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文献综述 REVIEW

质子泵抑制剂防治化疗引起胃肠道黏膜损伤的研究进展

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■背景资料
肿瘤化疗引起的胃肠道黏膜损伤可影响患者的生活质量及化疗效果, 是肿瘤学界普遍关注的问题, 近年来质子泵抑制剂(proton pump inhibitors, PPIs)被用于防治化疗引起的胃肠道疾病, 但鲜有文献对此作用机制及临床疗效进行评估.

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Advances in prevention and treatment of chemotherapy-induced gastrointestinal mucositis with proton pump inhibitors

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Abstract
Proton pump inhibitors (PPIs) are potent acid-suppressive medications commonly used for management of acid-related diseases. Over the past decade, gastrointestinal injury following chemotherapy has attracted wide attention from oncologists. Two international clinical practice guidelines, the National Comprehensive Cancer Network (NCCN) and the Multinational Association of Supportive Care in Cancer (MASCC) antiemesis guidelines, recommend omeprazole for the treatment of chemotherapy-induced epigastric pain. In recent years, PPIs have been widely used for the prevention and treatment of chemotherapy-induced gastrointestinal mucositis. This paper summarizes the mechanisms by which chemotherapy causes damage to the gastrointestinal tract, the mechanisms underlying the protection afforded by PPIs against gastrointestinal injury induced by chemotherapy, and their clinical applications.

Key Words: Proton pump inhibitors; Chemotherapy-induced; Gastrointestinal mucositis; Prevention treatment

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摘要
质子泵抑制剂(proton pump inhibitors, PPIs)具有抑制胃酸分泌和保护胃黏膜作用, 临床常用于治疗酸相关性疾病. 肿瘤化疗引起的胃肠道黏膜损伤, 一直受到肿瘤学界的重视, 在美国国立癌症综合网络(National Comprehensive Cancer Network, NCCN)与癌症辅助治疗多国协会(Multinational Association of Supportive Care in Cancer, MASCC)临床止吐指南中, PPIs之一的奥美拉唑被推荐用于治疗肿瘤化疗引起的上腹痛症状. 目前PPIs的适应症有增加趋势, 国内临床上广泛用于防治肿瘤化疗引起的胃肠道黏膜损伤. 本文就化疗引起胃肠道黏膜损伤机制、PPIs保护胃肠道黏膜机制及其防治化疗引起胃黏膜损伤的临床应用作一综述.

关键词: 质子泵抑制剂; 化疗引起; 胃肠道黏膜损伤; 防治

核心提示: 质子泵抑制剂(proton pump inhibitors)兼具抑制胃酸及细胞保护作用, 能有效防治化疗引起的胃肠道黏膜损伤, 有助于提高化疗患者生活质量. 临床医师应严格按照用药说明及临床指南应用此类药物.

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■研发前沿
近年来研究显示PPIs除抑制胃酸分泌外还具有抗炎、抗氧化等细胞保护作用, 可使胃肠道黏膜免受各种致病因素的危害, 其中包括化疗药物损害.

0 引言

1980年, 第一个质子泵抑制剂(proton pump inhibitors, PPIs)奥美拉唑始应用于临床, 现已成为治疗酸相关性疾病的主要药物[1]. 此后, 兰索拉唑、泮托拉唑、雷贝拉唑和埃索美拉唑等同类药物陆续上市, 其作用各有特点, 为临床用药提供了多种选择. 肿瘤化疗导致的胃肠道黏膜损伤一直是临床上比较关注的问题, Sartori等[2,3]通过两项随机试验证实PPIs可有效预防化疗引起的胃肠道黏膜损伤. 基于此研究结果, 2004年奥美拉唑被癌症辅助治疗多国协会(Multinational Association of Supportive Care in Cancer, MASCC)指南推荐用于治疗化疗引起的上腹痛及烧心症状[4]. 目前PPIs在国内临床上被广泛用于防治化疗引起的胃肠道黏膜损伤, 特别是预防化疗引起的恶心、呕吐等胃肠道反应的发生; 由于临床医师使用PPIs治疗此类胃肠疾病时多以国际指南作为用药参考, 而PPIs使用说明书均未明确提及此类适应征, 因此鲜有文献对其作用机制及治疗效果予以评估. 本文就化疗引起胃肠道黏膜损伤的机制、PPIs保护胃肠道黏膜的机制及其防治化疗引起胃肠道黏膜损伤的临床应用做一综述.

