中国药理学与毒理学杂志 2013 27 (1): 6-12 ISSN: 1000-3002 CN: 11-1115/R

论著

注射用丹参总酚酸(冻干)对人CYP450酶和P-糖蛋白体外抑制作用及对大鼠CYP1A2和CYP3A体内诱导作用

胡冰[1,2], 段超慧[2], 岳洁浩[2], 马英丽 周大铮[2], 李德坤[1], 叶正良[1]
1. 天士力之骄药业有限公司, 天津 300410;
2. 黑龙江中医药大学, 黑龙江 哈尔滨150040

收稿日期 2011-12-30 修回日期 2012-6-18 网络版发布日期 2013-2-21 接受日期

摘要 目的 探讨注射用丹参总酚酸(冻干)(SLI)对人CYP450酶和P-糖蛋白体外抑制作用以及对大鼠CYP1A2和CYP3A体内诱导作用。方法 ① 应用P450-Glo™ CYP450检测试剂盒,通过化学发光法测定SLI和经典抑制剂对细胞色素P4501A2(CYP1A2),CYP2D6,CYP3A4,CYP2C19和CYP2C9的IC_{50}值,通过比较SLI和经典抑制剂对相应细胞色素P450亚型的IC_{50}值来判断SLI对人CYP450酶的体外抑制作用。② Wistar大鼠分别iv给予SLI 3, 10和30 mg·kg^{-1}和诱导剂苯巴比妥钠20 mg·kg^{-1},采用探针底物法,通过比较代谢产物的生成速率来评价SLI对大鼠CYP1A2和CYP3A的诱导作用。③ 应用ATP酶检测试剂盒,通过化学发光法测定ATP酶活性来评价SLI是否为P-gp的底物或抑制剂。结果 ① CYP1A2,CYP2C9,CYP2C19,CYP2D6和CYP3A4抑制剂的IC_{50}与SLI对其的IC_{50} 进行比较(CYP1A2: 0.12 μmol·L^{-1} *vs* 840 μmol·L^{-1}; CYP2C9: 3.362 μmol·L^{-1} *vs* 704 μmol·L^{-1}; CYP2C19: 3.236 μmol·L^{-1} *vs* 306 μmol·L^{-1}; CYP2D6: 0.117 μmol·L^{-1} *vs* 2660 μmol·L^{-1}; CYP3A4: 0.078 μmol·L^{-1} *vs* 1780 μmol·L^{-1})。② 与空白对照组(86.4±6.3)nmol·g^{-1}·min^{-1}相比, SLI 3, 10和30 mg·kg^{-1}组CYP1A2活性分别为83.4±6.6, 82.5±4.0和(83.4±6.6)nmol·g^{-1}·min^{-1}。与空白对照组(16.1±0.9)nmol·g^{-1}·min^{-1}比较, SLI 3, 10和30 mg·kg^{-1}组CYP3A活性分别为15.7±0.6, 15.9±0.7和(15.9±1.0)nmol·g^{-1}·min^{-1},无显著性差异。3 以临床血药浓度为依据设计的一系列浓度的SLI 0.0002, 0.0006, 0.002, 0.006, 0.017, 0.052, 0.156和0.468 g·L^{-1}的ATP酶活性分别与空白对照组进行比较(5.8, 5.3, 5.8, 5.5, 5.8, 5.2,, 5.8, 5.3, *vs* 5.75 μmol·g^{-1}·min^{-1}), 无显著性差异。结论 SLI临床给药剂量既不能体外抑制人CYP1A2,CYP2D6,CYP3A4,CYP2C19和CYP2C9酶活性,也不能诱导大鼠CYP1A2和CYP3A,同时也不是P-gp的体外抑制剂或底物。

关键词 注射用丹参总酚酸(冻干) P-糖蛋白 细胞色素P450 CYP1A2 细胞色素P450 CYP3A
分类号 R963

Inhibitory effect of total salvianolate lyophilized injection, a herbal preparation, on human cytochrome P450 and P-glycoprotein *in vitro* and inductive effect on rat CYP1A2 and CYP3A *in vivo*

HU Bing[1,2], DUAN Chao-hui[2], YUE Jie-hao[2], MA Ying-li[2], ZHOU Da-zheng[1], LI De-kun[1], YE Zheng-liang[1]

1. Tasly Pride Pharmaceutical Co., Ltd., Tianjin 300410, China;
2. Heilongjiang University of Chinese Medicine, Harbin 150040, China

Abstract

OBJECTIVE To investigate the inhibitory effect of salvianolate lyophilized injection (SLI) on human cytochrome P450 (CYP450) and P-glycoprotein(P-gp) system *in vitro* and the inductive effect on rat CYP1A2 and CYP3A *in vivo*. **METHODS**① IC_{50} of cytochrome P-4501A2(CYP1A2), CYP2C9, CYP2C19, CYP2D6 and CYP3A4 inhibitors was evaluated by chemiluminescence using P450-Glo™ Screening Systems. The inhibition on CYP450 *in vitro* from SLI was evaluated by IC_{50}. ② Wistar rats were sc given SLI 3, 10 and 30 mg·kg^{-1} or inducer. The method of probe substrate was used for evaluating the induction of rat CYP1A2 and CYP3A from SLI by comparing the production rate of metabolites. ③ The ATPase activities of SLI were determined by ATPase assay kit, which can evaluate whether SLI is a substrate or inhibitor of P-gp. **RESULTS** ① IC_{50} of inhibitors and SLI was compared (CYP1A2, 0.012 μmol·L^{-1} *vs* 840 μmol·L^{-1}; CYP2C9, 3.362 μmol·L^{-1} *vs* 704 μmol·L^{-1}; CYP2C19, 3.236 μmol·L^{-1} *vs* 306 μmol·L^{-1}; CYP2D6, 0.117 μmol·L^{-1} *vs* 2660 μmol·L^{-1}; and CYP3A4, 0.078 μmol·L^{-1} *vs* 1780 μmol·L^{-1}). ② Compared with control group (86.4±6.3) nmol·g^{-1}·min^{-1}, the activities of rat CYP1A2 in SLI 3, 10 and 30 mg·kg^{-1} groups were 83.3±6.6, 82.5±4.0 and (83.4±6.6)μmol·g^{-1}·min^{-1}, respectively. Compared with control group (16.1±0.9)nmol·g^{-1}·min^{-1}, the activities of rat

CYP3A in SLI 3, 10 and 30 mg • kg^{-1} groups were 15.9±1.0, 15.9±0.7 and (15.7±0.6)nmol • g^{-1} • min^{-1}(P<0.05). 3 ATPase activity of SLI 0.0002, 0.0006, 0.0002, 0.005, 0.017, 0.052, 0.156 and 0.468 g • L^{-1} according to the clinical human blood-drug level was compared with that in control group, respectively (5.8, 5.3, 5.8, 5.5, 5.8, 5.2, 5.8, and 5.3 *vs* 5.8 μmol • g^{-1} • min^{-1}), but there was no significant difference. **CONCLUSION** SLI may neither induce rat CYP1A2 or CYP3A *in vivo*, nor inhibit human CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 *in vitro*. It is not a potential substrate or inhibitor for human P-gp *in vitro*.

Key words salvianolate lyophilized injection P-glycoprotein cytochrome P-450 CYP1A2 cytochrome P-450 CYP3A

DOI: 10.3867/j.issn.1000-3002.2013.01.002

通讯作者 叶正良,Tel:13602056330,E-mail:andrea1113@yahoo.cn andrea1113@yahoo.cn