NEW MODEL TO USE INDIVIDUAL BIOEQUIVALENCE TO PREDICT PHARMACOLOGICAL DRUG LEVELS IN ASTRONAUTS: IN VIVO AND IN VITRO PHARMACOKINETIC CORRELATIONS OF GROUND-BASED VALUES FOR SPACE FLIGHT

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PURPOSE. Acute and chronic hemodynamic responses to weightlessness in humans occur. (1-7) Preliminary reports indicate drug levels in a given astronaut vary when ground-based values are compared with those obtained during space flight and vary within the same person on different days of the space flight mission. (3-8) Population studies which use an average bioequivalence methodology may not fully reflect true PK and PD “intra and inter – individual” differences since bioavailability differs not only among persons but also within the same person. Thus, there is a need to determine individual bioequivalence when considering possible differences between formulations or when determining the effect of the same formulation in different environments, i.e., the 1-g of Earth vs. the 0-g of outer space. This study explores the relevance of using individual bioequivalence measurements (9-15) obtained on Earth to predict plasma levels of a pharmacological drug in a given astronaut when in the migrogravity of outer space.

INTRODUCTION. Pharmacokinetic and pharmacodynamic relationships are carefully studied in clinical trial designs (16). Similar studies must be conducted to predict pharmacological drug levels and responses during space flight. New ground-based models to evaluate pharmacokinetic and pharmacodynamic effects of drugs in different gravity loads have been developed (17) but more are needed. Bioavailability is determined by the rate (how fast) and extent (how much) of the active ingredient is absorbed and available at the site of drug action. The rate of drug absorption is defined by the maximum or peak concentration Cmax and the time to achieve max concentration, Tmax. The extent of drug absorption is defined as the area under the curve AUC. Because drug concentrations cannot usually be measured at the site of drug action, i.e., the human receptor site, the majority of the bioavailability studies measure the drug or the metabolite concentration in the blood or in other biological fluids, such as plasma, serum, and/or urine. Several types of study designs are classified as “Bioavailability Studies.”

METHODS. We describe an approach using population pharmacokinetic modeling with Maximal A-posteriori Probability (MAP) Bayesian estimation to evaluate bioavailability. This provides point estimates for individual patients and, as such allows measurements performed in both 1-g and 0-g environments to be correlated to outcome. We will demonstrate the principle employing a bioavailability study where a stable-labeled and cold isotope were administered, plasma and urine collected for 168 hours and modeled with a 9-differential equation, four output pharmacokinetic model.

CONCLUSIONS. Our new model uses individual bioequivalence data obtained in astronauts during ground-based studies and correlates both in vivo and in vitro ground-based data to predict pharmacokinetic drug levels in a given astronaut during space flight.