1 化疗引起胃肠道黏膜损伤的机制及PPIs保护胃肠道黏膜的机制

1.1 化疗引起胃肠道黏膜损伤的机制 化疗引起胃肠道黏膜损伤的机制尚未完全清楚, Sultani等和Sonis等[5,6]认为化疗引起胃肠道黏膜损伤大致可分为5个阶段, 首先细胞毒药物直接损伤细胞的DNA, 引起黏膜基底层上皮细胞和黏膜下层细胞凋亡, 广泛的组织损伤导致活性氧簇(reactive oxygen species, ROS)的产生, ROS可刺激巨噬细胞的生成, 引发包括SP1相关视网膜母细胞瘤控制蛋白、P53、核转录因子(nuclear factor kappa-B, NF-κB)在内的炎症级联通路, 造成细胞凋亡和组织的损伤. 第二个阶段, 一系列信号通路与转录因子被激活, 其中最重要的是NF-κB. NF-κB主要调控各种炎性分子的基因表达与合成, 其中包括白介素-1β(interleukin-1β, IL-1β)、IL-6、肿瘤坏死因子(tumour-necrosis factor, TNF)、黏附因子及环氧合酶2(cyclooxygenase-2, COX-2)等促炎细胞因子[7,8]. 第三个阶段, 各类促炎细胞因子与NF-κB相互影响形成一炎症恶性反馈环, 如TNF在反馈环中强化了NF-κB的活性, 导致炎症信号被进一步放大, 放大的炎症恶性反馈环又促进TNF、IL-6及IL-1β的产生, 使细胞凋亡和组织损伤进一步加重[6]. 第四个阶段, 胃肠道黏膜上皮的完整性遭到严重破坏, 溃疡形成. 溃疡处定殖的细菌可激活巨噬细胞渗透物和其他炎性细胞聚集到受损的组织中, 引起继发性感染. 最后一个阶段, 一般出现在停止治疗后的2 wk内, 是胃肠道黏膜上皮细胞自我修复和更新的一个过程, COX-2可能通过促进血管生成在这一“重建”过程中发挥重要作用[6,9,10]. 此外, 化疗引起胃肠道黏膜损伤还可能与其导致胃肠道菌群失衡有关. 化疗可引起胃肠道菌群的易位或过度生长, 破坏正常菌群对胃肠道的保护功能. 这些功能的破坏可导致胃肠道的局部感染或者菌血症的发生[11].

1.2 PPIs保护胃肠道黏膜的机制

1.2.1 提高胃黏膜防御屏障: 正常情况下, 胃肠道黏膜的防御机制包括黏膜结构的完整、上皮细胞的自我更新及其分泌的碳酸氢盐与磷脂黏液、微血管持续的血液流动等多个方面. 其中微血管持续的血液流动对维持胃肠道黏膜的正常结构与功能起着关键作用. 前列腺素(prostaglandin , PG)可维持胃肠道黏膜上皮细胞的自我更新及微血管的血液流动, 在胃肠道黏膜防御机制中发挥重要作用[12,13]. 人体内的PG主要包括PGE2、PGI2、PGD2及PGF2α 4种类型, 其中PGE2含量最多, 并对调节人体各种生理功能起着重要作用, 其中包括调节免疫应答、维持血压稳定、保持胃肠道黏膜完整性等. PG的合成依赖于COX)的活性, 其两个亚型分别为COX-1与COX-2[14]. Tsuji等[15]通过动物实验证实随着剂量的增加, 兰索拉唑可提高大鼠血清胃泌素水平及增加COX-2表达, 促进胃黏膜PGE2合成而发挥胃黏膜保护作用. 尽管胃泌素诱导COX-2表达的具体机制尚不清楚, 但是可以推断兰索拉唑保护胃黏膜的作用机制, 与内源性胃泌素激活胃泌素受体、增加COX-2介导的胃黏膜PGE2合成有关. Kobayashi等[16]研究还发现兰索拉唑可增加大鼠胃黏膜血管内皮生长因子受体(vascular endothelial growth factor, VEGF)的表达, VEGF可以促进血管内皮细胞生长加速血管再生. 而抑制PG的生成可减少VEGF的表达, 提示兰索拉唑修复胃肠道黏膜溃疡的机制可能与

■相关报道
代兴斌等对127例肿瘤化疗患者进行观察, 结果显示兰索拉唑与奥美拉唑对化疗药物引起的消化系反应均具有明显的预防及抑制作用.

增加VEGF的表达及提高PG合成有关; 不过也可能存在另一个机制, 即促进黏膜下基质内的基质金属蛋白酶2(matrix metalloproteinase-2, MMP-2)表达, 一种可重建细胞外基质促进细胞损伤修复的内切酶, 而这种机制与刺激内源性PG释放无关[16,17].

