PI-80

VALIDATION OF MONTE-CARLO PARAMETRIC EXPECTATION MAXIMIZATION ALGORITHM (MCPEM) IN ANALYZING POPULATION PHARMACOKINETIC/PHARMACODYNAMIC (PK/PD) DATA. C. M. Ng, PharmD, PhD, S. Guzy, PhD, R. J. Bauer, PhD, Genentech, XOMA (US) LLC, South San Francisco, CA.

BACKGROUND: This study describes a parameter estimation capabilities performed on the MCPEM algorithm in analyzing population PK/PD data using different PK/PD models.

METHODS: NONMEM was used to simulate the population data from different models ranging from simple PK model to PK/PD model with receptor mediated clearance and receptor down-modulation. The MCPEM algorithm implemented in S-ADAPT program was used to obtain the parameter estimates. Parameter estimates and their precision (standard errors) were compared to the true values. Model estimates were considered acceptable if $\geq$ 90% of estimated parameters are within 2 standard errors (SE) of the true values, $\geq$ 95% of the estimated parameters are within 3 SE of the true values, and SE derived from the information matrix were within 30% of the true SE.

RESULTS: In general, there was good agreement between the parameters estimates and the true values. The SE of the estimates of population mean and intra-individual variability were within 30% of the true values. The SE of the estimate of inter-individual variability were within 30% of the true values in the simple PK model with increase to more than 30% in estimates of several inter-individual variability in a more complex model, possibly due to limitation of the simulated data used for the model fitting.

CONCLUSION: This study results suggested that MCPEM algorithm used in the S-ADAPT program is able to estimate the true population values in the simulated data generated by NONMEM.

PI-81

MODELING OF THE THREE ANTIFUNGAL AGENT COMBINATION (AMPHOTERICIN B + MICAFUNGIN + NIKKOMYCIN Z) AGAINST ASPERGILLUS FUMIGATUS IN VITRO USING A NOVEL RESPONSE SURFACE PARADIGM. Y. F. Brun, PharmD, B. H. Segal, MD, C. G. Dennis, MS, R. C. Youn, BA, D. B. White, PhD, W. R. Greco, PhD, MBA, Roswell Park Cancer Institute, The University of Toledo, Buffalo, NY.

BACKGROUND: Various approaches to the assessment of synergy, additivity and antagonism among drugs have been developed, including graphical isobologram and statistical response surface methods. Response surface methods allow one to model all of the information present in full multiple-agent concentration-effect data sets, and to quantify local regions of synergy, additivity, and antagonism.

METHODS: In vitro, Aspergillus fumigatus was exposed in randomized wells of 96-well plates to combinations of Amphotericin B, Nikkomycin Z and Micafungin. It included full concentration-effect curves for each agent alone; 3 fixed-ratio each of the 3 binary mixtures; and 11 fixed-ratio ternary mixtures. Each curve had 11 different concentrations (plus control), all performed in quintuplicate. After 24-h exposure, fungal growth was assessed with an XTT assay.

RESULTS: We modeled each fixed-ratio combination alone using the 4 parameter Hill concentration-effect model. Then, we modeled each parameter versus the proportion of each agent using constrained polynomials. Finally, we modeled the three-agent response surface overall. The overall 4-dimensional response surface is complex, but can be explained in detail. Zones of synergy, additivity and antagonism are mapped on the surface.

CONCLUSIONS: Applying this response-surface method to a huge dataset for a three-antifungal agent combination is novel and has the potential to revolutionize the field of antifungal pharmacology.

PI-82

POPULATION PHARMACOKINETIC ANALYSIS OF LONG-ACTING NALTREXONE FOR INJECTION. S. Hayes, PhD, C. Farrell, PhD, J. Dunbar, PharmD, R. Turncliff, PhD, GloboMax®, The Strategic Pharmaceutical Development Division of ICON plc., Alkermes Inc., Marlow, United Kingdom.

BACKGROUND: Naltrexone (NTX) is used in the treatment of alcohol and opioid dependency. While oral NTX must be given daily, long-acting naltrexone (LA-NTX) was designed to provide continuous exposure to NTX for 1 month with a single IM injection.

AIMS: To characterize the population pharmacokinetics (PPK) of NTX and its major metabolite, 6β-naltrexol (6β-NOH), following LA-NTX administration using nonlinear mixed effects modeling.

METHODS: Data from 4 clinical studies of LA-NTX were pooled for the analysis: 3821 NTX and 3766 6β-NOH plasma samples from 453 subjects were available.

One-compartment disposition submodels, parameterized in terms of clearance (CL) and volume of distribution (V), were used to describe the PK of NTX and 6β-NOH. Absorption was modelled as sequential release from 3 depot compartments. The impact of covariates (demographics, alcohol/opiate use, renal/hepatic function) on PK parameter estimates was evaluated.

RESULTS: NTX CL (140 L/h) and V (38800 L) were dependent on weight (0.552 L/h/kg and 0.682 L/kg, respectively); 6β-NOH CL (64.5 L/h) was dependent on creatinine clearance (0.213 L/h/mL/min). Additionally, NTX CL and V, and 6β-NOH CL were 24%, 35%, and 30% higher, respectively, in alcohol and/or opioid dependent subjects. These covariate - parameter relationships were not clinically relevant.

CONCLUSIONS: A PPK model of LA-NTX describing inter- and intra-individual variability was developed. Dosing adjustments of LA-NTX should not be necessary for evaluated covariates.

PI-83

MODEL-BASED DESIGN OF AQUAVAN® INJECTION DOSE RANGING PHASE II STUDY. E. Gibiansky, PhD, L. Gibiansky, PhD, C. Wang, PhD, Guilford Pharmaceuticals Inc., Metrum Research Group LLC, Baltimore, MD.

BACKGROUND: AQUAVAN® Injection (AI) is a water-soluble prodrug of propofol. AI population PK/PD model was developed earlier using PK and MOAA/S (Modified Observer's Assessment of Alertness/Sedation) data from a colonoscopy study.

METHODS: Model-based simulations were used to design a new study: (i) Choose initial bolus doses that produce deep sedation (MOAA/S than 5 min) in $<$ 5% of patients; (ii) Choose titration regimens that provide sedation to most patients without sedating them too deeply; (iii) Optimize weight adjustment of dosing to maximize % of sedated patients while minimizing % of deeply sedated patients; (iv) Assess power and choose sample size with respect to sedation success.

RESULTS: The following dosing paradigm should balance efficacy and safety outcomes: weight-proportional dosing with boundaries at 60 and 90 kg (patients weighing $<$ 60 or $>$ 90 kg are dosed as 60 or 90 kg patients), initial doses of 5-8 mg/kg, and supplemental doses of 25% of the initial administered at 4 and 8 min. Initial doses should sedate patients who are more responsive while avoiding deep sedation. Supplemental doses should sedate most patients who are less responsive to sedation. With 25 patients per group, 5 mg/kg group is differentiated from 2 and 8 mg/kg groups with 99% and 79% power, respectively.

CONCLUSIONS: The model-based simulations optimized the design with initial doses of 2, 5, 6.5, and 8 mg/kg with boundaries at 60 and 90 kg. The validity of the predictions will be tested upon completion of the study.