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A PHARMACOKINETIC MODEL TO DOCUMENT THE INTERCONVERSION BETWEEN PALIPERIDONE'S ENANTIOMERS. A. Cleton, PhD, S. Rossenu, A. Vermeulen, A. Cleton, K. Talluri, A. Mertens, L. Janssens, S. Boom, Johnson & Johnson, Pharmaceutical Research and Development, Beerse, Belgium.

BACKGROUND/AIMS: Paliperidone is a mixture of two equally potent enantiomers. The proposed pharmacokinetic model aims at characterizing the pharmacokinetics of the two enantiomers of Paliperidone and their interconversion.

METHODS: In this single-dose, 5-period cross over study, 20 subjects were randomised to receive either a 30 min i.v. infusion of 1 mg Paliperidone, a 1 mg Immediate Release (IR) formulation or an 1 mg solution of the (+) or (−) enantiomer, a 3 mg Extended Release (ER) formulation of Paliperidone.

RESULTS: Plasma concentration-time profiles of each enantiomer were best described by a 2 compartment pharmacokinetic model, with a lag time after oral administration.

The median volume of the peripheral compartment is much higher for the (−) enantiomer (192 L) compared to the (+) enantiomer (70.6 L). The intercompartment clearance of the (+) enantiomer is lower than for the (−) enantiomer, 78.8 L/h and 282 L/h. The elimination clearance of the (+) enantiomer is lower than the clearance of the (−) enantiomer, 1.41 and 8.15 L/h. The interconversion clearance (CLi) between both enantiomers is 7.90 L/h and independent of (+) to (−) or (−) to (+) interconversion. The bioavailability after administration of the IR was 121% and for ER formulation 28%.

CONCLUSION: With this study a pharmacokinetic model has been developed to describe the disposition of Paliperidone and to characterise the interconversion between the two enantiomers of Paliperidone.

PII-73

PHARMACODYNAMIC (PD) MODELING OF SUBJECTIVE EFFECTS IN A RANDOMIZED DOUBLE BLIND CROSSOVER ABUSE LIABILITY STUDY OF OROS® (OROS-MP) AND IMMEDIATE-RELEASE METHYLPHENIDATE (IR-MP) IN RECREATIONAL STIMULANT USERS. K. A. Schoedel, PhD, D. A. Parasrampuria, PhD, R. Schuller, MSc, S. A. Silber, MD, E. M. Sellers, MD, PhD, FRCPC, Ventana Clinical Research Corporation, McNeil Consumer & Specialty Pharmaceuticals, Toronto, ON, Canada.

BACKGROUND: Subjective and objective drug effects are often analyzed similarly but this may not be the best approach. In this study, ranking using linear combination of factors and bootstrapping was more reasonable.

METHODS: In this PK/PD study, 49 subjects received oral single-dose OROS-MP (108 mg), IR-MP (60 mg) and placebo. Subjects completed PD scales over 24 hrs (ARCI, Cole/ARCI, Drug Effects VAS, Subjective Drug Value) using validated computer testing (SMS 6.1, Ventana Clinical Research Corp). Data were analyzed using ANCOVA. Subjects were "qualified" by IR-MP response using factor analysis and ANCOVA/bootstrapping was used to test effects of ranking the response.

RESULTS: IR-MP had higher scores than placebo. OROS-MP scores were greater than placebo but generally lower than IR-MP; key differences were seen in Any Effects VAS, Cole/ARCI Stimulation Euphoria/Motor, ARCI Amphetamine, MBG and BG (all $P<0.05$). Post-hoc analyses showed that when 10-15 poor responders (those least able to distinguish IR-MP and placebo) were excluded, VAS Liking partial AUEs became significantly different ($P<0.05$). Differences were most apparent for models using bootstrapping and multiple scales to select responders.

CONCLUSIONS: IR-MP and OROS-MP had greater subjective effects than placebo. OROS-MP had effects generally lower than IR-MP (even at a higher dose) demonstrating differences in abuse potential between formulations. Pharmacologic 'qualification' may improve assessment of subjective effects.

PII-74

A MODEL-BASED APPROACH FOR EVALUATING POTENTIAL CONTAMINATION OF BLOOD SAMPLES FROM A COMMON INDWELLING CATHETER AND ITS EFFECTS ON ESTIMATED ACTINOMYCIN-D PHARMACOKINETICS. D. A. Paccaly, PharmD, J. M. Skolnik, MD, P. C. Adamson, MD, J. S. Barrett, PhD, FCP, The Children Hospital of Philadelphia, Philadelphia, PA.

INTRODUCTION: A structural model derived from Actinomycin-D (Act-D) exposure following dosing through a central venous line (CVL) and sampling from a peripheral vein was modified to approximate contamination when dosing and sampling from the same CVL.

OBJECTIVE: To simulate three type of drug contamination to reflect the effect on PK parameters.

METHODS: Three approaches were studied: a fixed percentage of Act-D concentration (% fixed), an additional concentration decreasing exponentially over time (exp/time), and an additional concentration decreasing linearly over the time (lin/time), and analyzed using NONMEM. Resulting parameters are compared to the originals.

RESULTS: AUC and clearance (CL) estimates after % fixed and exp/time contamination were not different from the originals. In contrast, lower estimates of terminal $t_{1/2}$ were observed for the exp/time datasets. Estimates of AUC, clearance and terminal half-life calculated from the lin/time modified datasets were different from original data.

CONCLUSION: The contamination of blood samples using the exp/time model, the most probable model of sample contamination, projects no difference in the estimation of both AUC and CL. A shorter $t_{1/2}$ was estimated with the exp/time model and was unchanged with the % fixed model. We may use this simulation approach with other drugs providing that the limit of quantitation of the analytical method is low enough to see any significant PK parameter modifications.

PII-75

DOSE-DEPENDENCY OF PK/PD PARAMETERS OF CISATRACURIUM IN PENTOBARBITAL ANESTHETIZED DOGS. F. Varin, BPharm, PhD, C. Chunlin, MD, PhD, Université de Montréal, Montréal, PQ, Canada.

BACKGROUND: The objective of the present study was to confirm whether sensitivity (EC_{50}) and effect compartment equilibration rate (K_{e0}) varied with different doses of cisatracurium besylate in anesthetized dogs, as a finding previously reported in patients.

METHODS: Ten normal dogs were anesthetized with pentobarbital and mechanically ventilated. Two doses of cisatracurium (1.5xED95 and 6xED95) were administered in a cross-over design after an appropriate wash-out period. Neuromuscular function was monitored using TOF twitch stimulation. Arterial blood was drawn continuously after cisatracurium injection to characterize the front-end kinetics (first 2 min) and at frequent intervals thereafter. HPLC analysis was used to determine cisatracurium plasma concentration. PK-PD modeling was performed using both parametric and nonparametric approaches.

RESULTS: Nonlinear PK over the dose range was ruled out. Using parametric analysis, the K_{e0} and EC_{50} values were 0.0756 *vs* 0.1437 min^{-1} ($p<0.001$) and 293 *vs* 219 ng/ml ($p=0.003$) for the high and low doses, respectively. A similar trend was observed using nonparametric analysis.

CONCLUSIONS: A dose-dependent effect on PK/PD parameters was verified. The underlying mechanism is not clear and could be attributed to restricted diffusion in the biophase.