1.2.2 抗氧化作用: 一些体外研究发现PPIs可以阻止次氯酸引起的β-胡萝卜素的氧化、铁和铜介导的脱氧核糖的氧化以及铜引起的低密度脂蛋白氧化, 并可有效清除过渡金属化学反应所产生的羟基自由基(•OH)[18-20]. 在体内试验中, 研究者发现小鼠因受束缚及冷应激引起的胃溃疡主要由胃黏膜产生的羟基自由基(•OH)导致. 在冷应激前给予奥美拉唑处理的小鼠, 其胃黏膜表现出较低水平的羟基自由基(•OH)、脂质过氧化反应以及蛋白质氧化[21]. 在吲哚美辛引起胃溃疡的小鼠模型中, 研究人员发现, 小鼠胃溃疡与胃黏膜谷胱甘肽, 一种强力的内源性抗氧化因子的消耗有关. 埃索美拉唑可有效防止谷胱甘肽的损耗以保护胃黏膜的损伤, 其机制尚不清楚. 研究者估计在胃酸中埃索美拉唑转变成四环的次磺酰胺, 为胃黏膜提供硫基化合物以起到抗氧化的作用[22]. 另一个吲哚美辛致小鼠胃溃疡的研究中, Koch等[23]还发现埃索美拉唑可以提高过氧化歧酶水平和总抗氧化能力, 不过其机制也尚未清楚.

1.2.3 抗炎作用: 血红素加氧酶(heme oxygenase, HO)是血红素分解代谢的限速酶, 其亚型HO-1广泛存在于胃肠道黏膜[24-26]. HO-1表达水平上调作为一种自然防御机制可减少炎症的发生及黏膜组织的损伤[27,28]. 在应激及病理状态下, 如休克、缺氧、缺血及ROS可刺激HO-1表达水平上调发挥细胞保护作用[29-31]. 研究显示兰索拉唑可诱导大鼠胃黏膜上皮细胞HO-1表达增高, 其机制可能为兰索拉唑促使Kelch样ECH联合蛋白1(Keap-1)释放核转录因子Nrf2, 并激活Nrf2使其磷酸, 从而上调HO-1 mRNA和蛋白表达, 最终诱导HO-1的表达[32-34]. PPIs还可通过抑制促炎性细胞因子的释放发挥抗炎作用[35]. 胃黏膜产生IL-8, 一种强力的白细胞刺激物, 在幽门螺杆菌介导的炎症反应中发挥重要的作用. Handa等[36]观察发现在人胃癌细胞与脐静脉内皮细胞中, 奥美拉唑和兰索拉唑可能通过阻碍NF-κB的细胞通路以抑制幽门螺杆菌刺激IL-8的产生. 这种现象也可以在动物实验中观察到[36,37]. 在人工培养的气管上皮细胞中, 兰索拉唑可以降低一系列促炎症因子包括IL-6、IL-8及TNF-α的水平. PPI减少上皮和内皮细胞产生的促炎症因子的机制尚不清楚[38].

1.2.4 抑制胃酸分泌作用: 胃黏膜壁细胞中主要功能性靶点为H2受体和H^+-K^+-ATP酶. 组胺与H2受体结合导致胞内环磷腺苷(cyclic adenosine monophosphate, cAMP)浓度升高和蛋白激酶(protein kinase A, PKA)激活. PKA激活的效应之一则是细胞骨架蛋白磷酸化, 细胞骨架蛋白参与H^+-K^+-ATP酶由细胞质向细胞膜的转运, 从而使H^+-K^+-ATP酶可以接触到胞外的KCl, 使胞外K^+与胞内H^+进行交换, 形成胃酸分泌. 组胺H2受体对于壁细胞泌酸过程的特征性形态学改变至关重要, 而H^+-K^+-ATP酶承担着泌酸的最后一项功能[39]. PPIs为苯并咪唑衍生物, 以前体药物的形式在胃酸中激活, 转化为次磺酰胺类化合物, 与H^+-K^+-ATP酶亚单位上的半胱氨酸残基(Cys)中的巯基共价结合形成二硫键, 使质子泵不可逆地失去活性, 阻断酶的H^+/K^+转运机制, 从而抑制胃酸分泌的最后步骤, 以保护胃黏膜免遭胃酸侵袭[40].

