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# CYP2C19基因多态性与质子泵抑制剂对消化性溃疡患者抑酸效应的关系

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## Relationship between the acid-suppression efficacy of proton pump inhibitors and the CYP2C19 genetic polymorphism in patients with peptic ulcer

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## Abstract

**AIM:** To investigate the acid-suppression efficacy of proton pump inhibitors (PPIs) in relation to the CYP2C19 genetic polymorphism in patients with peptic ulcer.

**METHODS:** In an open, randomized controlled trial, 59 patients with active peptic ulcer were randomly assigned to receive one of three PPIs in a single dose (20 mg of each drug): omeprazole (OME) ($n$ = 19), rabeprazole (RAB) ($n$ = 20) and esomeprazole (ESO) ($n$ = 20). The level of 24 hours intragastric pH was dynamically monitored. The 24 hours and night acid-suppression effects of the three drugs were observed. The CYP2C19 genotype was detected by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) in all patients.

**RESULTS:** The extensive metabolizers/poor metabolizers (EMs/PMs) ratio in the OME, RAB and ESO groups was 16/3, 17/3 and 17/3, respectively. The 24 hours and night acid-suppression effects [(total time and time percent (pH > 4)] in PMs were significantly higher than those in EMs in the OME group [24 hours acid suppression: (total time: 10.65 ± 2.3 h *vs* 7.22 ± 2.1 h, $P$ < 0.05; time percent: 48.9 ± 15.5 *vs* 32.5 ± 12.6, $P$ < 0.05); and night acid suppression: (total time: 3.67 ± 1.2 h *vs* 2.25 ± 1.2 h, $P$ < 0.05; time percent: 38.3 ± 20.6 *vs* 20.8 ± 18.9, $P$ < 0.05)]. However, the above data showed that there was no significant difference between PMs and EMs in the RAB and ESO groups. The duration of nocturnal acid breakthrough in both the RAB and ESO groups was shorter than that in the OME group (3.08 ± 2.12 h and 2.98 ± 2.73 h *vs* 4.50 ± 2.86 h, both $P$ < 0.05), but the pH was higher (2.15 ± 0.70 and 2.45 ± 0.65 *vs* 1.15 ± 0.31, both $P$ < 0.001). There was no significant difference between the RAB and ESO groups for the above parameters.

**CONCLUSION:** The acid-suppression efficacy of OME is highly dependent on the CYP2C19 genetic polymorphism, while the CYP2C19 genetic polymorphism appears to have little influence on the acid-suppression efficacy of RAB and ESO. The acid-suppression of RAB and ESO are superior to that of OME, especially for night acid secretion.

Key Words: Omeprazole; Rabeprazole; Esomeprazole; Acid-suppression efficacy; CYP2C19 genetic polymorphism; Nocturnal acid breakthrough

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**■背景资料**
研究表明, 细胞色素P4502C19(CYP2C19)酶为奥美拉唑、兰索拉唑和泮托拉唑的主要代谢途径. CYP2C19基因多态性有明显的个体性及种族性差异, 因此上述药物疗效受到影响. 而雷贝拉唑主要经过非酶途径而不是CYP2C19代谢; 埃索美拉唑为奥美拉唑的S-异构体, 主要经CYP3A4代谢而只有一部分由CYP2C19代谢.

**■研发前沿**
近年来对CYP450基因型和表型相关性的研究越来越受到重视, 从临床合理用药方面来说, 人们希望利用基因型分析来了解个体中药物代谢酶的活性, 期望既能提高药物治疗水平同时又降低不良反应的发生; 从新药研发角度来说, 研究药物的代谢酶CYP450的功能能够指导新药的设计、筛选及优化.

■相关报道
肝药酶CYP2C19基因多态性对NAB发生率产生影响. PPI联合阿莫西林、克拉霉素或甲硝唑等抗生素组成的三联疗法治疗幽门螺杆菌(HP)感染酸相关性疾病的疗效与CYP2C19遗传多态性有关. 日本学者研究还发现, cagA阳性是CYP2C19 弱代谢型者发展为胃癌的危险因素.


