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文献综述 REVIEW

非甾体类抗炎药相关性小肠损伤研究进展

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背景资料
非甾体类抗炎药(non-steroidal anti-inflammatory drugs, NSAIDs)具有良好的解热、镇痛、抗炎、抗血小板疗效而广泛应用于临床, 但NSAIDs有一定的消化系毒性, 尤其会引起NSAIDs相关性小肠损伤, 目前治疗NSAIDs相关性小肠损伤尚无特效药.

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Advances in research of non-steroidal anti-inflammatory drugs induced small intestinal injury

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) have anti-inflammatory, antipyretic and analgesic properties and have been widely used in clinical practice; however, they can cause cytotoxicity in the gastrointestinal tract, especially in the intestine. The injurious effects of NSAIDs on the small intestine occur frequently and can lead to severe clinical outcomes. A multifactorial etiology is involved in the pathogenesis of these lesions. Current studies found that, in addition to the suppression of cyclooxygenase activity, several factors including enterobacterial invasion, neutrophil migration, enterohepatic cycling of NSAIDs, bile and mitochondrial injury have been implicated in the pathogenesis of these lesions. This article reviews the mechanisms and therapeutic strategies in NSAIDs induced intestinal injury.

Key Words: Non-steroidal anti-inflammatory drugs; Intestinal injury; Cyclooxygenase; Enterobacteria

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摘要

非甾体类抗炎药(non-steroidal anti-inflammatory drugs, NSAIDs)具有良好的解热、镇痛、抗炎、抗血小板疗效而广泛

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应用于临床, 但NSAIDs有一定的消化系毒性, 尤其会引起NSAIDs相关性小肠损伤. NSAIDs相关性小肠损伤发病率高、临床后果严重, 是一个多因素导致的过程. 近来, 研究显示环氧合酶、肠道菌群、炎症细胞、NSAIDs的肝肠循环、胆汁及线粒体损伤均参与了NSAIDs相关性小肠损伤的发病. 本文就NSAIDs相关性小肠损伤的机制及防治等进展作一综述.

关键词: 非甾体类抗炎药; 小肠损伤; 环氧合酶; 肠道菌群

核心提示: 非甾体类抗炎药(non-steroidal anti-inflammatory drugs, NSAIDs)相关性小肠损伤发病率高、临床后果严重, 而其发病机制未明. 近来, 研究显示环氧合酶、肠道菌群、炎症细胞、NSAIDs的肝肠循环、胆汁和线粒体损伤均参与了NSAIDs相关性小肠损伤的发病.

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0 引言

非甾体类抗炎药(non-steroidal anti-inflammatory drugs, NSAIDs)是常见的解热、镇痛、抗炎药, 常用于治疗风湿和炎症性疾病; 据统计, 世界范围内每天3000万人在服用NSAIDs, 在美国, NSAIDs的处方每年有11100万, 价值约4.8亿美元[1]. 然而, 长期服用NSAIDs可以引起胃黏膜损伤, NSAIDs相关性小肠损伤也很常见. 目前NSAIDs相关性小肠损伤的确切机制尚不明确, 临床中也缺乏有效的治疗药物. 本文就NSAIDs相关性小肠损伤的研究进展作一综述.

1 NSAIDs相关性小肠损伤的流行病学及临床表现

1.1 流行病学 世界范围内NSAIDs相关性胃和十二指肠损伤的发生率为9%-22%[2], NSAIDs占消化性溃疡病因的35%, NSAIDs引起的10%以上溃疡伴有穿孔、阻塞等并发症[3]. 临床试验结果显示, 服用萘普生的类风湿性关节炎患者中严重下消化系不良反应的发生率是0.9%[4]. 应用胶囊内镜的研究发现, 短期使用NSAIDs的患者中小肠损伤的发生率是50%-70%[5], 老年患者中小肠损伤的发病率更高. 一直以来, 临床中对NSAIDs引起的小肠损伤认识不足而重视不够. 实际上, 在长期服用NSAIDs的人群中约70%的患者会出现小肠损伤[6], NSAIDs相关性小肠损伤所致的出血发生率较NSAIDs相关性胃损伤更高[7], 而且在大多数患者中这种损伤处于亚临床状态[8].

