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孙文兵, 主任医师, 教授, 首都医科大学附属北京朝阳医院西院肝胆胰脾外科. 从事肝胆胰脾疾病的医疗、教学、科研工作35年. 发表SCI论文43篇, 国内期刊论文300余篇. 获全军科技进步二等奖和全军医疗成果二等奖各一项, 全军科技进步三等奖一项. 2002年被解放军总后勤部评为科技新星, 2009年被评为首批北京市卫生系统高层次技术人才, 2016年获北京市二级教授和“名医”称号.

## 本期责任人

编务 王栋梅; 送审编辑 张砚梁; 组版编辑 张砚梁; 英文编辑 王天奇;  
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主编

党双锁, 教授, 710004, 陕西省西安市, 西安交通大学医学院第二附属医院感染科

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COVER

Editorial Board Member of *World Chinese Journal of Digestology*, Wen-Bing Sun, Chief Physician, Professor, Department of Hepatobiliary Surgery, Chaoyang Hospital Affiliated to Capital Medical University West Campus, No.5 Jingyuan Road, Shijingshan District, Beijing 200043, China. cyhswb@qq.com

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*World Chinese Journal of Digestology*  
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## 钾离子竞争性酸阻滞剂在酸相关疾病中的应用

牛春燕, 罗晓春

**牛春燕**, 南京市溧水区人民医院(东南大学附属中大医院溧水分院)消化内科 江苏省南京市 211200

**罗晓春**, 厦门大学附属翔安医院内镜中心 福建省厦门市 361101

牛春燕, 教授, 主任医师, 研究方向为肝病、酸相关疾病、功能性胃肠病。

**作者贡献分布:** 罗晓春负责收集、整理文献; 牛春燕完成手稿撰写并负责审校。

**通讯作者:** 牛春燕, 教授, 主任医师, 211200, 江苏省南京市溧水区崇文路86号, 南京市溧水区人民医院(东南大学附属中大医院溧水分院)消化内科。nchy69@163.com

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### Application of potassium competitive acid blockers in acid-related diseases

Chun-Yan Niu, Xiao-Chun Luo

**Chun-Yan Niu**, Department of Gastroenterology, Nanjing Lishui People's Hospital (Zhongda Hospital Lishui Branch, Southeast University), Nanjing 211200, Jiangsu Province, China

**Xiao-Chun Luo**, Endoscopy Center, Xiang'an Hospital, Xiamen University, Xiamen 361101, Fujian Province, China

**Corresponding author:** Professor, Chief Physician, Chun-Yan Niu, Department of Gastroenterology, Nanjing Lishui People's Hospital (Zhongda Hospital Lishui Branch, Southeast University), No. 86 Chongwen Road, Lishui District, Nanjing 211200, Jiangsu Province, China. nchy69@163.com

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### Abstract

Acid-related diseases (ARDs) are common chronic

diseases of the digestive system. Proton pump inhibitors (PPIs) have become the first-line drugs for the treatment of acid-related diseases. However, PPIs display some limitations in clinical application, such as short half-life, slow action, insufficient acid inhibition, pharmacological effects affected by CYP2C19 gene polymorphism, and nocturnal acid breakthrough, which lead to insufficient symptom remission of ARDs, as well as refractoriness, relapse, and even direct decline in health-related quality of life and increased economic burden. Potassium competitive acid blockers (P-CABs) are a class of novel anti-secretory drugs, which can overcome the limitations of traditional PPIs and show satisfactory acid inhibition effect and safety in clinical application. They may become a new strategy to solve the unsatisfied medical needs in the treatment of ARDs, but their potential adverse reactions remain to be monitored. In this article, we review the challenges in the treatment of acid-related diseases, and the advantages and prospects of P-CABs in the prevention and treatment of ARDs.

