American Society for Clinical Pharmacology and Therapeutics

Abstracts of papers,* 2006 Annual Meeting
Baltimore Marriott Waterfront
Baltimore, Maryland, March 8-11, 2006

OI-A-1

PHARMACOKINETIC/PHARMACODYNAMIC (PK/PD) MODEL FOR TOLVAPTAN (TOL) IN PATIENTS WITH CONGESTIVE HEART FAILURE (CHF) AND/OR HYPONATREMIA (HYP). S. A. Van Wart, MS, B. B. Cirincione, MS, E. A. Ludwig, PharmD, X. Chen, MS, S. Shoaf, PhD, T. H. Grasela, PharmD, PhD, S. Mallikaarjun, PhD, Cognigen Corporation, Otsuka Maryland Research Institute, Buffalo, NY.

AIM: TOL is a oral vasopressin (V_2) receptor antagonist under development for treatment of CHF and/or HYP. Direct and indirect effect PK/PD models were evaluated to characterize the effect of TOL concentration (Cp) on urine flow rate (UFR) and the influence of water intake rate (WIR), loop diuretic use, and patient covariates.

METHODS: Data (1650 timed urine collections from 103 patients) were pooled from 3 Phase 2 studies in CHF and/or HYP patients given placebo or TOL (5 to 120 mg) once daily. Urine output and water intake were recorded for 2 days prior and during the first 4 days of TOL therapy. Patient covariates were evaluated using stepwise forward ($\alpha=0.05$) and backward ($\alpha=0.001$) procedures.

RESULTS: A direct effect model, with UFR estimated as a linear function of TOL Cp (slope = 0.381 mL/hr per ng/mL) and as a function of time (slope declined 1.8% per hr after first dose) described the data. Baseline E_0 (separate day and night estimates) was a linear function of WIR with a shift for loop diuretic use. Weight, vasopressin Cp, and presence of CHF also significantly impacted E_0. The model slightly underpredicted (median PE% ranged from −3 to −9%) but provided reasonably precise (median |PE|% ranged from 13-16%) daily urine volumes. For a 30 mg dose (n=12), the estimated net fluid loss due to TOL on the first treatment day was 1.3 L.

CONCLUSION: This PK/PD model relates TOL Cp to UFR with consideration of concurrent loop diuretic use, and provides individual estimates of daily net fluid loss for potential use in dose selection.

OI-A-2

THE EFFECT OF SIMVASTATIN, EZETIMIBE AND THEIR COMBINATION ON LIPIDS PROFILE, ARTERIAL STIFFNESS AND INFLAMMATORY MARKERS. S. Efrati, M. Averbuch, V. Dishy, L. Fridenzon, A. Bar-Chaim, A. More, R. Abu-Chamad, M. Fygenzo, J. Weissgarten, A. Golik, Asaf-Harofeh Medical Center, Zerifin, Israel.

BACKGROUND: Arterial stiffness (AS) and highly sensitive CRP (hsCRP) predict risk for cardiovascular events. Statins can improve inflammation and AS. The effect of ezetimibe on AS and hsCRP has not been studied. The aim of this study was to compare the effect of simvastatin with ezetimibe on AS and hsCRP.

METHODS: Forty hypercholesterolemic patients were studied. Group 1: previously untreated received simvastatin 40mg/d, group 2: previously treated with simvastatin 40mg/d received simvastatin 80mg/d; group 3: previously untreated received ezetimibe 10mg/d; group 4: previously treated with simvastatin 40mg/d received simvastatin 40mg/d and ezetimibe 10mg/d. Augmentation index (AIx, a measure of AS), and hsCRP were measured at baseline and after 3 months.

RESULTS: The reduction in LDL after treatment was significantly greater in groups 1 and 4 (39% and 37%) compared to groups 2 and 3 (18% and 16%). AIx decreased significantly in group 1 compared to the other groups (−22.1%, −0.4%, −0.3% and 0.4% in groups 1-4, p=0.035). Changes in hsCRP paralleled the changes in AIx: significant decreased in group 1 (−50.8%), compared to group 2 (+3.6%), p=0.002. In groups 3 and 4 hsCRP decreased, but there was no significant difference (−21.3% and −11.3%, p=0.81).

CONCLUSIONS: Compared to simvastatin, ezetimibe as monotherapy resulted in milder decreases in LDL cholesterol and had no effects on AS or hsCRP. Increasing the dose of simvastatin or the addition of ezetimibe to simvastatin had no beneficial effects on AS or hsCRP.

*Abstracts appear in presenting order. The first author, in most cases, is the presenting author. **PI**, **PII**, and **PIII** denote Poster Session I (Thursday, March 9), Poster Session II (Friday, March 10), and Poster Session III (Saturday, March 11). **OI**, **OII**, **OIII**, **OIV**, and **OV** denote Oral Session I and Oral Session II (Thursday, March 9) and Oral Session III, Oral Session IV, and Oral Session V (Friday, March 10). **LBOVI** denotes those abstracts that were accepted as late-breaker oral presentations. These abstracts will be presented on Saturday, March 11.