PII-15

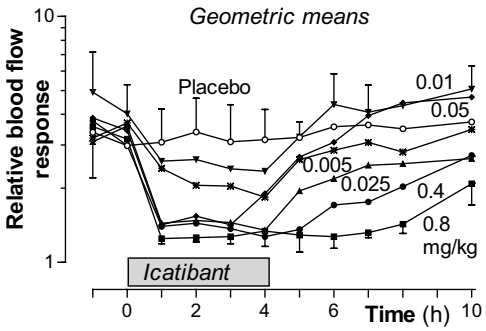
SENSITIVITY/RELIABILITY OF THE TIME-MATCHED BASELINE SUBTRACTION METHOD IN ASSESSMENT OF QTC INTERVAL PROLONGATION. S. H. Lee, PhD, H. Sun, PhD, P. Chen, MS, S. Doddapaneni, PhD, J. Hunt, BS, H. Malinowski, PhD, FDA, Rockville, MD.

Time-matched baseline subtraction (TMBS) is one of the recommended methods to assess QT prolongation of drugs. This study evaluates the sensitivity/reliability of TMBS. Individual heart rate corrected QT (QTc) data were obtained from 22 healthy females who had baseline QT on two consecutive days with ≥9 readings over 24h on either day. 1000 re-sample datasets were generated via randomly selecting individual data series from one of the 2 days as the basis for subtraction. For each dataset, the inter-day difference in QTc at time-matched points (ΔQTc) and its maximum (ΔQTc,max) were determined for all subjects. The mean ΔQTc,max for the 22 subjects and its distribution for the 1000 replicates were then computed. Individual QTc time profile showed fluctuations without a common pattern among all subjects or within a subject across the 2 days. No subject had a ΔQTc of>30ms (highest: 24 ms). The within-day standard deviation (SD) for individual subjects ranged 2.5-8.1 ms. Many subjects had even higher between-day SD. For the 1000 replicates, the mean ΔQTc,max ranged 3.8-13.3 ms and SD ranged 4.0-8.4 ms. This investigation raises a question on the sensitivity/reliability of TMBS method. Additional studies/populations will be similarly investigated.

PII-16

PHARMACOKINETIC AND PHARMACODYNAMIC PROFILE OF ICATIBANT. Y. Perrin, MD, MT. Nguyen*, MD, P. Rousso*, MD, T. Buclin*, MD, B. Rochat*, PhD, L. Decosterd*, PhD, M. Appenzeller*, F. Jaquet°, PhD, F. Brunner-Ferber§ PhD, B. Rosenkranz‡, MD, J. Knolle‡, PhD, J. Biollaz*, MD. *Pharmacology and Toxicology, University Hospital, Lausanne, °Five Office, §Brunner Naga, Switzerland, ‡ Jerini AG, Berlin, Germany.

Icatibant, a potent bradykinin (BK) antagonist specific for B2 receptors, was administered i.v. to 18 healthy males to assess its safety, pharmacokinetic, and pharmacodynamic profile for onset and duration of action. Part I (3 panels of 4 subjects) compared single 1h and 4h infusions (0.005 to 3.2 mg/kg) in ascending, double-blind, placebo-controlled design. Part II tested a 24h (0.15 mg/kg/day) vs. repeated 1h infusions (0.5 mg/kg q8h) in double-blind cross-over design. Icatibant (with 2 major metabolites) concentration was assessed by LC-MS-MS, and response by repeated i.v. bolus challenges of a BK dose selected for eliciting a 10-15 mmHg blood pressure drop with reflex tachycardia (Finapress photoplethys-mography) and facial flush (laser-Doppler blood flowmetry). BK blockade was obtained at all doses, with dose-dependent intensity and duration (fig), correlating with plasma concentration and lacking hysteresis. BK dose increase (4-fold) overcame blockade, suggesting competitive inhibition. Icatib-ant has a rapid distribution and elimination (half-life 1.8h) and linear kinetics over the dose range tested. It was well tolerated up to 1.6 mg/kg but 3.2 mg/kg induced transient head/trunk flushing, itching, with one orthostatic hypo-tension. In conclusion, the ability of Icatibant to safely and sustainedly block BK effects over a wide dose range suggests an appealing therapeutic potential in conditions involving BK overproduction.