1.2 临床表现 随着内镜技术的进步, 临床中发现NSAIDs相关性小肠损伤的发生率明显高于NSAIDs相关性胃和十二指肠损伤, 且病情危险性更高[9]. 然而, 目前对于NSAIDs相关性小肠损伤没有明确有效的药物, 而且由于患者的组织损伤和临床症状之间的相关性较差, 临床诊断也充满了挑战. 缺铁性贫血是NSAIDs相关性小肠损伤常见的首发症状[8], 长期服用NSAIDs可以引起小肠出血、坏死、溃疡、穿孔、蛋白丢失等损伤[10], 以及小肠阻塞、腹膜炎及横膈膜等疾病[11,12].

2 NSAIDs相关性小肠损伤的机制

NSAIDs相关性小肠损伤是由多因素导致的、多步骤的过程, 可以分为前列腺依赖途径以及非依赖途径. 环氧合酶(cyclooxygenases, COX)及其产物前列腺素(prostaglandins, PGs)在其病理过程中有重要作用. 研究[13-15]发现, NSAIDs也可以通过诱导细胞凋亡、增加小肠上皮细胞的通透性而导致小肠损伤, 而这些损伤方式与前列腺素无关.

2.1 PGs依赖途径 PGs存在于整个消化系, 对调节胃酸、碳酸盐、黏液的分泌、黏膜血流以及维持黏膜屏障完整性有重要作用[16]. COX介导了黏膜内PGs的合成, NSAIDs通过抑制炎症部位COX的活性来减少PGs的合成. COX有两种亚型: COX-1和COX-2, COX-1可以调控黏膜微循环[17]、介导PGs合成, 对维持黏膜稳态有重要作用, 抑制COX-1会增加黏膜通透性, 导致肠道细菌入侵, 引起诱导型一氧化氮合酶(inducible nitric oxide synthase, iNOS)的表达增加. 而COX-2在保护肠道黏膜和调节PG产量的过程中也有重要作用[18]. 选择性COX-1抑制剂和选择性COX-2抑制剂本身并不引起小肠损伤[19], 而当这些药物合用则可引起肠道出血性损伤. 对COX-1和COX-2抑制的双重抑制是NSAIDs引起肠道溃疡性损伤过程中重要环节.

研发前沿

NSAIDs在临床中有广泛的应用, 但长期使用则会引起NSAIDs相关性小肠损伤. 这一损伤是一个多因素导致的过程, 近来, 研究显示环氧合酶、肠道菌群、炎症细胞和NSAIDs的肝肠循环、胆汁、线粒体损伤均参与了NSAIDs相关性小肠损伤的发病.

相关报道

Saitta等发现在大鼠中应用β-D-葡萄糖醛酸酶的抑制剂可以显著降低双氯芬酸引起的小肠损伤, 因此推测胆汁在这种肠损伤中有一定作用. Zhou等发现NSAIDs经肝肠循环进入胆汁后引起胆汁对细胞间通透性的破坏性作用增强.

创新盘点

本文简要介绍了非甾体类抗炎药相关性小肠损伤的流行病学及临床表现, 详细阐述了环氧合酶、肠道菌群、炎症细胞、NSAIDs的肝肠循环、胆汁和线粒体损伤在NSAIDs相关性小肠损伤发病过程中的可能作用并简要介绍了最近的药物研究进展.

2.2 不依赖PG依赖途径

2.2.1 细菌因素相关证据: 肠道细菌在NSAIDs引起的小肠损伤中有重要作用, NSAIDs可以使肠道运动增强而打破了黏液层的完整性, 加速了细菌侵入黏膜; 肠道菌群可以释放内毒素, 主要成分是脂多糖(lipopolysaccharide, LPS), 内毒素上调iNOS的表达, 引起NO产量增加[20,21]. 革兰阴性杆菌的LPS配体-Toll样受体(Toll-like receptor, TLR)-在NSAIDs诱导的小肠损伤中有重要的作用[22], 在TLR-4突变的小鼠和MyDD88(-/-)的小鼠中这种肠道损伤减轻, 提示肠道菌群在NSAIDs相关性小肠损伤中可能是通过TLR4/MyDD88依赖途径而产生作用的[22]. 研究[23,24]显示, 吲哚美辛在无菌小鼠中不会引起黏膜损伤, 甲硝唑[25]、氨比西林[26]及益生菌[27]可以显著抑制NSAIDs相关性小肠损伤, 研究[27]证实, 益生菌对NSAIDs引起的小肠损伤具有保护作用. 因此肠道中微生态的平衡对NSAIDs导致的小肠损伤中有重要作用.

