药学学报 2008, 43(9) 905-911 DOI: ISSN: CN:

论文

探针药物咪哒唑仑有限采样法预测抑制状态大鼠肝脏CYP3A代谢活性的研究

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摘要：

本研究以细胞色素P450(CYP)3A探针药物咪哒唑仑的系统清除率(CL_s)为指标，评价有限采样法(LSS)预测肝脏CYP3A抑制状态的可行性。采用系列剂量的CYP3A选择性抑制剂酮康唑预处理大鼠，静脉注射咪哒唑仑(MDZ)后若干时间点收集血浆样品并检测MDZ浓度，经逐步回归分析和Jack-knife验证建立LSS模型。对经相同处理的另一随机群体进行验证分析，评价该LSS模型方程的准确性和重现性。通过绘制Bland-Altman散点图对由两点(60和90 min)或三点(30、60和90 min，或30、60和120 min)血浆药物浓度建立的LSS预测模型得到的CL_s估计值(CL_{est})与二房室模型拟合值(观察值，CL_{obs})进行偏差分析并计算95%可信区间，表明两种方法得到的CL_s具有较好的一致性，LSS法预测误差小，特别是两点LSS预测模型更为准确且简便。结果表明：以咪哒唑仑清除率为指标，采用有限采样法评价大鼠肝脏CYP3A抑制状态下的代谢活性是一种准确而简便的方法，为今后推广到临床评价肝脏代谢功能从而制定和调整治疗药物的给药方案提供了理论依据和实验室证据。

关键词： 有限采样法 CYP3A 咪哒唑仑 酮康唑

A limited sampling strategy of phenotyping probe midazolam to predict inhibited activities of hepatic CYP3A in rats

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Abstract:

The present study was to evaluate feasibility of a limited sampling strategy (LSS) in the prediction of inhibited hepatic CYP3A activity with systemic clearance of midazolam (MDZ), a hepatic CYP3A activity phenotyping probe. Rats were pretreated with a serial doses of ketoconazole, a selective inhibitor on CYP3A. Blood samples were collected and detected for MDZ at specified time points after intravenous injection of MDZ. Stepwise regression analysis and a Jack-knife validation procedures were performed in one group of rats as training set to establish the most informative LSS model for accurately estimating the clearance of MDZ. Another group of rats with same treatment was used as validation set to estimate the individual clearance based on predictive equations derived from the training set. Bland-Altman plots showed a good agreement between the systemic clearance calculated from DAS (CL_{obs}) and corresponding parameter that was derived from three LSS models (CL_{est}). LSS models derived from two or three sampling time points, including 60, 90 min, 30, 60, 90 min and 30, 60, 120 min, exhibited a good accuracy and acceptable error for estimating the CL_{obs} of MDZ to evaluate hepatic CYP3A activity, especially the 60, 90 min LSS model is most accurate and convenient. The results supported that limited plasma sampling to predict the systemic clearance of MDZ is easier than the usual method for estimating CYP3A phenotyping when the hepatic activity of CYP3A is reduced in the rat. The present study provided theoretical basis and laboratory evidence for LSS to clinically evaluate metabolizing function of liver and design rational drug regimen.

Keywords: CYP3A midazolam ketoconazole limited sampling strategy

收稿日期 2008-03-27 修回日期 网络版发布日期

DOI:

基金项目:

通讯作者: 娄建石

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参考文献：

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