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**Key Words:** Acid-related disorders; Proton pump inhibitors; Novel anti-secretory drugs; Potassium-competitive acid blockers

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### 摘要

酸相关疾病是一类消化系统中的常见慢性疾病。质子泵抑制剂现已成为治疗酸相关疾病的一线用药, 然而临床应用中逐渐显现出一些局限性, 如半衰期短、起效较慢、抑酸不充分、药理作用受CYP2C19

基因多态性影响、夜间酸突破等, 导致分酸相关疾病患者的症状不能获得充分缓解, 以及难治、复发、直接的健康相关生活质量下降和经济负担增大。钾离子竞争性酸阻滞剂是一种新型抗分泌药, 能够克服传统质子泵抑制剂的多种局限性, 在临床应用中显示出更好的抑酸效应和安全性, 可能成为解决酸相关疾病治疗中未满足的医疗需求的新策略, 但也需要继续观察潜在的不良反应。本文综述了酸相关疾病治疗中面临的挑战, 以及钾离子竞争性酸阻滞剂在酸相关疾病预防和治疗中的优势和前景。

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关键词: 酸相关疾病; 质子泵抑制剂; 新型抗分泌药物; 钾离子竞争性酸阻滞剂

**核心提要:** 质子泵抑制剂为治疗酸相关疾病(acid related diseases, ARDs)的传统一线药物, 但在临床应用过程中仍有一部分患者的疗效、生活质量和满意度欠佳, 这与 ARDs的个体间异质性、传统抑酸药物的药理学特性、以及患者的依从性等有关。新型钾离子竞争性酸阻滞剂直接阻断质子泵的K<sup>+</sup>交换通道, 克服了传统抑酸药物的局限性, 在抑酸强度、作用持续时间、缓解症状速度、疗效维持时间、预防复发和并发症方面具有优越的特征, 为ARDs治疗中临床未满足的需求治疗提供了新的选择。

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## 0 引言

酸相关疾病(acid-related disorders, ARDs)指与胃酸或胃酸分泌相关的一类疾病, 包括胃食管反流病(gastroesophageal reflux disease, GERD)、消化性溃疡、幽门螺杆菌感染相关疾病、阿司匹林和非甾体类抗炎药(nonsteroidal anti-inflammatory drugs, NSAIDs)相关胃十二指肠不良事件, 以及上消化道出血<sup>[1,2]</sup>。近年来随着内镜粘膜下剥离术(endoscopic submucosal dissection, ESD)的开展, ESD术后并发症(如上消化道出血和人工溃疡)趋于增多, 少见的有Zollinger-Ellison综合征。

ARDs无论在发病机制、临床表现或是疗效方面均存在较大异质性, 而且对抑酸程度、抑酸持续时间、疗程以及疗效的判断标准不同。比如, 胃溃疡和十二指肠溃疡的治愈标准为胃内pH≥4, 糜烂性食管炎(erosive esophagitis, EE)的治愈标准为胃内pH≥3, 上消化道出血的治愈标准为胃内pH≥6<sup>[1,2]</sup>。自从H<sub>2</sub>受体拮抗剂