## 摘要

**目的:** 研究奥美拉唑(OME)、雷贝拉唑(RAB)及埃索美拉唑(ESO)对消化性溃疡患者的抑酸效应及与CYP2C19基因多态性的关系.

**方法:** 采用随机、开放和对照研究, 将消化性溃疡患者59例随机分为3组, 分别给予OME肠溶片($n$ = 19)、RAB肠溶片($n$ = 20)或ESO肠溶片($n$ = 20)各20 mg单剂量口服, 动态监测24 h胃内pH, 观察3种药物对患者的24 h和夜间抑酸效应及夜间酸突破(NAB)的影响. 用多聚酶链反应-限制性片段长度多态性(PCR-RFLP)方法测定所有患者的CYP2C19基因型并分为强代谢型(EMs)和弱代谢型(PMs).

**结果:** OME组、RAB组及ESO组EM和PM的比例分别为16/3, 17/3及17/3. OME 24 h抑酸与夜间抑酸效应(胃内pH>4的总时间和时间百分比)在PMs和EMs中的差异有显著性[24 h抑酸: (胃内pH>4的总时间: 10.65±2.3 h *vs* 7.22±2.1 h, $P$<0.05; 时间百分比: 48.9±15.5 *vs* 32.5±12.6, $P$<0.05); 夜间抑酸: (胃内pH>4的总时间: 3.67±1.2 h *vs* 2.25±1.2 h, $P$<0.05; 时间百分比: 38.3±20.6 *vs* 20.8±18.9, $P$<0.05)]. 而RAB及ESO组24 h抑酸和夜间抑酸效应在PMs和EMs中的差异无显著性. RAB及ESO组NAB持续时间较OME组短(3.08±2.12 h, 2.98±2.73 h *vs* 4.50±2.86 h, 均$P$<0.05), NAB的pH高于OME组(2.15±0.70, 2.45±0.65 *vs* 1.15±0.31, 均$P$<0.001). RAB与ESO组间差异无显著性.

**结论:** 奥美拉唑的抑酸效应受患者CYP2C19基因多态性影响; 雷贝拉唑和埃索美拉唑的抑酸效应则受CYP2C19基因多态性影响极小, 3种PPIs的日间抑酸效应强于夜间, 雷贝拉唑和埃索美拉唑的抑酸效应优于奥美拉唑.



**关键词: 奥美拉唑; 雷贝拉唑; 埃索美拉唑; 抑酸效应; CYP2C19基因多态性; 夜间酸突破**

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■创新盘点
本文对CYP2C19基因多态性与3种具有代表性的PPIs抑酸效应关系的观察表明, 雷贝拉唑和埃索美拉唑的疗效较少受CYP2C19基因多态性影响, 无论在抑酸效应方面还是对夜间酸突破的控制效果均优于以CYP2C19酶为主要代谢途径的奥美拉唑.

## 0 引言

第1代质子泵抑制剂(proton pump inhibitor, PPI)的问世改写了酸相关疾病治疗的历史, 其疗效和安全性得到了广泛肯定. 第1代PPIs主要经CYP2C19代谢, 因此疗效受其基因多态性影响而存在个体间差异和不稳定性. 2001年又有新的PPI雷贝拉唑(rabeprazole, RAB)和埃索美拉唑(esomeprazole, ESO)上市, 这是两种不同于以往的PPIs. RAB主要经非酶途径代谢, 疗效受CYP2C19基因多态性影响极小. ESO是第1个奥美拉唑(omeprazole, OME)左旋体, 虽然也经CYP2C19代谢, 但因代谢比例不同而疗效明显提高. 我们旨在了解CYP2C19基因多态性对OME、RAB和ESO抑酸效应的影响.

表 1 59例消化性溃疡患者基因分型(mean ± SD)

| 分组 | $n$ | EMs($n$ = 50) | | | PMs($n$ = 9) | | |
|---|---|---|---|---|---|---|---|
| | | *wt/wt* | *wt/m1* | *wt/m2* | *wt/m1*+*wt/m2* | *m1/m1* | *m1/m2* |
| OME | 19 | 6 | 6 | 3 | 1 | 2 | 1 |
| RAB | 20 | 6 | 7 | 2 | 2 | 2 | 1 |
| ESO | 20 | 7 | 6 | 3 | 1 | 3 | 0 |
| 合计 | 59 | 19 | 19 | 8 | 4 | 7 | 2 |
| 比例 | | 83.6% | | | 16.36% | | |

## 1 材料和方法

1.1 材料 在我院经内镜诊断为活动期消化性溃疡、无PPIs治疗史的患者, 共59例, 年龄20-62岁. 随机分为3组: OME组19例(男/女: 13/6), RAB组20例(男/女: 14/6), ESO组20例(男/女: 15/5), 年龄范围(平均)分别为: 20-62(36±6.8)岁、21-61(32.5±7.2)岁和20-59(34±6.5)岁.

