

· 综述 ·

质子泵抑制剂对消化道菌群组成变化的相关性研究进展

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[摘要] 质子泵抑制剂(proton pump inhibitor, PPI)是抗幽门螺杆菌、治疗胃食管反流病及消化性溃疡的一线药物,在临床上应用十分广泛。作为消化科最常用的处方药,其使用量正逐年增加,随着药物的长期使用,近年来各种不良反应相继被报道。其中多项研究表明,PPI的使用将造成胃肠道菌群的紊乱,并与肠道感染风险升高呈正相关。本文就PPI与胃肠道菌群的关系做一概述。

[关键词] 质子泵抑制剂; 肠道菌群; 幽门螺杆菌; 小肠细菌过度生长; 肠道感染; 益生菌

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Progress in effects of proton pump inhibitors on changes of gastrointestinal microflora

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[Abstract] Proton pump inhibitor(PPI) was widely used in clinic as a first-line drug for the treatment of gastroesophageal reflux disease and peptic ulcer. As the most commonly used prescription drug in digestive department, its usage is increasing year by year. With the long-term use of drugs, a variety of adverse reactions had been reported in recent years. Several studies had shown that use of PPI would cause the disorder of gastrointestinal flora, and was positively correlated with increased risk of intestinal infection. This paper summarized the correlation between PPI and gastrointestinal flora.

[Key words] proton pump inhibitor; intestinal flora; *Helicobacter pylori*; small intestinal bacterial overgrowth; intestinal infection; probiotics

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质子泵抑制剂(proton pump inhibitor, PPI)是一类作用于H⁺/K⁺-ATP酶的抑酸药,能快速且持久地阻断胃酸分泌的关键环节,PPI不仅能抑制基础胃酸的分泌,也可以在组胺、乙酰胆碱及胃泌素等其

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他因素作用的环境下发挥良好的抑酸效果^[1]。国内相关共识及指南指出,PPI治疗抗幽门螺杆菌(*Helicobacter pylori*, Hp)的疗程需要2周^[2],治疗十二指肠溃疡的疗程为4周^[3],治疗胃溃疡的疗程为6~8周,治疗胃食管反流病的疗程至少需要8周^[4]。由于PPI是长期连续给药,其抑酸作用不会减弱,也不会出现耐受现象^[1],因此,许多患者往往超过规定疗程继续服用。然而,美国食品药品监督管理局(FDA)、欧

洲药品监督管理局(EMA)多次指出,长期使用PPI可能诱发肠道菌群紊乱导致肠道感染、低镁血症、骨质疏松与骨折等风险^[5]。

1 PPI的抑酸机制

PPI为苯并咪唑衍生物,作为一种前体药,其代谢生成的次磺酸和次磺酰胺与壁细胞分泌小管内的半胱氨酸位点(cys813、cys822等)双硫键共价结合,不可逆地使H⁺/K⁺-ATP酶失活,从而抑制胃酸分泌,直到新的质子泵生成,壁细胞的泌酸功能持续被抑制^[6]。临床上,患者在停用质子泵抑制剂3 d后,胃酸分泌逐渐增加,部分患者的病情容易反复。第1代PPI主要为奥美拉唑、兰索拉唑及泮托拉唑,主要在肝脏通过细胞色素P450的同工酶系统CYP2C19和CYP3A4代谢;第2代PPI主要为雷贝拉唑、埃索美拉唑及艾普拉唑,其代谢过程中对CYP2C19酶的依赖性较第1代减小^[7]。晨起壁细胞上的新生质子泵数量最多,进餐后活化迅速,PPI应在早餐前1 h服用,以截断较多的质子泵^[6]。

2 PPI作用胃肠道菌群的原理

2.1 胃内pH的升高

人胃内pH的基线值约为1.5,持续的强酸环境形成了一道化学屏障,将食物中的大多数病原微生物杀死。在治疗剂量下,PPI可延迟胃排空率,使胃内基础pH升高,pH值维持在5~6^[8]。当pH>4时,胃酸的灭活能力明显下降,厚壁菌、拟杆菌、放线菌等大量的口腔、食管菌群在胃中过度生长及增殖,数量可达之前的1 000倍左右^[9]。致病菌及机会致病菌直接进入下消化道,竞争性抑制肠内原生菌群,破坏肠道正常微生态与屏障功能。