(histamine-2 receptor antagonists, H<sub>2</sub>RAs)和质子泵抑制剂(proton pump inhibitors, PPIs)问世以来, ARDs得到了很好的治疗。但H<sub>2</sub>RAs很快就显示出许多不足, 包括作用时间相对较短、餐后胃酸分泌抑制不完全、抗分泌作用下降, 以及治疗后反跳性胃酸高分泌。PPIs已成为ARDs的一线治疗药物, 然而, 仍有相当数量的患者对抑酸药物的应答不良, 不能达到理想疗效, 严重影响生活质量和疾病预后。PPIs在药理学上存在一些局限性: (1)传统的PPIs为延迟释放剂型<sup>[3,4]</sup>, 需要3-5 d时间才能达到充分药理作用(起效慢), 需要餐前给药, 在酸性条件下很容易失活(酸不稳定性); (2)需要在壁细胞的分泌小管内转化为其活性形式(需要酸激活)<sup>[5,6]</sup>; (3)血浆半衰期为60-90 min (半衰期短), 而胃质子泵的半衰期为50 h, 每天约有三分之一被新的生物合成所取代, 这样, 在夜间合成的新质子泵不能暴露于PPIs中, 即使每天服用PPIs两次, 仍有低量酸分泌持续存在(夜间酸突破nocturnal acid breakthrough, NAB)<sup>[5]</sup>, 因此, 对夜间酸分泌控制差; (4)生物利用度低; 代谢受CYP2C19基因多态性影响; (5)此外, PPIs还可以通过抑制胃酸分泌或抑制药物代谢相关酶而干扰其他药物的代谢和效应<sup>[7]</sup>。这些局限性成为制约PPIs在ARDs中疗效的重要因素, 使ARDs的治疗面临诸多挑战: 现有的抑酸药物起效较慢, 不能快速缓解症状和产生持久疗效; 夜间酸分泌尚缺乏有效控制方案; CYP2C19基因多态性导致患者个体间药代动力学的巨大异质性; 维持症状长期缓解尚未达到理想状态。进一步导致医疗费用上升、患者满意度和生活质量下降等社会经济负担。因此, 亟待更多新型治疗方案以供选择。

## 1 新型抗分泌药钾离子竞争性酸阻滞剂: 酸相关疾病治疗的新选择

新型抗分泌药钾离子竞争性酸阻滞剂(potassium-competitive acid blockers, P-CABs)是一类吡咯衍生物, 直接阻断质子泵的K<sup>+</sup>交换通道, 理论上属于PPIs, 但无需转换为活性形式, 具有一种非常快速、竞争性强、可逆的酸分泌抑制作用, 不需要酸活化, 在酸性条件下稳定, 能迅速提高胃内pH值, 而且从质子泵缓慢解离, 因此不仅迅速起效、缓解症状, 而且由于半衰期较PPIs延长, 可保持持续、稳定的抗分泌作用。第一代P-CAB(revaprazan, YH1885)在韩国和印度上市后, 发现疗效并不优于奥美拉唑和埃索美拉唑, 后来的P-CABs linaprazan(AZD0865)、soraprazan、CS526、YH4808也因未显示出优越性, 并且引起转氨酶升高, 因此被停止研发<sup>[3]</sup>。沃诺拉赞(Vonoprazan)是一种新型P-CABs, 于2015年在日本首先上市。与传统PPIs和其他P-CABs比较, 抗分泌活性不依赖CYP2C19基因型<sup>[8]</sup>, 具有更迅



速、强大和持久的酸抑制作用, 几乎没有NAB<sup>[9]</sup>, 个体间药代动力学差异微小<sup>[10]</sup>. 已被用于治疗胃和十二指肠溃疡、反流性食管炎以及预防低剂量阿司匹林或非甾体抗炎药相关的胃和十二指肠溃疡复发<sup>[11]</sup>.

