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小剂量奎尼丁对安替比林消除的影响

药理学教研室 涂植光 *Speirs. C. J.**

摘 要 用高效液相法测定了小剂量(5mg)奎尼丁对6名健康受试者唾液中安替比林的药动学参数、尿中安替比林及其代谢物3-羟甲基安替比林、4-羟基安替比林和去甲基安替比林排泄率的影响。结果表明，小剂量奎尼丁对唾液中安替比林的半衰期、消除速率常数、清除率、药一时曲线下面积和表观分布容积等药动学参数均无影响，对尿中安替比林、3-羟甲基安替比林、去甲基安替比林及总代谢物排泄量亦无明显影响，但能减少尿中4-羟基安替比林的排泄量 ($p<0.05$)

关键词 安替比林；奎尼丁；药代动力学；药物相互作用

解热镇痛药安替比林(Antipyrine, AP)在体内的分布符合一室开放模型，其消除方式除约5%以原型从尿中排出外，绝大部分都需经肝药酶代谢转化后再从肾脏排泄[1]。现已明确，AP的主要代谢产物为3-羟甲基安替比林 (3-Hydroxymethylantipyrine, 3-OHMeAP)，4-羟基安替比林 (4-Hydroxyantipyrine, 4-OHAP)和去甲基安替比林

*Departmment of Clinical Pharmacology, Royal Postgraduate Medical School, UK

PHAGOCYTIC DYSFUNCTION OF NEUTROPHIL IN DIABETIC RATS INDUCED BY ALLOXAN

Li Qifu et al.

(Division of Endocrinology, Department of Internal Medicine)

In this study, phagocytic function of circulating neutrophils from diabetic rats induced by alloxan was investigated. The results showed that, (1)phagocytic rate and index of neutrophils from the diabetic rats significantly decreased($P<0.01$), (2)Phagocytic rate and index of neutrophils from normal rats decreased at high blood glucose concentration, and the degree of the reduction was significantly ($P<0.01$) correlated to glucose levels, but not very closely. Our data suggested that hyperglycemia may be one of the causes that damage the phagocytic function of neutrophils in diabetes mellitus

KEY WORDS Diabetes, Neutrophils, Phagocytic function, Alloxan

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(Norantipyrine, NorAP),这3种代谢物分别由肝药酶不同的酶系催化[2]。测定血液或唾液中AP药动学参数和尿中各种代谢物排泄量的改变，是目前临床药理学上最广泛地用以评估药物、各种生理、病理和环境因素对肝药酶活性影响的方法[1,3]。

最近，临床实验证实，奎尼丁是人体异喹胍（Debrisoquine）4-羟化酶、美多心安α-羟化酶的强效抑制剂[4,5]。为了解奎尼丁的这种抑制作用是否具有特异性，本文研究了小剂量奎尼丁对健康受试者唾液中AP药代动力学和尿中AP代谢物排泄量的影响。

材料与方法

1. 对象及标本收集 6名男性成年(27～41岁)自愿受试者，经常规化验检查无心、肝、肾疾患。在试验开始前两周及试验期间均不使用其它药物。试验开始日晨收集受试者唾液及尿液各约5ml后，空腹口服安替比林600mg，用药2h后准予进食，分别收集服药后2、4、6、8、12、16、24、36、和48h的唾液，每次约3-5ml，用预置有2g$Na_2S_2O_5$的容器收集服药后48h的全部尿液。尿液计量后留存10ml与唾液标本贮存于-30℃冰箱中备用。至少间隔1w以上再空腹服用奎尼丁5mg，4h后服用AP600mg，同上方法采集唾液及尿液标本。

2. 唾液中AP及尿液中AP代谢物测定 本实验所用的AP和4-OHAP标准品购自Aldrich公司，$Na_2S_2O_5$和NorAP标准品购自BDH公司，3-OHMeAP标准品由Breimer教授赠送，盐酸奎尼丁为Sigma公司产品。所用的有机溶剂均为HPLC级，其它试剂为AR级。

唾液中AP浓度按文献报告的HPLC法测定[3]。尿液中AP及其3种主要代谢产物按文献报告的HPLC法同时测定[3]，并作如下改进：流动相中不含$Na_2S_2O_5$，层析柱为Waters公司Novapak-C_{18}，4μ，3.9×150mm，泵为Waters公司的510型。使用Kontron Sampler进样器自动进样。每个唾液或尿液标本都同时测定双份。

3. 数据分析 唾液中AP药代动力学参数用Smart计算机程序按一室开放一级代谢动力学模型计算。尿中原型药及代谢物均按克分子数计算出占服药量克分子数的百分比。用奎尼丁前后的各种AP药动学参数和尿中代谢物排泄量数据均按配对资料行t检验。

结　果

1. 奎尼丁对唾液中AP消除动力学参数的影响

表1示奎尼丁对唾液中AP的半衰期($t_{\frac{1}{2}}$)、消除速率常数（Kel）、清除率（Cl）、表观分布容积（Vd）、药—时曲线下面积（AUC）等，均无显著影响。

表1 小剂量奎尼丁对唾液中AP药动学参数的影响

($\bar{X}\pm SD$, n=6)

	K_{el} (h^{-1})	$t_{\frac{1}{2}}$ (h)	Cl (ml/kg/min)	V_d (l/kg)	AUC (μg/ml·h)
未用奎尼丁	0.0540±0.0105	13.3±2.8	0.72±0.15	0.83±0.06	203.9±30.6
用奎尼丁后	0.0483±0.0099	14.8±2.5	0.73±0.17	0.91±0.16	208.4±63.8