2.2 胃泌素的升高

胃酸浓度的降低抑制了D细胞生长抑素的释放,G细胞胃泌素的分泌增加,导致静止时血清胃泌素水平升高^[5]。Lundell等^[10]整理了1 920例反流性食管炎或消化性溃疡患者的数据后发现,长期服用PPI(3.5~15年),胃泌素平均水平上升至正常值的1~3倍,肠嗜铬样细胞数量增加7.8%~52.0%。另外,胃泌素水平还与肠道中M2巨噬细胞数量呈负相关,并影响其表型分化及相关免疫反应^[11]。

2.3 营养物质的变化

在低胃酸情况下,食物不能被胃酸和胃蛋白酶彻底消化降解,尤其是蛋白质类物质,PPI诱导的低氯血症可通过干扰水解膳食蛋白中的维生素B₁₂而

引起维生素B₁₂的吸收障碍^[12]。在没有已知缺铁危险因素的患者中,胃酸抑制剂使用>2年的患者缺铁风险增加,且风险可随着抑酸作用的加强而不断增加,但停药后风险可逐渐降低^[13]。胃内pH环境的改变影响了melastatin-6、melastatin-7等瞬时受体电位通道(TRPM6/7),降低了肠上皮对Mg²⁺的亲合力,Mg²⁺的主动转运受到抑制,长期使用PPI制剂的患者存在低镁血症的风险^[14]。服用PPI导致胃排空减慢,营养物质的吸收也存在一定障碍,胃肠道内富营养化,加速了菌群的增殖。

3 PPI所致菌群改变对消化系统的影响

3.1 口腔

口腔作为消化道的开口,微生物数量庞大,密度较高。由于胃酸屏障的阻挡,口腔内细菌很难移行至下消化道进行定植,但2010年核梭杆菌从母亲口腔转移到胎儿组织并造成胎儿死亡的病例,提示了口腔菌群也存在从消化道转移及血液转移的可能^[15]。PPI与口腔微生物相关性的研究较少,目前认为口腔菌群的失调可能与胃酸屏障有关,在短期(4周)使用PPI后,口腔中链球菌丰度明显增加,而奈瑟菌和韦荣球菌丰度减少,菌群不协调将导致牙周病及肠道感染的风险增加^[16-17]。另外,根除胃内的幽门螺杆菌可改善PPI长期使用后维生素B₁₂缺乏的情况,并减少口腔溃疡的发生^[18]。

3.2 食管

PPI是治疗上消化道疾病的常用药物,可用于治疗胃食管反流病(gastroesophageal reflux disease, GERD)、Barrett食管等疾病。这类疾病多因为大量弱酸性反流酸回流到食管造成,其复发率和缓解率与治疗期间的酸抑制程度直接相关,长期(>8周)使用PPI非常普遍^[19]。在反流性食管炎及Barrett食管中,食管远端黏膜屏障暴露在增多的普氏菌、嗜血杆菌、吡啶单胞菌等革兰阴性菌中,革兰阴性菌外膜的脂多糖可激活Toll样受体和NF-κB途径,上调促炎细胞因子的基因表达,并增加iNOS及COX-2的释放舒张下食管括约肌、延缓胃排空^[20]。在PPI使用后,链球菌、放线菌、乳酸菌等革兰阳性菌丰度增加,虽然正常食管菌群的丰度增加,菌群结构得到了改善,但出现了下消化道菌群的异位定植以及食管菌群数量显著增加的情况^[21]。在正常情况下,口腔、咽部及食管所特有的细菌群落无法在低pH值的环境中生存,胃酸对特定菌群起着屏障作用,将食管、胃及肠道微生物群区分开来。PPI的治疗减弱

