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BIOCHEMICAL MEASURES OF HEPATIC FUNCTION AND BEVACIZUMAB CLEARANCE IN PATIENTS WITH COLORECTAL CANCER: A POPULATION PHARMACOKINETIC (PPK) APPROACH. P. Kuebler, PharmD, J. Lu, PhD, L. Xu, PhD, E. Holmgren, PhD, J. Hambleton, MD, D. Spyker, MD, Genentech, Inc., So. San Francisco, CA.

BACKGROUND/AIMS: Bevacizumab (BV) is a humanized monoclonal antibody against vascular endothelial growth factor. BV was approved in February 2004 for use in combination with 5-FU-based chemotherapy as 1st-line therapy for metastatic colorectal cancer. This analysis investigated the relationship between clearance (CL) of BV and biochemical measures of hepatic function (BHF).

METHODS: Individual CL values for the 2 pivotal trials were estimated with the POSTHOC option in NONMEM using a BV PPK model and compared to available BHF: albumin (ALB), AST, ALT, total bilirubin (TBIL), and alkaline phosphatase (ALK). The time-varying vs. baseline-only covariate effects were assessed by comparing the respective NONMEM fits.

RESULTS: Inter-subject analyses of CL and BHF showed:

- ALB and ALK associations with BV CL at baseline were statistically significant
- Differences in CL with extremes of ALB and ALK at baseline were modest (<25%) compared with inter-subject variability (>33%)
- No relationship between treatment-emergent changes in BHF and CL of BV was apparent.

CONCLUSION: Lower ALB and higher ALK were associated with higher BV CL (decreased exposure) and are likely surrogates for more advanced disease rather than hepatic dysfunction. These differences in CL were modest and unlikely to have a meaningful effect on BV exposure.

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PHARMACOKINETICS, SAFETY AND TOLERABILITY OF A NOVEL 100 MG/H TRANSDERMAL FENTANYL PATCH CO-ADMINISTERED WITH 100 MG ORAL NALTREXONE IN HEALTHY MALES. M. Lor, BSc, GrDip, M. Di Marco, PhD, J. Marier, PhD, L. Roux, MSc, N. Will, BSc, E. Aggerholm Saedder, MD, G. Morelli, MD, MDS Pharma Services, Nycomed, St.Laurent, PQ, Canada.

BACKGROUND/AIMS: Recommended initial dose of fentanyl (FEN) in opioid-naive patients is 25μg/h with upward titration. The aim was to assess the pharmacokinetics (PK), safety and tolerability of a FEN patch given with naltrexone (NAL), an opioid receptor antagonist.

METHODS: In a randomized crossover study, healthy male subjects (n=24) received a single 72h application of two formulations of FEN (100μg/h) given with oral NAL (100mg) in a clinical setting. Blood samples were collected and serum FEN was assayed using a LC/MS/MS method.

RESULTS: Mean (CV%) for AUC and Cmax were 142.7ng·h/mL (25.0) and 2.35ng/mL (34.8), respectively. PK parameters of FEN were similar for the reference product with and without NAL. Even though a high dose of FEN was administered, oral NAL prevented the occurrence of opioid adverse events (AEs). Of the 281 AEs, 139 were drug-related with 100 specific to the patch application site. Most AEs were mild and none were severe.

CONCLUSIONS: Co-administration of oral NAL did not affect the PK of FEN and prevented the occurrence of opioid AEs. Results from this study confirm that a 100μg/h dose of FEN was well tolerated and safe when given with NAL in healthy males.

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DEVELOPMENT AND EVALUATION OF A POPULATION PHARMACOKINETIC (PK) MODEL FOR DARBEPOETIN ALFA IN HEALTHY SUBJECTS. B. Agoram, PhD, L. Sutjandra, BS, J. Sullivan, MD, Amgen, Thousand Oaks, CA.

AIMS: Darbepoetin alfa (DA) is a novel erythropoiesis stimulating protein with longer half-life, which allows for less frequent dosing. DA is approved for treatment of anemia associated with chemotherapy and chronic kidney disease. We describe the development and evaluation of a population PK model of DA in healthy subjects.

METHODS: Serum DA concentration data were gathered from 50 healthy subjects (age 53–88 years) after intravenous and/or subcutaneous doses ranging from 0.75 to 9 μg/kg. Intensive PK profiles were obtained after single doses in all subjects.

RESULTS: A population PK model, including first order absorption, two-compartment disposition, and first order elimination, provided adequate description of data. The drug exhibited flip-flop kinetics after SC administration. The influence of baseline covariates such as age, body weight, height, baseline hemoglobin, and gender on the model parameters was evaluated to obtain the final model, which was tested with posterior predictive and bootstrap tests. Simulations were performed using the final model to compare the PK after fixed versus weight-based DA dosing.

CONCLUSIONS: A population PK model which describes the inter-individual and intra-individual variability in DA PK and PK parameter-baseline covariate relationships was developed using robust modeling methodologies. The model is being used to predict PKPD response of DA in various therapeutic settings.

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NO INTERACTION BETWEEN NEBIVOLOL AND DIGOXIN IN HEALTHY VOLUNTEERS. T. E. Lawrence, PhD, S. Liu, MS, J. W. Fisher, BA, T. Vukic-Bugarski, MD, C. M. Donnelly, MS, M. Y. Huang, PhD, R. J. Rackley, PhD, Mylan Pharmaceuticals Inc., Morgantown, WV.

BACKGROUND: Nebivolol is a new generation cardiovascular agent reported to have vasodilating actions owing to its ability to potentiate nitric oxide release from the endothelium coupled with highly cardioselective β_1-adrenergic antagonism. It has been studied worldwide in a variety of disorders such as hypertension, CHF and angina. As concomitant administration of nebivolol with digoxin is likely to occur when nebivolol becomes commercially available, the effect of nebivolol on the pharmacokinetics (PK) of digoxin was assessed in 13 healthy volunteers.

METHODS: Subjects received a 0.25 mg oral loading dose of digoxin BID on Day 1 followed by QD on Days 2–17. On Days 8–17, subjects also received a QD dose of 10 mg nebivolol. Blood samples for PK assessment of digoxin were taken at frequent intervals on Days 7 and 17.

RESULTS: Administration of nebivolol resulted in no clinically significant changes in the PK of digoxin (C_{max}: Ratio 1.07, 90% CI 0.94–1.21; AUC_{0-24hr}: Ratio 1.08, 90% CI 1.03–1.14). Moreover, there was no evidence of any cardiovascular or laboratory test result abnormalities.

CONCLUSIONS: No clinically significant changes in the PK of digoxin were observed with the co-administration of nebivolol. Therefore, no dose adjustments are considered necessary for digoxin when given concomitantly with nebivolol.