1.2 方法

1.2.1 CYP2C19基因分型 取外周血3 mL, 置于EDTA抗凝管中. 用DNA提取试剂盒按说明提取基因组DNA. 设计特异性引物, 通过多聚酶链反应-限制性片段长度多态性(polymerase chain reaction-restriction fragment length polymorphism, PCR-RFLP)法进行CYP2C19基因分型(琼脂糖凝胶电泳, 紫外灯下观察带型), 包括野生型(wild-type, *wt*)和两种突变型等位基因(CYP2C19$_{m1}$和CYP2C19$_{m2}$)从而确定表型: 强代谢型(extensive meteabolizer, EM)(包括强代谢型纯合子*wt*/*wt*以及强代谢型杂合子*wt*/*m*1或*wt*/*m*2)和弱代谢型(poor meteabolizer, PM)(*m*1/*m*1, *m*2/*m*2以及*m*1/*m*2).

1.2.2 试验用药及给药方法 禁食12 h以上, 次日晨采用随机方式给予OME、RAB或ESO肠溶片各20 mg单剂量*po*, 动态监测24 h胃内pH. 插管6 h后进午餐.

1.2.3 仪器及步骤 便携式pH监测仪(DIGITRAPPER MKⅢ 瑞典CTD公司); 检查前空腹12 h, 8 am插管至胃体部, 记录1 h基础pH后于

表 2 OME, RAB及ESO对EMs及PMs不同时间段抑酸效应的比较(mean ± SD)

| 分组 | | 基因型 | *n* | 胃pH>4总时间(h) | 胃pH>4时间百分比(%) | pH中位数 | pH均值 |
|---|---|---|---|---|---|---|---|
| 24 h抑酸效应 | OME | EMs | 16 | 7.22 ± 2.1 | 32.5 ± 12.6 | 3.62 ± 1.14 | 3.94 ± 0.83 |
| | | PMs | 3 | 10.65 ± 2.3[a] | 48.9 ± 15.5[a] | 3.55 ± 0.98 | 4.16 ± 1.01 |
| | RAB | EMs | 17 | 12.26 ± 1.63 | 56.2 ± 10.30 | 4.92 ± 1.53 | 4.97 ± 0.72 |
| | | PMs | 3 | 14.3 ± 1.45 | 60.8 ± 12.21 | 5.44 ± 0.76 | 4.85 ± 0.66 |
| | ESO | EMs | 17 | 13.15 ± 1.83 | 61.7 ± 10.3 | 5.92 ± 1.38 | 5.5 ± 0.78 |
| | | PMs | 3 | 15.32 ± 2.26 | 66.6 ± 11.09 | 6.87 ± 0.92 | 5.40 ± 0.60 |
| 夜间抑酸效应 | OME | EMs | 16 | 2.25 ± 1.2 | 20.8 ± 18.9 | 2.38 ± 1.50 | 1.97 ± 0.91 |
| | | PMs | 3 | 3.67 ± 1.2[a] | 38.3 ± 20.6[a] | 3.69 ± 0.96[a] | 2.95 ± 1.36 |
| | RAB | EMs | 17 | 3.89 ± 1.27 | 46.5 ± 11.2 | 4.32 ± 1.14 | 3.84 ± 0.87 |
| | | PMs | 3 | 4.36 ± 1.39 | 48.8 ± 12.3 | 4.68 ± 0.91 | 4.26 ± 1.02 |
| | ESO | EMs | 17 | 5.02 ± 1.12 | 49.6 ± 10.8 | 5.02 ± 1.32 | 4.9 ± 0.84 |
| | | PMs | 3 | 4.85 ± 1.4 | 52.6 ± 11.09 | 4.87 ± 0.92 | 5.32 ± 0.91 |

[a]*P*<0.05 *vs* EMs.

