diagnosed or previously treated (treatment not satisfactory) whose DBP after washout was 95–114 mmHg, were randomized to receive CC 8 mg od or PC (β-blocker, CCB or ACE I) at recommended starting doses. After 4 wks, if DBP $>$ 90 mmHg, the dose of CC was increased to 16 mg and the dose of PC was increased as per prescribing recommendations. After a further 4 wks, if DBP $>$ 90 mmHg, hydrochlorothiazide was added to both groups. BP, HR, adverse events and quality of life (QoL) were assessed at baseline and after 12 wks treatment. QoL questionnaires used: Psychological General Well Being (PGWB) & Subjective Symptom Assessment Profile (SSAP).

Results: There were 1123 patients randomized (CC = 769, PC = 354), 57% males, mean age 53.0 yrs. Demographics were similar for the two groups. The PC was 54.5% ACE I and 26.8% CCB. Mean BP was reduced $-18.3/-13.2$ and $-16.3/-12.1$ mmHg for the CC and PC groups. The response rate (DBP $\leq$90 mmHg or decrease $\geq$10 mmHg) was 79% for CC and 76% for PC (NS). There was a difference in favor of the CC group in overall well being in the PGWB of 3.35 ($p = 0.053$) and -2.48 (fewer symptoms) ($p = 0.006$) in the overall symptom assessment of the SSAP QoL questionnaires. Incidence of cough was 2.9% for CC and 10.7% for PC, ($p < 0.001$).

Conclusions: Both CC and PC groups reduced BP effectively, with similar response rates. There was a statistically significant improvement in overall symptom assessment (SSAP) and a trend towards improvement in overall psychological well being (PGWB) QoL scores for patients in the CC group. Tolerability was significantly better in the CC group, mainly due to a significant incidence of cough in the PC group.

Key Words: Candesartan cilexetil; antihypertensive effect; tolerability; quality of life

A059

OMAPATRILAT IS NOT A DIURETIC: SINGLE- AND MULTIPLE-DOSE ANALYSIS OF THE URINARY EXCRETION OF SODIUM

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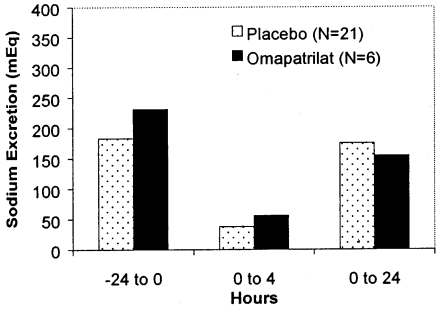
Omapatrilat is the most clinically advanced vasopeptidase inhibitor (VPI) under investigation for the treatment of hypertension and heart failure. VPIs are single molecules that simultaneously inhibit neutral endopeptidase (NEP) and ACE to enhance the biological activity of vasodilator peptides (eg ANP) and inhibit the renin angiotensin aldosterone system (RAAS). Two double blind placebo-controlled, dose-escalation trials were conducted in a total of 109 healthy men aged 18–50. All subjects were maintained on a 6 gram sodium and 4 gram potassium diet. The following dose ranges were evaluated: single-dose study, 2.5- to 500-mg; multiple-dose (daily for 10 days) study, 10- to 125-mg. Inhibition of NEP was demonstrated by sustained increases over multiple doses in daily urinary excretion of ANP and cGMP. At 3 hours post-dose, supine systolic and diastolic BP decreased by 5- to 14- and approximately 15-mm Hg at 25–75 mg, respectively. At all doses studied, including the highest dose (500 mg), sodium excretion was unaffected by omapatrilat (see Figure). Thus, unlike diuretics, the antihypertensive



efficacy of omapatrilat is not due to increased sodium excretion.

