% respectively) over this period (Devereux 1995). The reduction in BP, particularly in severe HTN, is thought to correlate with the increased use of pharmacologic agents over the last several decades.

In addition to LVM or LVMI, the geometric pattern of the hypertrophied LV has been shown to relate to CV events. Four geometric patterns have been described: 1) concentric LVH (increased LVM and increased relative wall thickness, RWT) 2) eccentric LVH (increased LVM and normal RWT); 3) concentric remodeling (normal LVM and increased RWT); 4) normal geometry (normal LVM and RWT) (Krumholz et al 1995; Verdecchia et al 1995; Ghali et al 1998). The pattern associated with the highest incidence of morbidity and mortality is concentric LVH (Verdecchia et al 1995, 1998). The incidence of CV events, in one study, was 30% in those with concentric LVH, 25% in those with eccentric LVH, 15% in those with concentric remodeling, and 9% in those with normal geometry (Koren et al 1991). In another study, subjects with LVH (LVMI of >125 g/m^2) at baseline experienced a 47% lower event rate when LVMI was reduced to <125 g/m^2 at follow-up (mean follow-up was 9 years) ($p = 0.002$) (Schlaich and Schmeider 1998). The prognostic importance of LV geometry independent of CHD risk factors and LVM/LVMI is controversial. A study of 694 hypertensive patients with normal LVMI (<125 g/m^2) showed that concentric remodeling of the LV was an important predictor of CV mortality, independent of conventional risk factors for CHD (Verdecchia et al 1998). However, other studies demonstrated that when traditional risk factors for CHD and LVM are taken into account, the geometric pattern of the LV is less predictive of CV events (Krumholz et al 1995; Phillips and Diamond 1999).

Pathophysiologic mechanisms for the development of LVH include both hemodynamic (increased BP, wall stress, and increasing arterial stiffness of central arteries) and non-hemodynamic factors (genetics, activation of the sympathetic nervous system, and the RAAS) (Gottdiener et al 1997). LVM has been shown to be closely related to SBP, while RWT appears to be more closely related to DBP. A large body of evidence relates the development of LVH to increased RAAS activity, in particular angiotensin II. Angiotensin II has been shown to stimulate fibroblast activity, synthesis, and release of cytokines and growth factors and myocardial fibrosis. Aldosterone has been associated with an increase in collagen in the myocardium, leading to interstitial fibrosis in ventricular tissue.

Angiotensin-converting enzyme inhibitors and left ventricular hypertrophy

Antihypertensive therapy is effective in producing regression of LVH (Liebson et al 1995; Moser and Herbert 1996; Schmieder et al 1996; Thurmann et al 1998). An analysis of six large HTN trials involving a total of 26 741 patients showed that long-term use of any antihypertensive medication except direct vasodilators leads to regression of LVH (Thurmann et al 1998). Further, a large meta-analysis of 39 trials of diuretics, beta-blockers (BBs), calcium channel blockers (CCBs), and ACE inhibitors (ACEIs) in hypertensive subjects showed that LVM was related to the treatment-induced decline in BP, particularly SBP ($p < 0.001$ vs $p = 0.08$ for DBP). Reductions in LVM of 13%, 9%, 6%, and 7% were demonstrated with ACEIs, CCBs, BBs, and diuretics, respectively (Moser and Herbert 1996). Diuretics have been shown in several trials to be effective in reducing LVM (Neaton et al 1993; Moser and Herbert 1996; Schmieder et al 1996; Thurmann et al 1998). Results of studies that have examined the effects of BBs and CCBs on regression of LVH have been mixed, with some studies suggesting that one or both of these agents are not effective (Neaton et al 1993; Moser and Herbert 1996; Schmieder et al 1996).

Agents that interrupt the RAAS, including ACEIs and antiotensin II receptor blockers (ARBs), may be more effective than other classes of antihypertensive drugs in reducing LVM. Whether reduced synthesis of angiotensin II, with its cytokine/growth factor-stimulating effects, potentiation of bradykinin with resultant stimulation of NO synthesis and release, and/ or inhibition of aldosterone synthesis are salient factors in LVH reversal related to use of these drugs is a matter of conjecture. Further, whether, in fact, these agents effect reversal of LVH via mechanisms other than BP lowering is a matter of active debate.

In the LVH regression substudy of the HOPE trial, the use of ramipril led to LVH regression in nearly 92% of patients (Devereux et al 2004). This effect was independent of blood pressure control. Consequently, the use of ramipril led to a reduction in death, MI, and stroke. Another interesting result was that the use of ramipril was associated with prevention of new HF.

Moexipril and left ventricular hypertrophy

The use of moexipril in hypertensive subjects has been demonstrated to have beneficial effects on LVH. In one trial of 72

patients with echocardiographic evidence of LVH (defined as a LVMI of >111 g/m^2 in men and >106 g/m^2 in women), a dose of 15 mg of moexipril daily led to a significant decrease in LVMI. The average LVMI was reduced from 121 +/– 20 g/m^2 to 103 +/–17 g/m^2 ($p < 0.001$) in a period of 24 weeks (Sayegh et al 2005). Another more robust study, the Moexipril and REgression of left ventricular hypertrophy in combination therapy (MORE) trial, examined the effects of moexipril in 426 hypertensive patients (Spinar and Vitovec 2005). While no predefined value was given for LVH, the baseline LVMI in this study was 149 g/m^2, which is well above any published accepted value for LVH by LVMI. The presence of LVH was established by echocardiography. Moexipril was added on to the existing therapy and titrated up as needed to achieve blood pressures of <140/90 mmHg. In this trial, BBs were used in over 50% of patients as either monotherapy or in combination with diuretics and/ or CCBs. After 6 months of follow-up, the average blood pressure was reduced from 161/97 mmHg to 136/82 mmHg ($p < 0.0001$), and the LVMI decreased from 149 +/– 51 g/m^2 to 137 +/–47 g/m^2 ($p < 0.0001$). Several interesting findings were observed. First, an improvement in left atrial size was demonstrated (39.81 mm vs 39.04 mm, $p = 0.002$) in addition to an improvement in LV size and LVMI. Second, an improvement in LV diastolic function was demonstrated with a significant increase in the E/A ratio from 0.91 to 0.94 ($p < 0.0005$). Third, there was a significant reduction in pulse pressure (PP) from 12.5 mmHg to 9.8 mmHg ($p < 0.01$). This is an important finding due to the very well established link between PP and cardiovascular morbidity and mortality. Therefore, it appears that moexipril as added therapy provides benefits beyond simple blood pressure lowering that have been demonstrated with other ACE inhibitors.

Conclusion

Moexipril is a nonsulfhydryl ACE inhibitor with prolonged duration of action and is suitable for once a day administration for the treatment of hypertension. In doses of 7.5, 15, and 30 mg alone or in combination with other antihypertensives, such as HCTZ and calcium channel blockers, moexipril is effective for the treatment of moderate to severe hypertension. Evidence is also emerging that moexipril, like other ACE inhibitors, is effective in reducing left ventricular hypertrophy. This is an extremely important feature as LVH has well established links to cardiovascular morbidity and mortality.

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