**■应用要点**

雷贝拉唑及埃索美拉唑的代谢和疗效几乎不受CYP2C19基因多态性影响, 因此抑酸效应优于以往PPIs. 特别是夜间抑酸效应的控制, 能够缩短NAB的持续时间, 因为这对于酸相关疾病症状的缓解和维持至关重要. 测定CYP2C19基因型在酸相关疾病治疗中药物选择、剂量调整、疗效预计特别是用药个体化和优化有非常重要的意义.

9 am *po* PPI, 监测期间正常饮食、起居, 限制酸、碱性饮料及食品; 次日晨9 am拔管, 数据分析[4].

1.2.4 观察指标 (1)抑酸起效时间(从服药开始至胃内pH>4的时间); (2)抑酸效应(pH>4的总时间T及时间百分比T%); (3)昼夜抑酸作用(8 am-8 pm为日间; 8 pm-8 am为夜间); (4)NBA的作用判断标准[5]: 服用PPI后, 夜间(睡眠后12 h内)胃内pH<4的总时间>60 min.

**统计学处理** 全部资料经计算机处理, 数据以mean±SD表示, 组间样本均数行*t*检验, 自身前后对照用配对*t*检验; 率的比较用$\chi^2$检验. *P*<0.05为差异有显著性.

## 2 结果

2.1 试验各组患者CYP2C19基因的分型情况(表1).

2.2 3种PPIs对不同CYP2C19基因型患者的昼夜抑酸效应 奥美拉唑昼夜抑酸效应(胃内pH>4的总时间、时间百分比)在PMs和EMs组中差异有显著性(*P*<0.05); 而在雷贝拉唑、埃索美拉唑的抑酸效应(胃内pH>4的总时间、时间百分比)以及24 h胃内pH值中位数及均值在PMs和EMs组中差异均无显著性(表2).

2.3 3种PPIs对不同CYP2C19基因型消化性溃疡患者的夜间抑酸效应 奥美拉唑的夜间抑酸效应(即夜间胃内pH>4的总时间、时间百分比以及pH值中位数)在PMs与EMs组中差异有显著性; 而雷贝拉唑及埃索美拉唑的夜间抑酸效应在PMs与EMs组中差异均无显著性(表2).

表 3 20 mg OME, RAB及ESO对NAB的影响(mean ± SD)

| 分组 | *n* | 发生率 *n*(%) | 时间范围 (h) | pH | 持续时间 (h) |
|---|---|---|---|---|---|
| OME | 19 | 9(47.4) | 1–7 | 1.15 ± 0.31 | 4.50 ± 2.86 |
| RAB | 20 | 8(53.3) | 2–6 | 2.15 ± 0.70[b] | 3.08 ± 2.12[a] |
| ESO | 20 | 10(50) | 2–6 | 2.45 ± 0.65[b] | 2.98 ± 2.73[a] |

[a]*P*<0.05, [b]*P*<0.001 *vs* OME.

2.4 3种PPIs对NAB的影响 由表3可看出, NAB(nocturnal acid breakthrough)的发生时间多在晚8 h以后. 59例患者中, 共27例(45.8%)发生NAB, 多发生在凌晨1-7时. RAB组及ESO组NAB的pH均明显高于OME组(*P*<0.001), 持续时间均较OME组短(*P*<0.05); 而RAB组与ESO组比较差异无显著性. 表明RAB及ESO对NAB的作用较OME强, 并可缩短NAB的持续时间.

