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前沿论坛

药代动力学人体预测及其在新药研发中的应用

李桦, 庄笑梅

军事医学科学院毒物药物研究所药物代谢研究室, 北京 100850

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摘要 药物代谢和药代动力学(DMPK)通过揭示药物的体内代谢处置过程, 理解药物药理效应和毒副反应的体内物质基础, 是连接药物分子及其性质与生物学效应的桥梁。DMPK人体预测应用模型拟合技术, 由人体外试验数据和动物体内外数据预测人体药代动力学性质, 并与药效动力学和毒性评价相关联, 可提高新药研发效率、降低临床失败率和节省资源。经典的异速放大法和体外-体内外推法主要用于预测人体清除率和稳态表观分布容积等重要的药代动力学参数。近10年来, 基于生理的药代动力学模型(PBPK)的快速发展和应用实践, 推动了DMPK人体预测在新药研发、药物监管、临床合理和个体化用药中的应用。PBPK模型不仅能预测消除和分布等参数, 还能用于药物人体药代动力学行为的预测, 包括血药浓度-时间曲线和药物-药物相互作用, 以及不同人群体内药代动力学和药代-药效预测。作为新药研发的转化科学技术以及个体化用药的指导工具, DMPK人体预测将具有更为广泛的应用价值。

关键词 药物代谢 药代动力学 人体预测 基于生理的药代动力学模型 新药研发

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Prediction of human pharmacokinetics and its application in drug discovery and development

LI Hua, ZHUANG Xiao-me

Laboratory of Drug Metabolism, Institute of Pharmacology and Toxicology, Academy of Military Medical Sciences, Beijing 100850, China

Abstract

Drug metabolism and pharmacokinetics (DMPK) plays an important role in the understanding of the material foundation of drug efficacy and safety in body, by revealing drug metabolism and disposition processes. It acts as a bridge to link drug property and its biological activity. By using modeling techniques, the human DMPK properties are predicted from human *in vitro* data and animal *in vitro* and *in vivo* data and correlated to the pharmacodynamic and toxicological evaluations of new drugs. Application of this approach has been contributed to the increased efficiency of drug discovery and development and the reduced clinical risk and cost. The traditional prediction tools, including allometric method and *in vitro-in vivo* extrapolation, were mainly used to obtain important human pharmacokinetic parameters, such as clearance(*Cl*) and apparent distribution volume at steady state (V_{ss}). In the recent decade, the physiologically based pharmacokinetic (PBPK) model was developed. It has been widely used as a key human prediction method in drug discovery and development, regulatory process, clinical practice and personalized medicine. Beside its ability to obtain the parameters of *Cl* and V_{ss}, the PBPK model is also used for various purposes, including prediction of human plasma concentration-time curves, potential pharmacokinetic alterations caused by drug-drug interactions and pharmacokinetics in different populations. With the improved modeling and prediction power, the human DMPK prediction will become a valuable tool of translational science.

Key words drug metabolism pharmacokinetics human prediction physiologically based pharmacokinetic model drug discovery and development

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通讯作者 李桦,E-mail:amms_hli@126.com,Tel:(010)66930664 amms_hli@126.com