药源性胃肠道出血及其病理机制的研究进展

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摘 要 药源性胃肠道出血是由于药物作用于胃肠道,引发胃肠黏膜糜烂、出血。引发胃肠道出血的常见药物包括非甾体抗炎药、抗血栓药、化疗药、抗菌药等,药物通过破坏胃肠道黏膜屏障、抑制血管生成、破坏机体凝血机制等途径诱发胃肠道出血,临床尚缺乏有效的防治办法。本文从药物临床研究现状和病理机制出发,综述了近5年国内外对药物引发胃肠道出血的研究进展,以期阐释药物引发胃肠道出血的作用特点,为发现防治药源性胃肠道出血的可能策略提供参考和线索。

关键词 胃肠道出血;机制;信号途径;进展

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Advances in drug-induced gastrointestinal bleeding and its pathological mechanism

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Abstract Drug-induced gastrointestinal bleeding is caused by drugs acting on the gastrointestinal tract, which damages the gastrointestinal mucosa causing erosion and ulceration. Many drugs can cause gastrointestinal bleeding including non-steroidal anti-inflammatory drugs, antithrombotic drugs, chemotherapy drugs, and antibacterial drugs, drugs induced gastrointestinal bleeding by destroying gastrointestinal mucosal barrier, inhibiting of angiogenesis, destroying coagulation mechanism and there are still few prevention methods. This study focused on the clinical research and mechanism of drugs. The research in recent 5 years were reviewed to illustrate drug-induced gastrointestinal bleeding, so as to illustrate the characteristic actions of drug and provide some references and clues for the prevention of drug-induced gastrointestinal bleeding.

Key words gastrointestinal bleeding; mechanism; signaling pathway; advances

胃肠道出血典型临床表现是便血,其中一半的患者会出现贫血和血液动力学改变。随着人口老龄化及各种药物的广泛应用,胃肠道出血发病率有所上升,30岁以后发病率增加200倍。胃肠道出血作为最常见的急症之一,10万胃肠道出血患者中约20~35人需要住院治疗,住院期间出血发生率急增至23.1%,病死率为2.5%~3.9%,1年后再出血率为13%~19%[1-3]。

药物口服经胃肠道吸收后在全身发挥作用,或直接作用于胃肠道,因而药物最易引发胃肠道不良反应。药物损伤胃肠道黏膜及血管,或使凝血机制发生障碍从而引起出血,药物所致出血是引起胃肠道出血的常见原因,常见的药物有非甾体抗炎药、抗血栓药、化疗药、抗菌药等,其中非甾体抗炎药引

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发的胃肠道出血占一半以上,目前临床尚缺乏改善药源性胃肠道出血的有效方法。本文综述了近5年国内外对药物引发胃肠道出血的研究进展,以期为药源性胃肠道出血的防治提供参考依据和线索。