## 2 沃诺拉赞在酸相关疾病中的应用

**2.1 沃诺拉赞与胃食管反流病** 胃食管反流病(gastroesophageal reflux disease, GERD)属于由多种发病机制引起的动力障碍性疾病, 动力障碍主要包括食管下括约肌功能不全和功能障碍、食管清除异常以及高达40%的胃排空延迟, 所有这些功能障碍都可导致食管粘膜长时间暴露于酸性胃内容物<sup>[12]</sup>, 从而引起黏膜损害. PPIs已成为GERD治疗最常用处方药. 然而, 在一日2次的PPIs剂量下, 仍有20%-40%的PPI-难治性GERD患者表现为持续的烧心和/或反流或者持续的夜间症状, 以及20%-40%的高级别(C/D级) EE和非糜烂性反流病(NERD)失败率、30%的维持治疗复发率<sup>[13]</sup>; 另外, PPIs对餐后烧心、GERD并发症及食管外症状并非十分有效<sup>[14]</sup>. 沃诺拉赞的8 wk RE治愈率接近100%, 沃诺拉赞(20 mg 1次/日)与兰索拉唑(30 mg 1次/日)在A/B级食管炎疗效无差异, 但在治愈高级别食管炎(C/D级)和预防C/D级食管炎复发、食管炎总体症状缓解、食管炎症状缓解速度以及难治性GERD方面, 均优于传统PPIs, 在CYP2C19快代谢型者中具有持续优势, PPI-耐药食管炎治愈率高达87.5%<sup>[15-18]</sup>. 一项长期研究显示, 沃诺拉赞可以保持症状长期缓解, 复发率较低, 一个月和一年时维持症状缓解率为89%和81.6%<sup>[19]</sup>. 一项基于自评式问卷(FSSG)的最新研究显示, 沃诺拉赞对EE、NERD、PPI-耐药GERD的初始治疗和维持治疗均有效, 明显改善患者烧心症状和满意度, 24 wk时各组缓解率分别为38.9%、45%及30%<sup>[20]</sup>, 即在提高生活质量方面具有显著效果. PPI-耐药EE患者应用沃诺拉赞后, 胃pH>4时间百分比显著增加, 从26.5%增加到78.0%, 食管pH<4的时间百分比降低, 此外, 酸清除时间和反流事件的总数, 包括酸和近端反流事件均显著减少, 表明沃诺拉赞是PPI-耐药RE患者的有效选择<sup>[16,21]</sup>. 沃诺拉赞还可以改善与GERD伴随的上腹部疼痛、餐后疼痛、便秘和腹泻<sup>[22]</sup>.

**2.2 沃诺拉赞与幽门螺旋杆菌感染** 幽门螺旋杆菌(*Helicobacter pylori*, *H. pylori*)感染与酸相关疾病尤其是消化性溃疡相关, 与胃恶性肿瘤密切相关. 目前*H. pylori*的全球整体根除率正在下降, 主要原因在于抗生素耐药逐渐增多和胃酸抑制不足. 理想根除方案需具备两个条件: 有效根除率>90%, 以及安全性<sup>[23]</sup>. 提高胃内pH值可使细菌进入生长期, 对抗生素如阿莫西林和克拉霉素的敏感性增加, 因此控制胃内特别是夜间pH、延长的

抑酸时间, 对保持联合抗菌的杀菌活性至关重要, 以沃诺拉赞为基础的根除方案在根除率、耐受性和不良反应方面优于传统PPIs<sup>[24]</sup>. 一项小型研究发现, 沃诺拉赞(20 mg bid)+阿莫西林(500 mg tid)二联治疗作为一线和二联方案, 对*H. pylori*的根除率分别达到95%和90%, 无需使用第二种抗菌药, 如克拉霉素<sup>[25]</sup>, 提示这种优化的双重疗法(剂量、给药次数和持续时间)可以作为一种简单、可靠和有效的一线根除治疗方案, 提高*H. pylori*的总体根除率<sup>[26]</sup>. 高剂量PPI和阿莫西林双重治疗的基本机制是, *H. pylori*对阿莫西林的耐药率非常低, 在胃pH值较高(>6)时对*H. pylori*的杀菌作用会增强. pH>6时细菌进入复制状态, 对阿莫西林敏感性增加<sup>[27]</sup>. 沃诺拉赞在根除克拉霉素耐药*H. pylori*菌株时优于传统PPIs<sup>[28]</sup>, 这为克服克拉霉素耐药、提高*H. pylori*根除率提供了有前景的选择. 另外, 沃诺拉赞、阿莫西林和克拉霉素均经CYP3A4代谢, 因此联合给药可能导致清除延迟<sup>[6]</sup>, 从而延长血浆滞留时间、延长药物持效时间. 以沃诺拉赞为基础的三联方案也显示出高达98%的*H. pylori*根除率<sup>[29]</sup>. 美国和欧洲正在进行基于沃诺拉赞的二联方案和三联方案治疗*H. pylori*感染的3期临床试验<sup>[30]</sup>, 如果有效性和安全性得到证实, 那么将为*H. pylori*根除提供新的方案, 同时在减少抗生素使用和降低抗生素耐药、降低医疗成本、提高*H. pylori*根除率方面做出很大贡献.