2.2.2 炎症因素相关证据: 细菌入侵、黏膜损伤可以吸引中性粒细胞至炎症部位, Wallace等[28]发现, 中性粒细胞减少大鼠模型对NSAIDs导致肠道损伤有一定的抵抗力. 中性粒细胞减少时其浸润减少而改善了NSAIDs相关性小肠损伤, 提示中性粒细胞浸润在此病理过程中有重要作用. 中性粒细胞向炎症部位迁移和聚集, 并产生超氧阴离子自由基, 最终导致肠道损伤. NO与超氧阴离子相互作用产生对肠道黏膜的完整性有破坏作用的过氧化亚硝酸盐. 研究[29]显示, 别嘌呤醇, 超氧化物歧化酶、过氧化氢酶通过抑制超氧化物阴离子的产生或者清除超氧化物阴离子而保护肠道免受损伤.

2.2.3 肝肠循环因素相关证据: NSAIDs的肠肝循环是其产生小肠损伤的重要因素之一, NSAIDs药物被吸收后在肝脏中进行葡萄糖醛酸化反应而分泌入胆汁. 细菌的β-D-葡萄糖醛酸酶可以水解NSAID-葡糖苷酸, 使得NSAIDs在回肠中易于吸收. 抑制这种酶的活性可以防止NSAIDs的肝肠循环而降低这些药物引起的小肠损伤[30]. 研究[31]显示, 在大鼠中应用β-D-葡萄糖醛酸酶的抑制剂可以显著降低双氯芬酸引起的小肠损伤. 在用NSAIDs诱导小肠损伤后延迟3 h使用这种抑制剂时则观察不到这种保护作用, 这与此抑制剂的半衰期短的特点一致[31]. 研究[31]显示, 动物在胆管结扎时NSAIDs相关性黏膜损伤发生率降低, 因此推测胆汁在这种肠损伤中有一定作用. 而且, 联用NSAIDs和胆汁作用于小肠细胞的毒性远远大于单用其中任何一个. Wallace等[32]发现NSAIDs经肝肠循环进入胆汁后引起胆汁对细胞间通透性的破坏性作用增强, 比单用药物及胆汁任何一种的毒性都大. Satoh等[33]推测NSAIDs结合胆汁后通过肠道细菌的降解作用可以转化成为自由活性的物质, 消胆胺也可以通过隔离胆汁预防此类损伤.

2.2.4 线粒体因素相关证据: NSAID导致消化系黏膜损伤的“三级打击”学说, 首先, 脂溶性NSAIDs在黏膜表面的吸收入肠细胞后直接抑制线粒体的氧化磷酸化作用, ATP的产生减少, 钙离子从线粒体内溢到胞质增多[34]. 其次, 氧化磷酸化受抑制后由于钙离子外溢而导致细胞间紧密连接受损, 引起肠道的通透性增加[35]. 胞质中钙离子浓度升高激活了钙离子敏感性激酶, 增强细胞的脂质过氧化[36]. 最终, 增高的黏膜通透性导致肠腔内容物胆汁酸、蛋白水解酶和肠道细菌等入侵肠黏膜屏障导致炎性细胞激活而引起非特异性炎症反应[35]. 研究显示, 线粒体解偶联剂在未能引起PGs水平变化时就可以导致线粒体形态学的变化、肠道黏膜通透性增加及炎症反应. Somasundaram等[37]在动物中应用电镜的研究显示, 线粒体形态学变化发生在NSAIDs引起的小肠早期溃疡形成之前. 线粒体的呼吸作用消耗了细胞中90%的氧气, 是在生理性条件下细胞活性氧(reactive oxygen species, ROS)的主要来源[38]. 吲哚美辛可以增加线粒体中ROS产量而显著增加小肠细胞的凋亡, 而外源性补充PGs并不能降低这些细胞的凋亡[13]. 电镜研究[37]结果显示在NSAIDs引起的小肠损伤中线粒体源性ROS起了重要作用, 在用吲哚美辛处理的小肠细胞中观察到线粒体形成空泡、肿胀、线粒体嵴的消失等形态学改变.