1.1 非甾体抗炎药诱发的胃肠道出血

非甾体抗炎药(NSAID)是临床常用的解热镇痛抗炎药,超过3 000万人每天服用NSAID,但胃肠道副反应多,尤以胃肠道出血和穿孔为严重。长期使用NSAID,环氧合酶(COX)的合成被抑制,导致前列腺素生成减少,从而对胃肠黏膜造成损伤[4]。临床观察发现,4 728名服用NSAID的60岁以上老年患者,其中928名患者出现胃肠道出血(19.6%),统计分析发现,许多因素与NSAID引起的胃肠道出血有关,消化性溃疡病史(OR = 4.068)、心脑血管疾病病史(OR = 1.476)、糖尿病病史(OR = 1.408)、与抗血小板药物联用(OR = 3.106)、幽门螺杆菌感染(OR = 1.312)是最重要的危险因素[5]。肠内窥镜评估402例肠道出血个体中,49例被诊断为由NSAID引起。NSAID引起肠病患者的再出血率为20.4%,平均持续时间为23.4个月,统计分析发现,年龄≥65岁以上、未使用黏膜保护剂是引起再出血的危险因素[6]。长期低剂量阿司匹林(LDA,75 ~ 325 mg/d)的患者一年内胃肠道出血发生率显著高于对照组(HR = 2.75,95% CI = 2.066 ~ 3.65)[7];LDA显著增加胃肠道出血风险(RR = 1.4,95% CI = 1.2 ~ 1.7),在治疗前两个月胃肠道出血风险最高,停用LDA的患者胃肠道出血风险显著降低(RR = 0.71,95% CI = 0.42 ~ 1.2),LDA与其他非甾体抗炎药、氯吡格雷和选择性血清素再摄取抑制剂联用增加出血风险[8]。通过分析3 785例胃肠道出血的患者,其中901例(23.80%)患者最近(<30 d)服用NSAID,包括高剂量阿司匹林(>500 mg/d),服用NSAID的患者胃肠道出血风险显著增加(RR = 4.86,95% CI = 4.32 ~ 5.46)[9]。通过随访295例服用LDA致胃肠道出血患者,随访时间为5年,其中39例患者被确诊患有复发性胃肠道出血,与停用LDA患者相比,继续服用LDA致复发性胃肠道出血风险增加近3倍(SHR = 2.76,95% CI = 1.26 ~ 6.07),但同时显著降低严重心血管事件发生率(SHR = 0.33,95% CI = 0.17 ~ 0.63)[10]。细胞色素P450 2C9酶(CYP2C9)是NSAID重要的代谢酶,CYP2C9基因具有多态性,研究发现,与携带CYP2C9 * 2的个体相比,携带CYP2C9 * 3基因型的个体服用NSAID更易发生胃肠道出血,CYP2C9 * 3基因突变时NSAID相关胃肠道出血风险增加,而CYP2C9 * 2基因突变没有这种效应。对于CYP2C9 * 3基因突变的个体应合理调整用药剂量,降低胃肠道出血发生风险[11]。质子泵抑制剂(PPIs)常用于减轻NSAID引起的胃十二指肠损伤,它降低LDA上消化道出血风险(OR = 0.27,95% CI = 0.16 ~ 0.43)[12],但是可以通过改变肠道微生物群加重阿司匹林诱导的小肠出血[13]。

实验研究表明,双氯芬酸(4 mg/kg,14 d)通过下调occludin表达破坏大鼠肠道上皮屏障,随后通过激活TLR-4/MyD88/NF-κB信号通路上调肿瘤坏死因子-α(TNF-α)、白介素-1β(IL-1β)等炎症因子水平和髓过氧化物酶(MPO)活性引起回肠黏膜出血等病理损伤[14]。吲哚美辛(200 μmol/L)通过上调pVHL表达,促进缺氧诱导因子-1(Hif-1α)降解诱导小肠隐窝上皮细胞(IEC6)细胞活力下降;小鼠经口给予吲哚美辛(10 mg/kg,3 d)通过诱导pVHL表达增加介导Hif-1α降解,引起小鼠小肠出血等病理学损伤[15],并抑制小肠远端区域的收缩活动,对肠组织的损伤依赖于胆汁分泌,并能促进肠球菌的过度生长[16-17]。洛索洛芬钠(60 mg/kg,5 d)引起大鼠空肠和回肠出血性病变,谷氨酸钠促进VEGF的表达和血管生成,改善洛索洛芬钠引起的小肠损伤[18]。阿司匹林(200 mg/kg,5 d)通过下调COX-1/2表达抑制PGE_2生成,抑制β-catenin信号转导,从而抑制小肠上皮细胞增殖和分化,导致小肠组织紧密连接蛋白ZO-1表达降低,破坏小鼠肠道屏障,引起小肠黏膜损伤;瑞巴派特(rebamipide)可改善肠道屏障结构,促进小肠上皮细胞再生,降低COX-2表达和β-catenin积累改善阿司匹林诱导肠黏膜损伤出血[19]。

1.2 抗血栓药诱发的胃肠道出血

1.2.1 口服抗凝血药诱发的胃肠道出血

口服抗凝血药(OACs)通过影响凝血过程不同环节,阻止血液凝固,可用于预防脑卒中或其他血栓性疾病,但可诱发原有胃十二指肠溃疡出血,还可直接导致胃肠黏膜出血。胃肠道出血是接受维生素K拮抗剂(VKA)治疗的常见并发症,每年发生率高达4% ~8%,根据胃肠道出血的严重程度患者可能需要

