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Differences in Bioavailabilities (BA) determined using pharmacokinetic and pharmacodynamic parameters of endogenous compounds

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BA may be determined using both plasma concentrations of a drug and its pharmacological effects. However, resulting BA can be substantially different as shown in this inhalation insulin study. In a randomized crossover study, 30 healthy subjects (30±1 years) received 10 IU Actrapid® subcutaneously and 187 IU (6.5 mg) of recombinant human insulin powder by inhalation using the Cyclohaler™ dry powder inhaler under euglycemic glucose clamp conditions. Relative BA following the inhalation administration compared with the subcutaneous dose were 12.0±1.8% and 6.3±0.6% when determined using baseline-adjusted insulin and glucose infusion rate (GIR), respectively. To explain differences in BA, a pharmacokinetic-pharmacodynamic model was developed and BAs were predicted at different doses of inhalation insulin with the fixed 10 IU subcutaneous dose. BA predicted using 3.25 mg inhaled insulin and GIR were 12% and 7.5%, respectively. Without baseline adjustment BA determined with insulin and GIR were similar (11% and 9.0%, respectively). However, a hysteresis plot of GIR vs corresponding insulin concentration showed more potent GIR responses for the same plasma concentrations of insulin following the subcutaneous dose, although the potency of insulin in Actrapid® and the inhalation powder formulations was the same. Thus, there may be some differences in the delivery of insulin to the target site following SC and inhalation administration. In conclusion, the difference in BA of insulin and glucose could be explained in part by the non-linear pharmacokinetic-pharmacodynamic relationship. However, there may be other contributing factors (baseline adjustment, different delivery to active site) as well.

Biography

Formerly a Senior Director, Dr. Chyung Cook is presently a Principal Scientist in Pharmacokinetics and Bioanalytical Sciences at Baxter Healthcare where his primary responsibility has been directing clinical and pre-clinical PK/PD, drug metabolism and bioanalytical research. Prior to joining Baxter in 2003, Dr. Cook was as a Senior Fellow in Monsanto-Searle and Pharmacia. With his Ph.D. in Medicinal Chemistry he is honored as an AAPS Fellow and has published over 150 peer-reviewed articles and abstracts. His research includes complex PK/PD evaluation, application of drug metabolism in toxicology, food effects and absorption mechanism, BA/BE evaluation, and stereo-selective metabolism.