中南大学学报(医学版) 2014, 39(4) 349-354 DOI: 10.11817/j.issn.1672-7347.2014.04.005 ISSN: 1672-7347 CN: 43-1427/R

论著

不同剂量的胡椒碱对去甲替林在小鼠脑血分布中的影响

蔡立婧，刘家稳，李兰林，杨少林，阳剑，张啟智，彭文兴

1. 中南大学湘雅二医院药学部，长沙 410011；2. 江西省人民医院药剂科，南昌 330006；3. 衡阳市中心医院，湖南 衡阳 421001

摘要：

目的：研究胡椒碱对小鼠体内去甲替林药代动力学及脑血分布的影响，为胡椒碱对P-糖蛋白(P-gp)调节作用的研究提供依据。方法：216只小鼠随机分为4组，分别连续服用生理盐水、维拉帕米或不同剂量胡椒碱8 d，并于第8天给予以上药物1 h后腹腔注射去甲替林，于给药后5，15，30 min和1，2，4，6，8，12 h采集血及脑组织，并采用LC-MS/MS法测定去甲替林的浓度，计算血、脑中主要药代动力学参数和脑血浓度比值。结果：与生理盐水组相比，胡椒碱组血和脑组织中去甲替林浓度变化很小，差异无统计学意义(P>0.05)。低剂量胡椒碱能够使去甲替林的脑血浓度比值及药物浓度-时间曲线下面积(AUC0-12 h)减小，高浓度胡椒碱则无此影响。结论：低剂量胡椒碱可能可以诱导血脑屏障上P-gp的活性，而高剂量胡椒碱对血脑屏障上P-gp无此作用。

关键词： 胡椒碱 去甲替林 P-糖蛋白 血脑屏障 药代动力学

Effect of piperine on metablism and distribution of nortriptyline in mice

CAI Lijing, LIU Jiawen, LI Lanlin, YANG Shaolin, YANG Jian, ZHANG Qizhi,PENG Wen

1. Clinical Pharmaceutical Research Institute, Second Xiangya Hospital, Central South University, Changsha 410011;
2. Department of Pharmacy, Jiangxi Provincial People’ Hospital, Nanchang 330006;
3. Central Hospital of Hengyang City, Hengyang 421001, China

Abstract:

Objective: To study the pharmacokinetics and brain/plasma concentration ratio of nortriptyline at multiple doses in mice which were pre-treated with physiological saline, piperine and verapamil.
Methods: A total of 216 male Kun Ming mice [(25±3) g] were equally divided into 4 groups randomly. Each group was intragastrically administered physiological saline (B), piperine (170 μg/kg), piperine (5 mg/kg) and verapamil (5 mg/kg) for 8 days. On the 8th day, 1 h after giving the above drugs, each mice was intraperitoneally injected nortriptyline (13 mg/kg). The mice were sacrificed by picking off eyeballs at the time intervals of 5, 15, 30 min, and 1, 2, 4, 6, 8 and 12 h, and the cerebra were collected and weighted. Nortriptyline in mouse plasma and brain was determined by HPLC-MS/MS. The pharmacokinetic properties of the plasma, brain and brain/plasma were calculated.
Results: The AUC0-12 h of brain/plasma concentration ratio in the 170 μg/kg piperine group was significantly lower than that in the other groups (P<0.05), while the AUC0-12 h of

brain/plasma
concentration ratios in the 5 mg/kg piperine group and the verapamil group were not significantly
different from those of untreated mice.
Conclusion: Piperine (170 μg/kg) may induce P-glycoprotein expression in the blood-brain barrier, while piperines at 5 mg/kg has no influence on P-glycoprotein expression in the bloodbrain
barrier.

Keywords: piperine nortriptyline P-glycoprotein blood-brain barrier pharmacokinetics

收稿日期 2014-02-19 修回日期 网络版发布日期

DOI: 10.11817/j.issn.1672-7347.2014.04.005

基金项目:

国家自然科学基金(30873114)。This work was supported by National Natural Science Foundation (30873114).

通讯作者: 刘家稳， Email: 4604430@qq.com

作者简介: 蔡立婧，硕士，主要从事药代动力学与药物相互作用的研究。

作者Email:

参考文献：

1. Bhardwaj RK, Glaeser H, Becquemont L, et al. Piperine, a major constituent of black pepper, inhibits human P-glycoprotein and CYP3A4
[J]. J Pharmacol Exp Ther, 2002, 302(2): 645-650.
2. Kindell SS. Studies on selected genotoxic and toxic properties of piperine
[D]. Philadelphia, PA: Drexel University, 1984.
3. Khajuria A, Thusu N, Zutshi U. Piperine modulates permeability characteristics of intestine by inducing alterations in membrane dynamics: influence on brush border membrane fluidity, ultrastructure and enzyme kinetics
[J]. Phytomedicine, 2002, 9(3): 224-231.

4. Atal CK, Dubey RK, Singh J. Biochemical basis of enhanced drug bioavailability by piperine: evidence that piperine is a potent inhibitor of drug metabolism
[J]. J Pharmacol Exp Ther, 1985, 232(1): 258-262.
5. Han Y, Chin Tan TM, Lim LY. In vitro and in vivo evaluation of the effects of piperine on P-gp function and expression
[J]. Toxicol Appl
Pharmacol, 2008, 230(3): 283-289.
6. Ononiwu IM, Ibeneme CE, Ebong OO. Effects of piperine on gastric acid secretion in albino rats
[J]. Afr J Med Med Sci, 2002, 31(4): 293-
295.
7. Bajad S, Bedi KL, Singla AK, et al. Piperine inhibits gastric emptying and gastrointestinal transit in rats and mice
[J]. Planta Med, 2001,
67(2): 176-179.
8. Ganesh Bhat B, Chandrasekhara N. Effect of black pepper and piperine on bile secretion and composition in rats
[J]. Nahrung, 1987, 31(9):
913-916.
9. Venkatakrishnan K, von Moltke LL, Greenblatt DJ. Nortriptyline E-10-hydroxylation in vitro is mediated by human CYP2D6 (high affinity) and CYP3A4 (low affinity): implications for interactions with enzymeinducing

drugs
[J]. J Clin Pharmacol, 1999, 39(6): 567-577.
10. Pattanaik S, Hota D, Prabhakar S, et al. Effect of piperine on the steadystate pharmacokinetics of phenytoin in patients with epilepsy
[J].