临时或永久停药。研究发现,胃肠道出血后 1 周恢复 VKA 用药出血复发风险增加(HR = 2.5,95% CI = 1.4 ~ 4.5),恢复用药的最佳时期在 3 ~ 6 周[20]。

与传统 VKA 相比,新型口服抗凝药(NOACs)直接抑制凝血因子而发挥抗凝作用。通过随访 742 名服用达比加群酯(110 mg/d)的 65 岁以上非瓣膜性心房颤动(NVAF)患者,平均随访时间为 1.8 年,胃肠道出血发生率为 0.75%[21]。试验纳入 143 例同时服用利伐沙班与地尔硫䓬的 NVAF 患者作为病例组,中位随访时间 12.4 个月;纳入 143 例服用利伐沙班的 NVAF 患者作为对照组,随访时间 16.5 个月,病例组胃肠道出血发生率为 23.1%,对照组胃肠道出血发生率为 28%,说明使用地尔硫䓬不增加胃肠道出血风险[22]。

研究发现,与 VKA 相比,使用 NOACs 治疗房颤(AF)患者胃肠道出血风险增加 2 倍(HR = 2.63,95% CI:1.50 ~ 4.62),进一步分析可知增加的出血风险仅限于女性[23]。服用华法林的 153 例患者胃肠道出血发生率 8%;服用利伐沙班(>10 mg/d)的 147 例患者胃肠道出血发生率 9.8%[24]。达比加群酯引发(150 mg,每天 2 次)胃肠道出血的发生率较华法林高(1.56% *vs* 1.07%;*P* = 0.001,RR = 1.48,95% CI = 1.18 ~ 1.85),剂量减半后胃肠出血发生风险降低(1.56% *vs* 1.15%),此时与华法林相比,差异无统计学意义[25]。通过分析患有 NVAF 的老年患者,与华法林相比,达比加群酯增加胃肠道出血风险(HR = 1.28,95% CI = 1.14 ~ 1.44)[26]。

实验研究表明,华法林(3.5 mg/L,30 d)上调髓过氧化物酶(MPO)、丙二醛(MDA)水平,下调过氧化物歧化酶(SOD)诱导肠道氧化应激损伤;上调促炎因子 IFN-γ、IL-17 水平诱导大鼠肠组织白细胞浸润和炎症反应;抑制肠系膜淋巴结细胞增殖,引起肠出血[27]。

1.2.2　抗血小板聚集药诱发的胃肠道出血　抗血小板聚集是血栓栓塞性疾病防治的重要措施,临床常采用阿司匹林联合氯吡格雷进行双重抗血小板治疗(DAPT),由抗血小板药引发的胃肠道出血临床常见。随访 549 例服用 P2Y12 抑制剂出现不良反应的患者,其中氯吡格雷致胃肠道出血发生率最高(PRR = 4.56,95% CI:4.34 ~ 4.78)[28]。在中国人群中,与阿司匹林单独用药相比,阿司匹林与氯吡格雷联合用药能降低脑卒中复发风险(RR = 0.55,95% CI = 0.34 ~ 0.89)且不增加出血风险[29]。

急性冠状动脉综合征(ACS)患者或接受经皮冠状动脉介入治疗(PCI)患者推荐使用阿司匹林联合氯吡格雷或其他抗血小板药物进行抗血栓治疗。被诊断为心房颤动(AF)的个体在 ACS 或 PCI 后推荐使用 OACs 与 DAPT 进行三重抗栓治疗(TT)。研究发现,与服用阿司匹林或氯吡格雷进行单独抗血小板治疗相比,DAPT(ARR = 3.13,95% CI = 2.64 ~ 3.72)和 TT(ARR = 4.85,95% CI = 1.51 ~ 15.57)治疗的患者胃肠道出血风险显著增加[30]。胃肠道出血是冠状动脉疾病(CAD)患者服用抗血栓药物最常见的并发症。通过分析有胃肠道出血症状的 716 例 CAD 患者,与接受阿司匹林进行单抗治疗的 CAD 患者相比,TT 在 90 d 和 180 d 病死率显著增加[31]。通过分析 2 528 例患有胃肠出血的个体,其中 917 例个体服用抗凝或抗血小板药进行抗血栓治疗,与未接受抗血栓药治疗的对照组相比,抗血小板药会增加个体胃肠道再出血风险[32]。