PII-17

RATING SCALES FOR HEARTBURN (HB) STUDIES. S. Korn, MD, M. Villani, R. Tipping, J. G. Levine, MD, Merck Research Laboratories, West Point, PA.

Categorical or VAS scales at fixed intervals after a provocative meal (PM) have been used to show H2-receptor antagonists (H2RAs) prevent meal-induced HB. We investigated measurement characteristics of a 10-point ordinal rating (1= mildest ever through 10= worst ever) versus validated 4-category Likert rating (none, mild, moderate, severe). Methods: Double-blind parallel study with 282 HB-sufferers randomized to take famotidine (fam) 20 or placebo before 4 self-selected PMs eaten at home. HB intensity rated on 4-point scale q30 minutes post-meal for 3 hours, then maximum HB during the 3 hours rated on 10-point scale (value of 0 assigned if no HB). Construct validity assessed using Spearman correlation (SC) between the scales. Discriminant validity assessed by comparing mean of 10-point scale scores among groups of meal sessions with none, mild, moderate, or severe peak HB. Responsiveness between scales compared using effect size. Results: Peak HB with fam 20 significantly less than placebo according to periodic 4-point and single 10-point ratings. SC coefficient between scales was 0.943. Mean scores on 10-point scale show clear distinction among categories for peak HB on 4-point scale. Effect size with 10-point scale (−0.249) was virtually identical to that with 4-point scale (−0.252). Conclusion: Ability of single ordinal rating of peak HB to differentiate between treatments is similar to that seen with 4-category Likert rating.

PII-18

POPULATION PHARMACOKINETICS OF ROSUVASTATIN IN NORMAL SUBJECTS AND SUBJECTS WITH DYSLIPIDEMIA. T. Tzeng, PhD, P. Mitchell, MS, H. Zhang, MS, L. Kung, MS, D. Schneck, MD, B. K. Birmingham, PhD, AstraZeneca, AstraZeneca LP, MegaMed PRI, Wilmington, DE.

Purpose: To conduct a population pharmacokinetic (PK) analysis assessing the effects of renal function and other covariates on rosuvastatin (RO) pharmacokinetics. **Methods**: A total of 10,078 RO plasma values collected from 16 clinical trials after single/multiple oral dosing of 5 to 80 mg RO to 945 volunteers, renal-impaired subjects, or dyslipidemic subjects (DS) were used. A structural PK model was built using data from 10 phase I studies. Demographic covariates, creatinine clearance (CLCR), and RO dose were evaluated. **Results**: Structural PK model was a two-compartment model with linear elimination and simultaneous first- and zero-order absorption. Final model parameters (typical values) are: CL/F (257 L/hr), V_C/F (899 L), V_2/F (1380 L), Q_2/F (67.9 L/hr), K_a (1.14 hr^{-1}), D_2 (4.48 hr), and F_2(0.857). Age, smoking status, body weight, body surface area, and lean body mass had no effect on any PK parameters. CL/F was not significantly changed in subjects with mild/moderate renal impairment. CL/F was decreased in Japanese living in Japan (56% of Caucasians) and in DS (29% of volunteers). V_C/F increased with increasing IBW slightly or in DS (153% of volunteers). Compared to Caucasians, Japanese exhibited lower V_2/F (72%) and K_a (42%) and Black had lower K_a (5%) and D_2 (69%). Females had a lower D_2 (77% of males). **Conclusions**: Mild or moderate renal impairment did not alter RO PK. Ethnicity and subject status are 2 factors influencing systemic exposure to RO.