表2 小剂量奎尼丁对AP及其代谢物尿排泄比率（%剂量克分子数）的影响

($\bar{X}\pm SD$, n=6)

	3-OHMeAP	4-OHAP	NorAP	AP	总排泄率
未用奎尼丁	14.0±1.8	30.1±4.1	17.8±5.2	3.8±1.4	65.8±7.9
用奎尼丁后	12.6±2.4	24.9±2.9*	16.9±4.4	4.0±1.4	58.2±8.8

注* $P<0.05$

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2. 奎尼丁对尿中AP代谢物及原型药排泄量的影响

如表2中所见，小剂量奎尼丁除减少4-OHAP尿排泄量外，对3-OHMeAP、NorAP和AP及代谢物总排泄量都无明显影响。

讨 论

人体异喹胍4-羟化反应表现为遗传性多态性（Genetic Polymorphism），即人群中存在强代谢者（Extensive Metabolizer）和弱代谢者（Poor Metabolizer）两种代谢类型，这是当前临床遗传药理学研究中十分活跃的一个领域[6]。不少药物，特别是一些作用于心血管系统的药物，其在体内的生物转化亦表现出与异喹胍4-羟化反应受相同基因控制的遗传性多态性[6,7]。奎尼丁在体内和/或试管内实验均证实是异喹胍4-羟化酶、丁呋心安1′-羟化酶、美多心安α-羟化酶和金雀花碱脱氢酶等受相同基因控制的遗传性多态性酶系的高效抑制剂[4,5,8,9]。我们进一步的研究还表明，甚至小剂量（5mg）奎尼丁亦可显著抑制人体异喹胍4-羟化酶，使强化代谢者尿中排泄的异喹胍：4-羟基异喹胍比率增加数倍（待发表）。这与试管内实验观察到的奎尼丁是异喹胍4-羟化酶的强抑制剂，其IC_{50}仅0.0007mmol/L一致[4]。

文献报告，AP在人体内的药代动力学及其3种主要代谢物的生成，均不受上述遗传性多态性的影响[10,11]。本实验也观察到，小剂量奎尼丁对人唾液中AP的药代动力学参数，尿中AP，NorAP，3-OHMeAP和代谢物总排泄量均无明显影响，但能略减少尿4-OHAP的排泄量。这一结果，和我们在试管实验中发现的在人肝微粒体AP的3种代谢酶中，奎尼丁对AP_4-羟化酶有较强的抑制作用，其IC_{50}为0.107mmol/L，而对AP3甲基—羟化酶和2-脱甲基酶，奎尼丁的IC_{50}则分别为0.550和0.450mmol/L的结果相符[12]。即便对AP_4-羟化酶，无论是比较尿中排泄比率变化或试管实验的IC_{50}，奎尼丁的抑制作用都远较对异喹胍4-羟化酶和丁呋心安1′羟化酶的抑制为弱[4]。因此，本实验结果进一步支持小剂量奎尼丁可作为特异性工具药，应用于人体异喹胍4-羟化酶类遗传性多态性的研究[4,5]。

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EFFECTS OF SMALL DOSE OF QUINIDINE ON THE ELIMINATION OF ANTIPYRINE IN MAN

Tu Zhiguang et al.

(Department of pharmacology)

The effects of single dose (5mg) of quinidine on the pharmacokinetics of antipyrine in saliva and the excretion ratios of antipyrine and its three main metabolites in urine were studied on 6 healthy volunteers with HPLC. Quinidine did not affect the antipyrine saliva pharmacokinetrics parameters, half life($t_{\frac{1}{2}}$), elimination constant(Kel), clearance rate(Cl), apparent distribution volume(Vd)and the area under the C-T curve (AUC), had no effects on the urine excreted total amount of antipyrine metabolites and the ratios of antipyrine, 3-hydroxymethylantipyrine and norantipyrine either, but could significantly reduce the urine excretion ratio of 4-hydroxyantipyrine($P<0.05$)

KEY WORDS Antipyrine, Quinidine, Pharmacokinetics, Drug interaction

(上接109页)

A COMPARATIVE STUDY BY VERTICAL PAGE OF LDH, MDH AND EST ENZYMES IN PARAGONIMUS SKRJABINI AND PARAGONIMUS WESTERMANI (2n, 3n) IN CHINA

Wu Xin Zhong et al.

(Department of Parasitology)

The comparative analyses of LDH, MDH and EST enzymes between *Paragonimus skrjabini* (*Ps*), *Paragonimus westermani* (diploid) (*Pw*(2n)) and *Paragonimus westermani* (triploid) (*Pw*(3n)) in China were carried out by vertical PAGE.

Distinct isozymic differences were demonstrated between *Ps* and *Pw*. In the three enzyme systems observed, there were less isozymic similarities between *Ps* and *Pw*(2n) or *Pw*(3n). However, there were isozymic similarities to some extent between *Pw*(2n) and *Pw*(3n). It is indicated that *Pw*(2n) and *Pw*(3n) are more closer than *Ps* in the phylogenetic relationships and also suggested that taxonomically *Paragonimus skrjabini* is an independent species

KEY WORDS *Paragonimus skrjabini*, *Paragonimus westermani*, Isozymes, Lactic dehydrogenase(LDH), Malate dehydrogenase(MDH), Esterase(EST)