PI-59

STEADY STATE (SS) PHARMACOKINETICS (PK) OF IRBESARTAN ALONE AND IN COMBINATION WITH FLUCONAZOLE (F). S.J. Kovacs, PharmD,* J.H. Wilton, PhD,* R.A. Blum, PharmD,* The Clinical Pharmacokinetics Laboratory at Millard Fillmore Hospital, Buffalo, NY.

Irbesartan, an angiotensin II receptor antagonist, has a similar metabolic profile to losartan (L). Significant increases in SS $AUC_{(0\text{-}t)}$ and C_{max} have been reported for L when given concomitantly with F, a potent CYP2C9 inhibitor. The effect of fluconazole on irbesartan PK was investigated.

Fifteen healthy, male volunteers were studied. Irbesartan 150 mg daily was administered on days 1-20; fluconazole 200 mg daily on days 11-20. Blood samples were collected over 24 hours on day 10 and day 20. Plasma concentrations of irbesartan were quantified by HPLC with fluorescence detection. $AUC_{(0\text{-}t)}$ and C_{max} data were analyzed separately by ANOVA; T_{max} by Wilcoxon Matched Pairs.

Mean $AUC_{(0\text{-}t)}$ on day 20 was increased approximately 63% [95%CI: 1.43, 1.86]. Mean C_{max} on day 20 was increased approximately 19% [95%CI: 1.04, 1.37]. Median T_{max} on day 20 was not different from that on day 10 (p=0.21).

	$AUC_{(0\text{-}t)}$ (ng·h/mL)	C_{max} (ng/mL)	T_{max} (h)
Day 10	59060±28344	2906±716	1.5 (1.0-1.5)
Day 20	91406±34101	3437±792	1.5 (0.5-3.0)

Fluconazole increased the steady state PK of irbesartan likely mediated by CYP2C9 inhibition. These findings are similar to those reported for losartan. The interaction between fluconazole and irbesartan may warrant clinical consideration when prescribed concomitantly.

PI-60

EFFECT OF GRAPEFRUIT JUICE ON THE PHARMACOKINETICS OF LOSARTAN IN HEALTHY VOLUNTEERS. R. Zaidenstein, MD, B. Avni, MD, V. Dishi, MD, M. Gipps, PhD, S. Soback, DVM, PhD, M. Koren, MD, R. Simantov, MD, A. Golik, MD, Internal Medicine Department "A", "Assaf Haroffeh" Medical Center, Zerifin, and Kimron Veterinary Institute, Beit Dagan, Israel.

Losartan (LOS) an angiotensin receptor blocker is metabolized to E-3174 through cytochrome P-450 (CYP) isoenzymes CYP3A4 and CYP2C9, Grapefruit juice (GJ) inhibits CYP3A4. Thus the effect of GJ on the pharmacokinetics of a single dose of LOS in healthy volunteers was investigated. **Methods:** Nine healthy volunteers aged 29-50 years were given on day one 200 ml of water 1 hour before and together with morning LOS. Following a week of washout LOS was given with 200 ml of GJ in the same order, serial blood samples were collected. Plasma concentrations of LOS and E-3174 were determined by HPLC. **Results:** Ingestion of GJ increases the AUC of LOS as compared to water from 34787±11040 to 39731±11091 ng/ml/min. However AUC of E-3174 decreases after GJ from 164675±67422 to 133374±43728.

Conclusions: Coadministration of LOS and GJ produces a statistically significant increase in AUC of LOS and decrease in AUC of E-3174 in healthy volunteers. Concomitant ingestion of LOS and GJ may reduce LOS' clinical effect.

PI-61

PHARMACODYNAMIC EFFECTS OF MULTIPLE DOSES OF OMAPATRILAT IN HEALTHY SUBJECTS. O. Vesterqvist, PhD, W. Liao, PhD, MD, J.A. Manning, PhD, H.D. Uderman, MD, C.L. Delaney, MS, B.N. Swanson, PhD, Bristol-Myers Squibb PRI, Princeton, NJ.

Background: Omapatrilat (Oma) is a potent inhibitor of both NEP and ACE enzymes. The pharmacodynamic effects of multiple daily oral doses of 10-75 mg of Oma in healthy men were examined. **Methods:** In a randomized, placebo-controlled study, NEP activity was assessed by measuring urinary and plasma atrial natriuretic peptide (ANP) and cyclic guanosine monophosphate (cGMP). The effects on the renin-angiotensin system were studied by measuring serum ACE activity and plasma renin activity (PRA). **Results:** Urinary ANP increased in a dose-dependent manner from 10.7±3.5 to 31.9±8.2 ng/24 hr after oral doses of Oma from 0 to 75-mg, respectively, on Day 1 that was sustained on Days 3 and 10. NEP inhibition was further supported by elevation of urinary and plasma cGMP. Serum ACE activity decreased by >80% over 24 hr at all doses. A dose-dependent PRA increase was seen on Day 1 from 1.7±0.9 to 23.7±15.5 ng/mL/hr at 4 hr after 0 to 75-mg. PRA increased further on Day 10. **Conclusion:** Omapatrilat is a potent inhibitor of both NEP and ACE activity on chronic dosing. Its potentiation of ANP, a peptide with vasodilatory actions, may provide additional benefit compared to an ACE inhibitor in the treatment of hypertension and heart failure.

PI-62

CONCENTRATION-EFFECT (PK/PD) RELATIONSHIPS OF TWO RILMENIDINE INFUSIONS IN HYPERTENSION. N. Frey, PharmD, M. Dubar, PharmD, JMA van Gerven, MD, PhD, RC Schoemaker, MSc, AF Cohen, MD, PhD, R. Jochemsen, PhD, Centre for Human Drug Research, Leiden, The Netherlands, and Institut de Recherches Int. Servier, Courbevoie, France.

Aims: To study the PK/PD-relationships of two 'slow release' *iv* infusions of rilmenidine in mild to moderate hypertension.

Subjects and methods: Forty-five patients stopped their antihypertensives. Hypertension recurred in 26 patients, who completed a 2-way partial crossover, double-blind, placebo-controlled study with three *iv* infusions: low-profile (0.35 mg/h rilmenidine from 0-2 hrs and 0.075 mg/h from 2-12 hrs; 1.45 mg total); high-profile (0.8 mg/h from 0-2 hrs and 0.17 mg/h from 2-12 hrs; 3.3 mg total); or placebo. Drug levels and the systolic/diastolic blood pressures (SBP/DBP) were measured hourly for 15 hrs and after 24 hrs. The effects on SBP/DBP and PK/PD-relationships were compared among treatments.

Results: The average time profiles of SBP/DBP followed the serum drug levels. At baseline, the average SBP/DBP varied between 161.5/92.6 and 168.3/98.3 mmHg. The low-profile caused an average 15 hr-SBP-reduction of 6.2 (95%CI: 0.3, 12.1) mmHg *vs* placebo. SBP/DBP returned to 159.2/90.5 mmHg after 24 hr. The high-profile caused a SBP-reduction *vs* placebo of 22.7 (16.9, 28.5) mmHg on average over 15 hrs, and 10.4 (1.4, 19.4) mmHg after 24 hrs. PK/PD-relationships were direct and linear over a wide concentration range, and DBP decreased 3.0 mmHg/ng·mL^{-1} (CV=35%).

Conclusion: Minimal effect plasma levels can be determined, based on rilmenidine's direct and linear PK/PD-relationships.