Key Words: Vasopeptidase inhibitors; omapatrilat; natriuresis; vasodilator peptides; ANP

A060

AMLODIPINE VS LOSARTAN IN THE TREATMENT OF MILD TO MODERATELY SEVERE HYPERTENSION

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In a multicenter study we assessed the antihypertensive efficacy of once-daily amlodipine (A) versus losartan (L) in adults. Following a 2-wk placebo run-in, patients were randomly assigned to double-blind treatment with either A 5 mg (N = 218) or L 50 mg (N = 222). During the following 12-week Titration Phase, patients received a fixed dose for the first 6 weeks. Those who failed to meet the BP goal of reduction of average sitting diastolic BP (ASDBP) to $<$ 90 mmHg could then have their dose titrated. After the Titration Phase, patients entered the 4-week Maintenance Phase at their optimal dose. At baseline, mean sitting diastolic BP (mmHg) was 100.0 $\pm$ 3.91 and mean sitting systolic BP was 154.0 $\pm$ 12.51. Although not statistically significant, for the primary endpoint of number of patients to reach ASDBP reduction goal, there was a trend of a greater percentage of patients in the A group compared to the L group attaining the goal BP at the end of maintenance (A: 64%; L: 55%, $p = 0.070$). In the A group, 61% of the patients entered maintenance after dose titration to 10 mg and in the L group, 66% of the patients entered maintenance after dose titration to L 50 mg + HCTZ. At the last maintenance visit of this dose-adjusted subgroup, there was a statistically significant difference between treatments in Favor of A (59% of the A patients met BP goal, compared to 42% of the L patients, $p = 0.009$). The advantage of A over L in the Black subgroup at the end maintenance was also statistically significant (62.5% of A patients met BP goal, compared to 41.4% of L patients, $p = 0.033$). The least-squares adjusted mean reduction in ASDBP from baseline to the last treatment visit in ASDBP was statistically significantly greater in the A group than in the L group (A: baseline = 100.3, endpoint = 87.6; L: baseline = 99.7, endpoint = 89.4, $p = 0.002$). Both treatment groups showed statistically significant reductions in 24-hr ambulatory BP; between-treatment differences were not statistically significant. The results of this study support the

efficacy and safety of A and L for the treatment of mild to moderately severe essential hypertension in adults, and suggest that A may be superior to L in lowering blood pressure in Black subjects.

Key Words: Hypertension; amlodipine; losartan

A061

AMLODIPINE VS CHLORTHALIDONE VS PLACEBO IN THE TREATMENT OF STAGE I SYSTOLIC HYPERTENSION

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There is a growing realization of the critical importance of treating systolic hypertension. Diuretics are effective in lowering systolic blood pressure in patients with isolated systolic hypertension and reducing associated cardiovascular events. The purpose of this study was to compare the effects of amlodipine versus chlorthalidone in adults (>50 years) with Stage I systolic hypertension. 150 patients were randomly assigned to double-blind treatment with amlodipine (N = 48) or chlorthalidone (N = 50) or placebo (N = 52), and entered an 8-week Titration Phase. At Titration Week 4, patients who failed to meet the blood pressure (BP) goal had their dose titrated from 5 to 10 mg for amlodipine or from 15 to 30 mg for chlorthalidone. Following the Titration Phase, subjects entered a 12-week Maintenance Phase.

At baseline the mean age was 65.7 years, mean sitting SBP (mmHg) was 148.3 ± 4.85, and mean sitting DBP was 81.0 ± 5.69. For the primary endpoint of sitting SBP, the changes from baseline to the last treatment visit were −15.0 for amlodipine, −14.6 for chlorthalidone, and −3.9 for placebo, all significant (ANOVA, $p \leq 0.05$ for all groups). The changes in both drug groups were significantly greater than placebo (both comparisons, $p \leq 0.001$), but not statistically significantly different from each other. Similar results were observed for the secondary measures, including patients reaching SBP goal, mean changes from baseline in SBP, DBP, pulse pressure, and ambulatory BP. At the end of maintenance, the percentages meeting BP goal in the amlodipine group and the chlorthalidone group were similar, 67% vs 69%. Both were significantly greater compared to placebo (25%), ($p = 0.001$). Similar results were obtained for ambulatory DBP, mean arterial pressure and pulse pressure. Changes in heart rate were small and not statistically significant between groups.

