BIOPHARMACEUTIC PROPERTIES OF DRUGS: NEW TOOLS TO FACILITATE DRUG DISCOVERY AND DEVELOPMENT

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Properties of a good drug include safety, efficacy, half-life and bioavailability. With the current approach to drug discovery based on receptor-based and cell-based screening methods, compounds are frequently moved into development with poor bioavailability. With low bioavailability, drug administration is typically limited to parenteral routes, thus limiting the potential wide-spread utility of these therapeutic agents. The first and most important factor limiting a drug's bioavailability is the intestinal membrane permeability which in turn determines the maximum fraction of the dose administered that can be absorbed. We have recently utilized new intubation methods for performing permeability measurements in humans and establishing a fundamental human data base for correlating intestinal jejunal membrane permeabilities with permeabilities determined in other systems, e.g., animals, tissue culture, as well as physical chemical properties. Correlations between these systems and human

permeabilities will lead to fundamental advances in our ability to predict the maximum fraction dose absorbed and can significantly advance the success rate in the drug discovery development process. A second physical chemical factor that can limit drug absorption is the drug solubility, particularly of hydrophobic compounds. Compounds of this type frequently result from receptor screening based approaches to drug discovery. An integrated model that includes drug dissolution, dose, and transit will be utilized to illustrate the fundamental processes controlling fraction dose absorbed and the critical parameters controlling drug absorption, dose, dissolution and permeability integrated into a systematic approach to predicting drug absorption. These methods can be utilized to augment the drug discovery process to improve the oral absorption of therapeutic agents. In particular, prodrug approaches can be rationally applied to improving membrane permeabilities using carrier-mediated transport mechanisms associated with nutrients. For example, utilizing the human peptide transporter responsible for absorption of di- and tri-peptides, β-lactam antibiotics and ACE inhibitors, it will be demonstrated that this carrier can be utilized, coupled with a prodrug approach to improving the systemic availability of nucleoside type drugs. Finally, advances in drug development are critically coupled with advances in drug regulatory processes. The advances in our understanding of the critical biopharmaceutic properties of drugs can be utilized to develop standards for

bioequivalence studies during the drug development processess. Thus, based on these principles it may be possible to considerably reduce the number of bioequivalence questions that arise during a normal drug development process, thus, accelerating drug development and reducing the cost of new drug therapy. In summary, advances in our understanding of drug biopharmaceutic properties is leading to new methods and understanding of factors controlling oral drug absorption. These factors in turn can be used to develop screening methods for improving the selection criteria for drugs chosen for development as well as used to simplify the drug discovery and development process through the selection of appropriate screening methods. Thus, we can expect to see screening for drug biopharmaceutic properties playing an increasing role in the drug discovery development process.