2 PPIs防治化疗引起胃肠道黏膜损伤的临床应用

2.1 减轻胃肠道反应 化疗引起胃肠道反应以恶心、呕吐最为常见, 人体超过95%的5-羟色胺(5-hydroxytryptamine, 5-HT)由胃肠道黏膜分泌, 细胞毒药物造成胃肠道黏膜损伤致使黏膜上的嗜铬细胞释放5-HT, 与5-HT3受体结合产生神经冲动经迷走传入神经传入呕吐中枢引起患者呕吐[41,42]. 代兴斌等[43]研究显示兰索拉唑、奥美拉唑联合止吐药在防治呕吐、恶心、食欲不振方面的有效率明显高于单用止吐药(格拉司琼+地塞米松). 提示PPI能提高止吐药物对化疗引起胃肠道反应的控制率, 且药物安全性高. 其机制可能与PPIs保护胃肠道黏膜, 减少黏膜嗜铬细胞释放5-HT有关.

2.2 预防急性胃溃疡 细胞毒药物对胃肠道黏膜的直接损害加上胃酸侵袭常导致急性胃十二指肠溃疡形成. Sartori等[2,3]通过随机对照实验证实奥美拉唑组患者在化疗过程中急性胃溃疡的发生率、上腹痛及烧心感症状的出现率明显低于安慰剂组, 差异有统计学意义. 安慰剂组的患者化疗后内镜评分均高于化疗前, 奥美拉唑组并无此表现. 表明奥美拉唑能有效预防化疗引起的上消化系黏膜损伤, 减少胃肠道溃疡的发生. 其机制主要与PPIs减少胃酸分泌有关.

2.3 防治化疗性胃食管反流病 化疗引起胃食管返流病的机制不完全清楚, 可能与细胞毒药物抑制黏膜细胞正常增殖分裂、刺激炎性因子分泌、减弱食管下段括约肌功能引起胃容物返流等因素有关, 临床上头颈部及胸部肿瘤患者经常接受化疗及放疗联合治疗, 这更增加了食管黏膜损伤的风险[44,45]. Uwagawa等[46]在其研究中发现, 雷贝拉唑能够明显改善化疗引起的胃食管返流病症状频率评分, 提示化疗引起胃食管返流与胃酸分泌过度有关系, 也表明PPI可以改善化疗引起的胃食管反流病的症状.

2.4 PPIs的安全性 一项长达15年的开放性试验显示, 长期使用泮托拉唑治疗严重酸相关性疾病有良好的安全性及有效性. 研究从1999-09开始至2007-09结束, 研究人员定期记录患者在治疗期间的各项参考指标, 结果显示长期使用泮托拉唑不会导致患者胃部腺体萎缩和肠上皮化生, 虽然可引起胃部腺体可逆性轻至中度扩张, 但不会增加肿瘤发生的风险[47]. 一项Meta分析提示使用PPIs超过180 d并不增加患者患社区获得性肺炎的风险, 但是使用高剂量或者使用时间少于30 d的患者患社区获得性肺炎的风险增加[48]. 另一项Meta分析显示PPIs可轻微提高髋骨及脊柱骨折的风险[49]. 此外PPIs还可导致低镁血症、低钙血症及低钾血症等电解质紊乱的发生[50,51].

3 结论

PPIs因其显著的抑酸效果被广泛用于治疗酸相关性疾病, 如胃食管反流病, 上消化系溃疡及卓-艾氏综合征等[52]. 近十几年来, 因PPIs对胃肠道黏膜的保护作用而应用于治疗化疗引起的胃肠道黏膜损伤. 两项国际指南美国国立癌症综合网络(National Comprehensive Cancer Network, NCCN)与MASCC均提示在化疗患者出现上腹痛及烧心症状时可使用PPIs进行治疗. 以上综述表明PPIs可有效防治化疗引起的胃肠道黏膜损伤. 尽管如此, PPIs多种潜在的不良反应值得临床医生注意, 只有正确掌握PPIs的作用机制及适应症, 才能避免药物过度使用, 确保患者得到安全合理的治疗.

■创新盘点

关于PPIs药理作用的研究比较多, 但对其防治化疗引起的胃肠道黏膜损伤作用机制的报道较少, 本文对此机制及临床应用等作一综述, 为指导临床合理使用PPIs提供科学依据.

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■应用要点

目前，国内外临床上广泛存在超出药品说明书标示的适应症使用PPIs的情况，本文有助于临床医师深入了解PPIs的作用机制，正确掌握其适应症，使PPIs得到科学合理的使用.

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■同行评价
本文综述PPIs保护胃肠黏膜免受化疗损伤的作用机制及临床应用等对临床更好的应用PPIs有很好的指导作用.