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Strategic approaches to optimize the power of bioequivalence studies of highly variable drugs through pharmacogenomics

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In bioequivalence studies of highly variable drugs, intra-individual variability is usually greater than in other studies (CVw>30%). This makes it necessary to significantly increase the number of subjects so as to attain an adequate statistical power. The conventional two-periods, two-sequences, crossover studies rule out between subject variability but variability within subjects remains. Then, to be able to compare the fraction absorbed between reference and test drugs with reasonable accuracy and precision, it is important that the subjects' clearance remains steady through both periods. Subjects with high CVw in drug bioavailability could show differences in drug plasma concentrations, between formulations, due to their inherent between-period changes in metabolism. This might not be fully related to differences in the absorption of formulations under comparison. Regulatory agencies have introduced special study designs in order to address this problem and the latter leads to laborious study conduction and tricky statistics. However, it can be expected that the inclusion of subjects with reduced metabolic enzyme capacity in the study might decrease CVw and hence sample size and cost. The drug metabolizing enzyme genes CYP2C9, CYP2C19, CYP2D6, CYP3A4 and CYP3A5 account of more than 40% of the metabolism of the most frequently prescribed drugs. For example, genetic polymorphism of CYP2D6 influence pharmacokinetic of mitazapine with a 79% increase in AUC for poor vs. extensive metabolizer. On the other hand, for CYP3A5*1/*3* and CYP3A5*3/*3 genotypes, tacrolimus clearance is 16 ml/min/mg and 6 ml/min/mg, respectively. During this speech, the strategic approach to increase bioequivalence study power will be developed.

Biography

Francisco E Estevez-Carrizo got his MD at the State University in Montevideo in 1980. In 1981, he did his Post-doctoral in Clinical Pharmacology at the Karolinska Institute, Stockholm. He was a Fulbright Scholar at Penn State University in 1991. In 1984 he was a resident and board certificate specialist in Clinical Pharmacology. From 1993 he worked as Associate Professor of Pharmacology and Therapeutics at the State University, Montevideo. In 2002, he was appointed as full Professor of Clinical Pharmacology at the University of Montevideo. Currently he is working as a Chief Medical Officer at the Center for Clinical Pharmacology Research in Montevideo, Uruguay. His research interests include Bioequivalence/Pharmacogenomics. He has authored several articles published in peer reviewed journals.

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