**2.3 沃诺拉赞与NSAIDs相关性胃十二指肠损伤** NSAIDs是应用最广泛的药物之一, 每天有超过3000万人服用NSAIDs, 30%-50%的NSAIDs使用者表现为内镜下黏膜损伤及消化性溃疡, 上消化道并发症的风险增加3-5倍<sup>[31]</sup>. 胃酸可能是NSAIDs诱发黏膜损伤的必要条件, 即pH依赖性, 酸性损伤程度取决于NSAIDs局部作用导致的胃酸反弥散程度<sup>[32]</sup>. 在胃酸分泌增加的患者中, NSAIDs引起的胃黏膜损害加重, 而胃内pH越高, 黏膜损伤的范围、程度以及可能性就越低. NSAIDs和类固醇激素还可导致*H. pylori*感染及增加消化性溃疡出血风险<sup>[33]</sup>. 很大一部分患者需要持续服用NSAIDs, 随着时间推移, 即使同步联合PPIs治疗, 也会失去保护作用. 胃溃疡和十二指肠溃疡的治疗要求为胃内pH≥4, 沃诺拉赞因延长的酸分泌控制时间, 保持胃内的高pH, 有望提供更好的黏膜保护作用, 在阿司匹林和NSAIDs相关溃疡的复发以及NSAIDs相关溃疡的二级预防中显示出有效性和安全性<sup>[34,35]</sup>, 但尚有待于NSAIDs相关溃疡的一级预防临床数据. *H. pylori*感染和高危患者使用NSAIDs是消化性溃疡的两个主要危险因素, 因此, 能够真正24 h胃酸控制, 从而提供更好黏膜保护和NSAIDs相关溃疡一级预防, 以及提高*H. pylori*根除率是*H. pylori*感染和NSAIDs相关溃疡未满足的临床需求. 沃诺拉赞对于长