3 NSAIDs相关性小肠损伤的防治

3.1 抑酸剂使用的相关问题 PPI和H_2RA对治疗NSAIDs引起的胃和十二指肠损伤效果明显, 但对NSAIDs引起的小肠损伤无效, 甚至可以加重损伤. 许多临床研究显示了长期使用PPI或者H_2RA可引起小肠菌群的过度生长(small intestinal bacterial overgrowth, SIBO)和胆汁酸

代谢的紊乱等消化系改变[38-40]. 研究[41]显示, PPI是通过诱发菌群失调而导致NSAIDs相关性小肠损伤加重的, 其中主要是肠道中双歧杆菌数量减少, 而肠道中补充双歧杆菌则可逆转这种现象. SIBO患者中将初级胆汁酸降解为次级胆汁酸的细菌数量增加而导致胆汁代谢紊乱[38,39,42]. 次级胆汁酸对肠道上皮细胞有破坏作用, 细菌将初级胆汁酸降解为次级胆汁酸可以促进溃疡发生[43]. 细菌降解胆汁酸增加了胆汁酸的疏水性, 增强了这种破坏作用[44], 胆汁酸代谢紊乱可加重NSAIDs相关性小肠损伤. 将初级胆汁酸转化为毒性更强的次级胆汁酸的细菌性酶对胆汁中NSAIDs的解离有重要作用, 这些细菌性酶可能是NSAID相关性小肠损伤治疗的新靶点.

3.2 探索中的新药 Satoh等[45]研究了上消化道保护剂米非司酮、伊索拉定、瑞巴派特对双氯芬酸引起的肠道损伤的作用; 结果显示, 米非司酮、伊索拉定、瑞巴派特可以抑制大剂量双氯芬酸引起的肠道损伤的形成, 也可以防治雷尼替丁和奥美拉唑引起的肠道损伤的加重. 米索前列醇可以改善使用2 wk双氯芬酸引起的小肠损伤, 但是米索前列醇会引起难以耐受的不良反应[46]. 研究[47]显示, 云母可以防治大鼠中双氯芬酸引起的小肠损伤,可能是通过增加EGF的表达而增强了黏膜屏障. H_2S是对消化系有潜在保护作用的物质, 研究显示, 使用一种可以释放H_2S的萘普生衍生物(ATB-346), 即使在很大剂量时也不引起胃黏膜损伤[32]. 在胃黏膜屏障受损的大鼠中使用这种药物也不引起明显的损伤, 而萘普生和塞来昔布则可以引起广泛的出血性损伤[32]. Blacker等[44]研究了ATB-346在诸如关节炎、肥胖、高血压等NSAIDs相关性小肠损伤易感患者中的效果, 结果显示, 患者中无一例引起明显的消化系损伤. 而且, 当与低剂量阿司匹林和PPI联用时, 也不引起明显的小肠损伤, 而萘普生和塞来昔布在同等的剂量下则引起严重的肠道溃疡和出血[44].

4 结论

NSAIDs相关性小肠损伤的发生率高、临床后果严重, 逐渐引起了临床医师的共同关注. 其发病机制尚不明确, 但可以确定的是除了药物本身对环氧合酶的抑制外, 其他多种因素也参与了此病的发生. 目前临床中尚无确切有效的药物, 对其发病机制的探索和理解可以为临床治疗找到新的靶点, 更多的相关的基础和临床研究亟待进行.

应用要点

本文简要阐述了NSAIDs相关性小肠损伤的流行病学及临床表现, 详细介绍了NSAIDs相关性小肠损伤的相关机制研究进展, 并对其治疗方面的进展作了概述, 对理解NSAIDs相关性小肠损伤机制有一定的帮助, 对临床治疗有一定的提示作用.

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名词解释

肠肝循环: 指由肝脏排泄的药物, 随胆汁进入肠道再吸收而重新经肝脏进入全身循环的过程, 具有肠肝循环的药物其作用时间一般较长;

细菌内毒素: 革兰阴性细菌细胞外壁层上的特有结构, 即脂多糖, 内毒素有为外源性致热原, 他可激活中性粒细胞等, 使之释放出一种内源性热原质, 作用于体温调节中枢引起发热.

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同行评价

本研究选题紧扣和平民百姓相关的NSAIDs对肠黏膜损伤的机制及药物进展, 选题恰当, 参考文献较新, 值得广大临床医师和基础医学者阅读.