了这道屏障,长期的低胃酸环境使消化道上部的细菌沿胃肠道进行定植,导致胃部、小肠、大肠均出现口腔及食管菌群的增殖。

3.3 胃

PPI是治疗胃十二指肠溃疡、Hp感染的常用药物。研究发现,PPI对Hp具有体外抗菌活性,且以雷贝拉唑为最强,不仅能抑制细菌尿素酶,且对Hp有较大的亲和力,硫醚衍生物的结构还能够抑制对克拉霉素耐药的Hp的生长与活性^[7]。但是在Hp感染的情况下,若使用PPI治疗,阿司匹林等非甾体抗炎药(nonsteroidal antiinflammatory drug, NSAID)导致的胃部糜烂、溃疡,小肠上皮损伤的风险及胃癌的患病机率将会大大上升^[22]。并且,Hp感染的患者长期(>1.5年)使用PPI更容易出现腺体萎缩^[10]。所以,在长期使用PPI前根除Hp十分重要,目前没有任何治疗方案能保证100%根除Hp,根除率与多种因素有关,包括治疗方案、患者遗传多态性、吸烟等不良饮食嗜好等。常用铋剂四联疗法(铋剂+PPI+四环素+甲硝唑)根除Hp,可导致肠道微生物的短期失调,其中变形杆菌的相对丰度增加,拟杆菌及放线菌的相对丰度降低,在停药6周后,菌群结构才基本恢复正常^[23]。若反复根除Hp失败,不仅会加重消化道内菌群的失调,且胃窦长期的低胃酸环境,可能导致Hp由胃窦向胃体位移,从胃窦为主的胃炎发展为胃体为主的胃炎,而胃体的炎症和萎缩则会进一步降低胃酸分泌,由胃体萎缩为主的低胃酸型胃炎向胃癌转变的可能性显著升高^[24]。在胃酸正常分泌的环境中,变形菌门、厚壁菌门、拟杆菌门、放线菌门和梭杆菌门是胃黏膜微生物群中的优势菌群,普氏菌属、链球菌属、奈瑟菌属、卟啉单胞菌属和嗜血菌属丰度较大^[25]。当胃内pH值高于4.0时,球菌科、草酸杆菌科、鞘脂单胞菌科在胃内出现增殖,嗜甲基菌随着长期使用PPI而逐渐增加^[25]。并且,短期(2周)使用PPI就能使胃黏膜微生物的多样性显著升高,随着PPI的长期(>8周)使用,此变化也一直持续^[21,26]。

3.4 胰腺

PPI的使用不会影响急性胰腺炎患者的临床病程及结局,如住院时间、开始饮食时间或疼痛的缓解^[27]。但是PPI可通过对H⁺/K⁺-ATP酶的胃内HK α 1和HK β 亚基(ATP4A、TP4B)和胃外HK α 2亚基(ATP12A)的影响,抑制胰腺分泌,慢性胰腺炎胰腺外分泌功能受损,对于胰腺囊性纤维化特别是脂肪漏患者,PPI可作为附加药物,与胰酶制剂同时服

用,可减少胰酶在胃酸中的灭活,增加其在十二指肠的活性^[28-29]。胰腺自身没有固定的微生物群,但小肠内的细菌负荷会随着PPI的使用逐渐增加,若胰腺中出现肠道菌群如肠球菌、梭菌的异位定植,很可能出现坏死胰腺组织的继发性感染及内毒素血症^[30]。

3.5 胆管

胆管开口于十二指肠,胆管疾病(原发性硬化性胆管炎等)的发生与肠内微生物的变化息息相关,肠道微生物影响胆汁酸的代谢,并参与肝胆疾病的发展^[31]。使用PPI易导致小肠内微生物过度繁殖,胆管炎的发病率增加,一部分肠道细菌经胆管上行至肝脏,还可能引起门静脉压力增高及门脉菌血症^[32]。