期低剂量阿司匹林应用者复发性溃疡预防的疗效和安全性正在临床III期研究评估中<sup>[29]</sup>。

**2.4 沃诺拉赞与ESD术后溃疡和上消化道出血** 术后溃疡和消化道出血是ESD最常见并发症, ESD后胃溃疡愈合通常需要8 wk, 但也取决于病变大小、位置、*H. pylori*感染和胃萎缩程度。目前PPIs是预防ESD后出血和治愈溃疡的常用药物, 但对于最有效的治疗方案尚存争议。沃诺拉赞为ESD后人工溃疡提供了更快速有效的治疗, 在治疗的前2周内, 沃诺拉赞比PPIs更有效地治疗*H. pylori*阳性ESD诱发的胃溃疡患者, 4 wk溃疡愈合率显著高于其他PPIs<sup>[7]</sup>。一项回顾和前瞻性研究及一项Meta分析研究表明, 沃诺拉赞可预防和减少ESD后出血(包括迟发性出血), 并促进溃疡愈合, 机制可能与ESD期间高胃pH值有关<sup>[36]</sup>, 当延长疗程至8 wk或联合黏膜保护剂时, 疗效更为显著<sup>[37]</sup>。沃诺拉赞还能有效预防使用持续抗血栓治疗(抗血小板药物如低剂量阿司匹林, 西洛他唑等; 抗凝药物如华法林或直接口服抗凝剂)患者的ESD术后出血<sup>[38]</sup>。持续的胃内pH>6, 可促进血小板聚集、血栓形成和稳定性, 对上消化道出血有益。出血性胃十二指肠溃疡时纤溶活性增强, 而胃酸抑制可降低其活性。多个指南认为大剂量静脉注射PPIs可降低近期出血, 并有可能减少内镜治疗的需要。然而, 传统的PPIs作为胃保护剂难以达到长时间维持胃液pH≥6, 所提供的抑酸时间、抑酸效应尚未达到最佳, 尤其是对高危患者, 如: 高龄(>65岁, 特别是>70岁), 有消化性溃疡病史, 病情危重, *H. pylori*感染, 同时使用2种或以上NSAIDs, 使用其他类型胃损伤药物<sup>[32]</sup>。口服沃诺拉赞的药效学特性可达到与静脉注射PPIs相同或更好的效果, 可能满足上消化道出血管理中未满足的需求。一项系统综述和荟萃分析结果表明, PPIs和H<sub>2</sub>RAs治疗可显著降低食管静脉曲张套扎术患者的出血率, 但抑酸治疗组和未接受抑酸治疗组之间死亡率、溃疡、胸痛、吞咽困难和吞咽困难的发生率以及住院时间没有显著差异<sup>[39]</sup>, 提示PPIs和H<sub>2</sub>RAs在改善这类患者预后方面尚存不足。目前尚未见P-CABs应用于静脉曲张性上消化道出血的临床研究。鉴于P-CABs在ARDs中的应用, 可能具有潜在应用前景。P-CABs能否达到快速治愈任何溃疡及其并发症的出血, 并防止远期溃疡复发, 提供长时间抑酸, 改善预后(如减少再出血、输血、外科手术的需求, 降低死亡率), 能否在静脉曲张性上消化道出血治疗中提供新的选择, 需要进一步研究和观察。

### 3 沃诺拉赞的不足和不良反应

**3.1 不足** P-CABs耐药的NERD确实存在, 可能与弱酸反流或功能性烧心有关<sup>[15,40]</sup>。最近一项系统性分析显示,

以沃诺拉赞为基础的三联方案的优势仅在一线*H. pylori*根除方案中明显, 在二线方案中则不优于传统PPIs<sup>[28]</sup>。另一项最新Meta-analysis指出, 沃诺拉赞仅在根除克拉霉素耐药*H. pylori*菌株时优于传统PPI, 但在根除克拉霉素敏感*H. pylori*菌株时与传统PPIs疗效相似<sup>[41]</sup>。现有的2项研究比较了沃诺拉赞和PPIs对胃溃疡和十二指肠溃疡的疗效, 结果未显示出统计学差异<sup>[42,43]</sup>, 可能与病例选择的偏倚以及病例数量较少有关, 尚有待于进一步研究。

**3.2 不良反应** 已报道的沃诺拉赞治疗引起的不良事件包括鼻咽炎、腹泻、便秘、上呼吸道感染、跌倒、胃肠炎和湿疹<sup>[11]</sup>, 星尘状胃粘膜<sup>[44]</sup>, 出血性小肠结肠炎<sup>[45]</sup>, 这需要进行进一步观察并且引起重视。几乎所有与PPIs相关的不良反应都发生在长期治疗的患者中, 通过定期评估患者对抑酸治疗的需求, 尽可能缩短治疗时间, 可以消除或大大降低不良后果的风险。任何新的治疗方法都可能导致过度使用和滥用, P-CABs也不例外, 应当重视。评估沃诺拉赞(10 mg或20 mg)对治愈后EE 5年维持治疗的安全性研究正在日本进行<sup>[46]</sup>。

## 4 结论

综上所述, 沃诺拉赞因其特殊的化学结构和药理学特性, 在酸相关疾病的治疗中显示出等同于或优于传统PPIs的抗分泌疗效, 为ARDs治疗面临的挑战提供了新的选择, 尤其是对于PPIs难治性酸相关疾病或PPIs未满足的临床需求, 但因临床应用时间并非很长, 远期疗效和安全性、耐受性仍有待于进一步观察。

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