新近实验研究显示,阿司匹林通过抑制血栓素 A2(TXA2)的合成,抑制血小板活化,导致原有溃疡出血[33]。ADP 受体拮抗剂氯吡格雷(2、10 mg/kg,4 d)通过抑制 VEGF-VEGFR-ERK 信号通路,降低 VEGF 表达水平抑制溃疡组织血管生长并延缓溃疡的修复;氯吡格雷(1×10^{-6} mol/L)抑制 VEGF-VEGFR-ERK 信号通路抑制 HUVEC 增殖[34]。替卡格雷(10、20 mg/kg,7 d)通过抑制 VEGF-ERK 信号转导途径抑制血管生成从而增加大鼠实验性胃溃疡面积,延缓胃溃疡愈合[35]。

1.3　化疗药诱发的胃肠道出血

化疗药通常剂量大且疗程长,对胃肠道的损伤十分常见。达沙替尼(dasatinib)治疗慢性粒细胞白血病患者(CML)出现出血性结肠炎不良反应事件[36];通过 ROCK 途径磷酸化 MLC,激活 myosin Ⅱ活性诱导 F-actin 结构发生聚合现象,引发小肠出血[37]。通过随访接受伊布替尼治疗的 111 例套细胞淋巴瘤(MCL)患者,中位随访时间为 26.7 个月,其中最常见的血液学不良事件是血小板减少(22%)和贫血(18%)[38]。血管生成抑制剂贝伐

单抗治疗大肠癌患者期间出血风险显著增加(RR = 1.96,95% CI = 1.27 ~ 3.02)[39-40]。据报道,依维莫司和瑞格非尼治疗期间出现胃肠道出血[41-43]。

实验研究显示,甲氨蝶呤(MTX,20 mg/kg,4 d)通过降低SOD、谷胱甘肽过氧化物酶(GSH-Px)活性和上调MDA水平诱导氧化应激反应及活化NF-κB/p65引起大鼠严重肠组织病理学损伤,包括肠黏膜糜烂、炎性细胞浸润、坏死和出血[44]。与野生鼠相比,MTX(40 mg/kg,4 d)破坏TLR2 KO鼠肠上皮屏障完整性,上调基质金属蛋白酶mRNA表达,诱导肠组织细胞凋亡增加。TLR2介导p-gp外排MTX以降低细胞内药物浓度和减轻药物毒性。缺乏TLR2信号转导加重MTX诱导小肠损伤可能与p-gp活性和表达降低有关[45]。5-氟尿嘧啶(5-FU,250 mg/kg,3 d)显著上调CXCL4表达,CXCR3是CXCL4的功能性受体,与野生鼠相比,5-FU诱导的CXCR3 KO鼠小肠组织细胞凋亡减少,CXCL4通过与CXCR3结合诱导p38-MAPK激活,从而诱导p53和Bax表达促进细胞凋亡[46]。顺铂(CDDP,10 mg/kg,1 d)降低小鼠紧密连接蛋白ZO-1和occludin表达破坏肠道通透性,通过活化NF-κB和ERK1/2上调TNF-α、MPO等炎症因子水平从而促进肠道炎症反应,引起肠道损伤[47]。

