

论文

MDR1基因多态性对口服环孢素A药代动力学的影响

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摘要:

目的非线性混合效应模型(NONMEM)考察中国健康人多药耐药基因(MDR1)中26外显子的C3435T多态性与环孢素A(CsA)药代动力学特性间的关系。方法HPLC法测定20名健康男性单次口服CsA微乳溶液制剂500 mg后24 h内不同时间点的药物浓度。MDR1的基因多态性测定采用DNA限制性片段长度多态性法,并用基因测序法验证。数据处理与模型拟合采用NONMEM法。结果中国健康人中含MDR1 C3435T CC或CT型的相对生物利用度较TT型高40%。结论MDR1中C3435T多态性是个体间CsA相对生物利用度差异的影响因素。

关键词: 环孢素A P-糖蛋白 多药耐药基因 非线性混合效应模型

Effect of MDR1 polymorphic expression on oral disposition of cyclosporine A

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Abstract:

AimTo determine the relationship between C3435T mutation in exon 26 of the human multidrug resistant 1 gene and cyclosporine (CsA) pharmacokinetic (PK) parameters among healthy Chinese volunteers by nonlinear mixed effect model (NONMEM). MethodsTwenty healthy subjects were given orally a single dose of 500 mg CsA in microemulsion solution. Blood CsA concentrations were measured with HPLC and the genotype for the C3435T polymorphism of MDR1 gene was determined with the PCR and restriction fragment length polymorphism. The results were further confirmed by sequencing. NONMEM was performed to assess the effect of genotype on CsA PK profile. ResultsMDR1 C3435T genotype was identified as the best predictor of CsA systemic exposure. The relative bioavailability of CsA was 40% higher in subjects who carried at least one 3435C allele compared to that of TT type individuals in the study population. ConclusionThe MDR1 C3435T genotype offers a potential basis of mechanism to explain inter-subject differences in CsA oral bioavailability.

Keywords: P-glycoprotein multidrug resistance gene nonlinear mixed effect model cyclosporine A

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