3.6 肝脏

PPI常用于肝硬化患者来降低胃内高酸环境,减少食管胃底静脉曲张的发生率^[33]。肝硬化患者由于胃肠动力改变及使用抗生素的情况,往往已经出现了肠道菌群的不平衡,韦荣球菌属、梭菌属、链球菌属的丰度较正常人增加,肠道共生菌(嗜酸乳杆菌等)减少,大量口腔细菌在肠道定植^[34]。服用PPI制剂后,肠道菌群的紊乱将更加严重,更容易导致小肠细菌过度生长(small intestinal bacterial overgrowth, SIBO)的发生^[35]。异位定植的肠球菌可通过识别Toll样受体2诱导肝脏炎症并加快肝脏疾病的进展,导致终末期肝病患者的自发性细菌性腹膜炎的发生率大大增加^[36]。最近的对照研究发现,PPI制剂的使用可能会增加肝性脑病的风险,并与服用剂量呈正相关^[37]。

3.7 小肠

PPI不会直接改变肠道的pH值,而是将胃与肠道的pH值趋于一致,并改变了人类肠道微生物结构中的特定分类群。长期的慢性酸抑制和低氯血症导致小肠肠壁的通透性增加,肠道内微生物总量增加,多样性减少,小肠SIBO的潜在风险大大增加^[35]。与非使用者相比,服用PPI的患者患SIBO的风险高2.72倍,并存在口腔与结肠菌群的异位定植^[38]。在PPI治疗胃食管反流病停药后,多数患者在12周内出现复发病状,且SIBO阳性患者的复发风险高于SIBO阴性患者^[39]。可能由于SIBO引起胃肠动力改变,轻度慢性炎症反应和免疫反应持续作用于胃肠道平滑肌,导致回流复发率增高^[40]。临床上,PPI还常用于预防及治疗重症患者的应激性溃疡,大量长期使用可能导致消化道感染及不良反应,而研究表

明肠内营养能减少相关并发症的发生^[41]。

3.8 大肠

大肠拥有人体最大的微生物群落,随着近端肠道细菌的过度生长,细菌负荷将传递到结肠,其中肠球菌科、链球菌科、乳酸杆菌的数量增加,而拟杆菌和梭菌类群Ⅳ的数量减少,菌群对肠道壁营养的竞争加强,导致肠道微生物的多样性水平降低^[42]。移植至远端肠道的细菌与结肠上皮细胞相互作用,艰难梭菌、弯曲杆菌、志贺氏菌、沙门氏菌和其他肠道感染的风险增加,引起结肠上皮内淋巴细胞、巨噬细胞及肥大细胞的增殖活跃^[43]。有研究表明长期(8周)使用PPI可致肠道内双歧杆菌属、乳杆菌属数量减少,且PPI的使用剂量、频率与难辨梭菌感染(*Clostridium difficile* infection, CDI)风险呈正相关^[44]。克林霉素和阿莫西林是抗Hp四联药的常用抗生素,与CDI的发展密切相关,会导致结肠细菌的严重耗竭,以及革兰阳性球菌丰度的增加^[45]。长期的抑酸作用也增加了克罗恩病的患病率,并且同时服用PPI和H₂受体拮抗剂的患病风险高于单用PPI^[46]。

4 结 论

综上所述,由于PPI可导致胃肠道菌群紊乱及其他并发症,应严格掌握长期用药的适应证,避免长期、大剂量用药,但如果长期使用PPI是必要的(例如长期服用阿司匹林/NSAID相关的胃出血风险很高的患者、患Barrett食管的患者等),建议先根除Hp,以防止胃体萎缩,降低胃癌的发生风险。对于患有牙周病的患者,建议行Hp根除后再进行牙周的基础治疗。益生菌产生短链脂肪酸,激活宿主免疫系统,降低肠道pH,以降低微生物活性,能减少肠道菌群失调的情况,减轻消化道不适症状,可以与PPI制剂联用来减少复发与不良反应的发生^[47]。需要长期应用PPI的患者,特别是曾患有肠道感染等的高风险人群,应定期进行血生化检验及胃镜肠镜检查,及早发现胃肠道的器质性改变。

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