1.4 抗菌药诱发的胃肠道出血

抗菌药对胃肠黏膜直接造成损伤,多种抗菌药物均能诱发胃肠道出血。β-内酰胺类抗生素引起胃肠道出血的作用机制是通过抑制肠道内产生维生素K的菌群,导致维生素K缺乏,阻断维生素K依赖性凝血过程,进而引发胃肠道出血。肺炎患者接受静脉滴注头孢哌酮(4.5 g,每天2次,7 d)治疗时出现上消化道出血,停用头孢哌酮并接受维生素K1(40 mg,3 d)治疗后凝血功能改善,血肿消失[48]。糖尿病患者接受头孢拉定(2 g,5 d)治疗时上消化道出血,停用头孢拉定并接受维生素K(10 mg,1 d)治疗后凝血功能改善[49]。头孢曲松(100 mg/kg,21 d)降低新生小鼠肠道组织ZO-1表达,上调Muc2表达损伤肠道屏障;降低总细菌浓度但升高细菌丰富度和多样性,干预肠道菌群的构建[50]。磺胺类药物甲氧苄氨嘧啶(TMP)与磺胺甲噁唑(SMZ)联用引起患者维生素K缺乏,阻断维生素K依赖性凝血过程,进而引发胃肠道出血,接受维生素K(10 mg,2 d)治疗后凝血功能改善[51]。氟喹诺酮属于喹诺酮类抗菌药,研究发现它显著增加个体胃肠穿孔发生风险(RR = 1.9,95% CI = 1.34 ~ 1.59),在70岁以上及男性患者中发生风险更大[52]。

1.5 其 他

患者因服用抗抑郁药5-羟色胺再摄取抑制剂发生胃肠道出血的概率为0.31[53],可能是通过抑制血小板聚集引发出血[54]。使用皮固醇住院患者胃肠道出血风险增加40%(OR = 1.43,95% CI = 1.22 ~ 1.66)[55]。免疫抑制剂通过抑制溃疡愈合诱发消化道出血(OR = 5.83,P = 0.03)[56]。成纤维细胞生长因子-2(FGF2,5×10^8 pfu)与戊聚糖聚硫酸钠(PPS,60 mg/kg,7 d)联用增加小鼠小肠血管渗漏性,引发肠出血,血管生成素-1(Ang-1,5×10^8 pfu)可预防并发症[57]。霉芬酸酯(5 ~ 100 μmol/L,3 d)可能通过诱导MLC2的磷酸化和破坏ZO-1、occludin结构从而降低跨上皮细胞电阻值,破坏Caco-2上皮细胞屏障引起肠损伤[58]。

2 总结与展望

上述研究显示,临床应用非甾体抗炎药、抗血栓药、化疗药、抗菌药等可引起严重的胃肠道出血,多条信号途径参与其病理机制,包括激活线粒体应激、激活内质网应激、激活NF-κB通路、激活ROS产生、促进细胞骨架重构、抑制VEGF生成、抑制TXA2合成、抑制维生素K合成等(图1)。目前报道的药源性胃肠道出血所涉及的关键分子有VEGF、COX1/2、NF-κB、ROCK、MLC等,有望成为药源性胃肠道出血防治的潜在靶标。

与单独用药相比,联合用药增加胃肠道出血发生风险,个体年龄、性别、基因差异、用药剂量、幽门螺杆菌感染、消化性溃疡等病史都是影响胃肠道出血的危险因素(表1)。大多数胃肠道出血需停药并给予治疗,但恢复用药会增加胃肠道再出血风险。临床实践中应该正确评估胃肠道出血相关的风险因素,为患者带来更大的获益。质子泵抑制剂常用于减轻非甾体抗炎及抗血小板药引起的胃十二指肠损伤,但是它可以加重阿司匹林诱导的小肠出血。目前临床尚缺乏对于药物引发胃肠道出血的有效防治办法,因此从临床应用的