The incidence of adverse vents in all groups was as expected, and most were mild. The results of this study support the antihypertensive efficacy and safety of amlodipine and chlorthalidone for the treatment of Stage 1 systolic hypertension in adults.

Key Words: Systolic hypertension; amlodipine

A062

STEADY STATE PK OF DOXAZOSIN GITS VERSUS DOXAZOSIN STANDARD AND THE POTENTIAL BENEFITS OF GITS IN THE TREATMENT OF HYPERTENSIVE PATIENTS

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This open-label, randomised, multiple-dose, two-way crossover study compared the pharmacokinetic (PK) profiles of doxazosin gastrointestinal therapeutic system (DOX GITS) and doxazosin standard release formulation (DOX STD). Thirty-five healthy male subjects were randomised to receive single daily doses of either DOX GITS or DOX STD for 21 days (DOX GITS treatment: placebo for 7 days, 4 mg for 7 days and 8 mg for 7 days; DOX STD treatment: 1 mg for 2 days, 2 mg for 5 days, 4 mg for 7 days and 8 mg for 7 days). There was a 7-day washout period between treatments, and all doses were administered 1 hour before breakfast. Steady state (SS) was attained after 7 days of treatment with DOX GITS and DOX STD 4 mg and 8 mg. Compared with DOX STD, the relative bioavailability of doxazosin from DOX GITS at SS was 54% at 4 mg and 59% at 8 mg. C_{max} values at SS were significantly lower ($P < 0.05$) for DOX GITS compared with DOX STD (GITS/STD ratios of 39% and 42% for the 4 mg and 8 mg doses, respectively). C_{min} was similar for both formulations at all doses. The fluctuation index (FI) of DOX GITS 4 mg and 8 mg was significantly reduced ($P < 0.05$) when compared with DOX STD 4 mg and 8 mg (results consistent with the controlled-release properties of DOX GITS). Both formulations were well tolerated.

Plasma Concentrations of DOX at SS, Mean ± Standard Deviation

Parameter (n = 31)	DOX GITS (4 mg/8 mg)	DOX STD (4 mg/8 mg)
C_{max} (ng/mL)*	11.3 ± 5.6/28.0 ± 12.1	29.3 ± 8.4/66.8 ± 17.6
C_{min} (ng/mL)	6.4 ± 3.2/17.8 ± 9.3	7.4 ± 3.7/19.0 ± 8.2

** $P < 0.05$ DOX GITS vs. DOX STD.*

The reduced FI with DOX GITS is likely to result in more uniform BP control.

Key Words: Doxazosin; pharmacokinetics; extended release; sustained release

A063

RANDOMIZED DOUBLE-BLIND COMPARISON OF OMAPATRILAT WITH AMLODIPINE IN MILD-TO-MODERATE HYPERTENSION

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The antihypertensive efficacy of the vasopeptidase inhibitor, omapatrilat, was compared with the calcium channel blocker, amlodipine, using ambulatory blood pressure monitoring (ABPM) in a 10-week double-blind trial. 430 subjects age ≥18 years (mean age 53.7 years) with diastolic blood pressure (DBP) 95–110 mmHg were randomized into 2 parallel groups. One group received once-daily omapatrilat 20 mg for 2 weeks, 40 mg for 2 weeks, then 80 mg for 6 weeks; and the second, amlodipine 5 mg for 2 weeks, then 10 mg for 8 weeks [forced titration]. After all prior antihypertensive medications had been discontinued, 24-hour ABPM was used to establish baseline values for ambulatory BP parameters: systolic BP (ASBP), diastolic BP (ADBP), and mean BP (AMBP). 24-hour ABPM was repeated after 10 weeks of double-blind treatment and change from baseline for ambu-