基于PBPK模型预测丹参酮ⅡA磺酸钠与氯吡格雷联用的药物相互作用Δ

张　蝶*，张立超，孙梦茹，钱凤丹#（上海中医药大学附属市中医医院药学部，上海　201800）

中图分类号　R969.2　　**文献标志码**　A　　**文章编号**　1001-0408（2026）13-1746-05
DOI　10.6039/j.issn.1001-0408.2026.13.15

摘　要　目的　构建丹参酮ⅡA磺酸钠（STS）与氯吡格雷（Clo）及其代谢产物的生理学药代动力学（PBPK）模型，预测二者联用时的药物相互作用（DDI），并分析影响DDI的关键因素，为临床合理用药提供参考。**方法**　检索PubMed、DrugBank、SwissADME，收集Clo及其代谢产物与STS的理化特征参数，构建两药及其代谢产物的PBPK模型。以Clo硫醇代谢产物（Clo-AM）的稳态血浆浓度-时间曲线下面积（AUC）和最大血浆浓度（c_{max}）为指标，评估STS与Clo联用时的DDI；采用单因素敏感性分析筛选影响STS与Clo联用时DDI的关键因素。**结果**　与单用Clo相比，Clo联用STS 40 mg 7 d后，Clo-AM的AUC比值和c_{max}比值分别为0.75和0.63；当STS剂量增加至80 mg时，Clo-AM的AUC比值和c_{max}比值进一步下降至0.62和0.56。敏感性分析结果表明，Clo-AM的脂溶性、STS-CYP2C19抑制常数、STS-CYP3A4抑制常数、Clo-AM的肝清除率的归一化敏感性系数的绝对值分别为15.19、11.34、10.98、3.08，为STS与Clo联用时DDI的高敏感参数。**结论**　所建PBPK模型可用于预测STS与Clo联用时的DDI；STS与Clo联用可能导致Clo-AM暴露水平下降；Clo-AM的脂溶性参数以及CYP3A4、CYP2C19的抑制参数是影响Clo-AM暴露的关键因素，其中STS对CYP3A4和CYP2C19的抑制作用可能是介导其与Clo发生DDI的重要机制。

关键词　氯吡格雷；丹参酮ⅡA磺酸钠；生理学药代动力学模型；药物相互作用；氯吡格雷硫醇代谢产物；影响因素

Prediction of the drug-drug interaction between sodium tanshinone ⅡA sulfonate and clopidogrel based on the PBPK model

ZHANG Die，ZHANG Lichao，SUN Mengru，QIAN Fengdan（Dept. of Pharmacy，Shanghai Municipal Hospital of Traditional Chinese Medicine Affiliated to Shanghai University of Traditional Chinese Medicine，Shanghai 201800，China）

ABSTRACT　OBJECTIVE To develop physiologically based pharmacokinetic（PBPK）model for sodium tanshinone ⅡA sulfonate（STS），clopidogrel（Clo），and its metabolites，to predict the potential drug-drug interaction（DDI）between STS and Clo during co-administration，and to identify the key factors influencing the predicted DDI，and provide evidence for rational clinical medication. **METHODS** Physicochemical and pharmacokinetic parameters of Clo，its metabolites，and STS were retrieved from PubMed，DrugBank，and SwissADME for PBPK model development. The steady-state area under the plasma concentration-time curve（AUC）and maximum concentration（c_{max}）of clopidogrel thiol H4（Clo-AM）were used as indicators to evaluate the DDI between STS and Clo. Single-factor sensitivity analysis was performed to identify key parameters influencing DDI between STS and Clo during co-administration. **RESULTS** Compared with Clo alone，after 7 days of Clo combined with STS 40 mg，the AUC ratio and c_{max} ratio of Clo-AM were 0.75 and 0.63，respectively. When the dose of STS was increased to 80 mg，the AUC ratio and c_{max} ratio of Clo-AM were 0.62 and 0.56，respectively. Sensitivity analysis indicated that the absolute values of normalized sensitivity coefficients for the lipophilicity of Clo-AM，the inhibition constants of STS for CYP2C19 and CYP3A4，and the hepatic clearance of Clo-AM were 15.19，11.34，10.98，3.08，respectively. These parameters were the highly sensitive parameters in the DDI between STS and Clo during co-administration. **CONCLUSIONS** The established PBPK model can be used to predict the DDI between STS and Clo during co-administration. Co-administration of STS and Clo may lead to decreased exposure of Clo-AM. The lipophilicity-related parameters of Clo-AM and the inhibition parameters related to CYP3A4 and CYP2C19 are key parameters influencing the prediction of Clo-AM exposure，among which the inhibitory effects of STS on CYP3A4 and CYP2C19 may be an important mechanism mediating the DDI between STS and Clo.

KEYWORDS　clopidogrel；sodium tanshinone ⅡA sulfonate；PBPK model；drug-drug interaction；clopidogrel thiol H4；influencing factor

Δ**基金项目**　上海药学服务青年创新项目（No.SPAYXFW2025A05，No.SPAYXFW2025B02）

＊**第一作者**　主管药师，硕士。研究方向：中西药联用的相互作用。E-mail：dearzhang123@hotmail.com

\# **通信作者**　副主任药师，硕士。研究方向：中西药联用的相互作用。E-mail：qianfengdan@126.com