## 3 讨论

临床研究证实, 第1代PPIs(奥美拉唑、蓝索拉唑、泮托拉唑)高度依赖于肝内细胞色素P450酶(CYP2C19)进行代谢, CYP2C19存在羟化多态性(有强代谢型、弱代谢型), 已发现的CYP2C19基因主要突变有两种: $CYP2C19_{m1}$(外显子5突变型)及$CYP2C19_{m2}$(外显子4突变型)[6-7], 这种基因多态性有明显的个体间及种族间差异[8]. 理论上, 强代谢型代谢作用最强, 药物在体内被快速代谢, 药物的疗效受到影响; 弱代谢型代谢作用弱, 药物在体内代谢慢, 虽不影响PPI疗效, 但容易引起药物蓄积, 引起不良反应. 第1代PPIs都是在相

同的基本结构-甲基吡啶-亚磺酰-苯并咪唑基础上进行不同修饰而形成的衍生物, 均为*R*-与*S*-混旋异构体, 在肝内由CYP2C19及CYP3A4代谢, 主要是CYP2C19.RAB在吡啶环和苯并咪唑环上进行不同基团取代(即缺少奥美拉唑5-甲基基团上的吡啶环, 本结构通过CYP2C19代谢)构成PPI前药, 主要经过非酶途径而不是CYP2C19代谢, 因此抑酸效应很少受CYP2C19基因多态性影响, 我们的研究也证明了这一点[4]. 新近上市的ESO为*S*-异构体, 主要经CYP3A4代谢而少部分由CYP2C19代谢, 也就是说, ESO通过CYP2C19及CYP3A4代谢的比例与第1代PPIs不同, 由于两种同工酶光学选择性的代谢, 其抑酸能力明显提高. 药代动力学研究表明, ESO肝脏首过效应小于奥美拉唑, 血浆清除率低, ESO 40 mg药物浓度-时间曲线下面积(AUC)比奥美拉唑大5倍[7].

胃内pH>4的时间、时间百分比是决定质子泵抑制剂抑酸效应(如快速起效、症状快速缓解及维持)的关键因素, 胃内pH>4的时间、时间百分比与AUC直接相关[9], 而AUC又受药物代谢酶的立体选择性代谢影响, 因此很容易理解CYP2C19基因多态性及其对药物代谢的影响[10-15]. 我们的研究表明RAB的抑酸效应优于第1代PPIs[16]. 本研究中, 59例患者的CYP2C19基因型及表型分布与我们对人群调查的结果一致, 强代谢型占83.64%, 弱代谢型占14.42%[17]. CYP2C19基因多态性对OME抑酸效应有明显的影响, PMs显示出较EMs更高的胃内pH、pH>4的总时间和时间百分比; 而在RAB及ESO, 不同基因型则未见有明显差异, 表明二者的抑酸效应很少受CYP2C19基因多态性影响, 同时, 在夜间抑酸效应及对NAB作用方面, RAB及ESO优于奥美拉唑, 与已有报道一致[18-31]. CYP2C19基因分布频率存在很大的种族间和个体间差异, 白色人种纯合子EM, 杂合子EM, PM的频率分别为70%, 30%和2%-6%; 亚洲人种分别为40%, 50%和11%-22%; 韩国人种分别为42%, 46%和12%. 这可解释为什么白种人比亚洲人需要更高剂量的PPI以及为什么第1代PPI疗效个体差异大. CYP2C19基因型对于使PPIs在酸相关疾病中的治疗优化或个体化可能会非常有意义. 由于本文观察的例数有限, 还需要增大样本量作进一步的研究.

总之, 本文对3种有代表性的质子泵抑制剂抑酸效应的研究表明, 奥美拉唑的抑酸效应明显受CYP2C19基因型影响, 这可以解释其临床疗效的个体间差异及不稳定性, 而RAB及ESO的代谢与CYP2C19基因型无明显相关性, 因此抑酸效应优于以往PPIs. 特别是夜间抑酸效应的控制, 能够缩短NAB的持续时间[32-33], 因为这对于酸相关疾病症状的缓解和维持至关重要. 测定CYP2C19基因型在酸相关疾病治疗中药物选择、剂量调整、疗效预计特别是用药个体化和优化有非常重要的意义.

**■名词解释**

夜间酸突破现象: 指在应用质子泵抑制(PPI)的情况下, 夜间(当晚22时至次日8:00 am)胃内pH值小于4.0的时间持续超过60 min.其与消化性溃疡、反流性食管炎(GERD)、糜烂性食管炎、Barret's食管等酸相关性疾病密切相关. 同时, NAB的发生还与Hp(*Helicobacter pylori*), 的感染有着密切的相关性.

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**■同行评价**

本文分析了3种PPIs与患者CYP2C19基因多形性的相互关系, 有一定的应用价值.