具有止血、屏障保护和调节相关信号通路的中成药制剂及其有效成分中,开发出防治胃肠道出血的药物或先导化合物,具有广阔的应用前景,值得进一步深入研究。

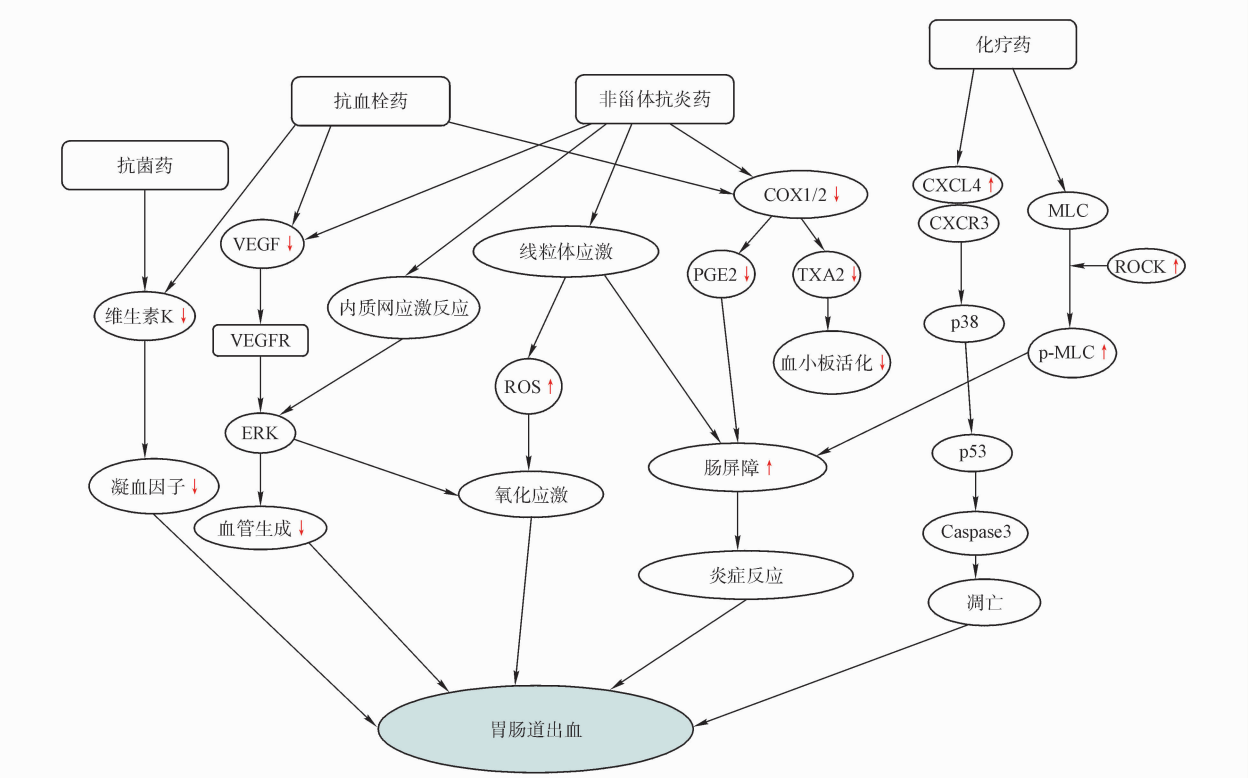

图 1　药物引起胃肠道出血的信号通路图(↑促进;↓抑制)

表 1　药物引起胃肠道出血的风险因素及作用机制

药　物	风险因素	作用机制	参考文献
非甾体抗炎药	消化性溃疡病史,心脑血管病史,糖尿病史,与抗血小板药联用,幽门螺杆菌感染		[5]
阿司匹林	年龄,未使用黏膜保护剂		[6]
	CYP2C9 * 3 基因突变		[11]
	与其他非甾体抗炎药、氯吡格雷合用恢复用药		[8]
		下调 COX-1/2;抑制 β-catenin 信号转导	[10]
双氯芬酸		抑制血栓素 A_2 的合成	[19]
		TLR4-MyD88-NF-κB 信号通路	[33]
吲哚美辛		上调 pVHL 表达促进 hif-1α 降解	[14]
达比加群酯			[15]
华法林	年龄,性别,剂量	上调 MPO,MDA,下调 SOD	[21,23,25,27]
氯吡格雷	与抗血栓药联用	VEGF-VEGFR-ERK 信号通路	[30 – 32]
达沙替尼		激活 ROCK/MLC	[34]
甲氨蝶呤		下调 SOD,上调 MDA	[37]
5-氟尿嘧啶		上调 CXCL4 表达;诱导 p38-MAPK 激活	[46]
顺铂		下调 ZO-1,Occuludin 表达;活化 NF-κB,ERK1/2	[47]

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