

多糖类抗血栓药物舒洛地特与低分子肝素的多方位比较分析

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摘要 目的: 舒洛地特与低分子肝素都是多糖类抗血栓药物, 多方位比较二者的异同, 对监管提出建议。方法: 从构效关系入手, 探讨质控基本要求, 对作用机理、临床应用、不良反应等多方位进行全面梳理并比较二者的抗凝、抗血栓强度及临床应用价值。结果与结论: 舒洛地特与低分子肝素作为抗血栓药物, 二者抗血栓作用相当, 抗凝作用舒洛地特比低分子肝素强, 并且无出血风险。由于多组分多糖类药物质量控制难度较大, 本文提出对原料药和制剂的监管需要从起始物料源头开始, 参照生物类似药进行生产全过程质量控制, 以保证多糖类药物的质量稳定、安全有效。

关键词: 舒洛地特; 低分子肝素; 抗凝; 抗血栓; 质量控制

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Multi-dimensional Comparison between Sulodexide and Low Molecular Weight Heparin of Polysaccharide Antithrombotic Drugs

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Abstract Objective: To compare the similarities and differences between sulodexide and low molecular weight heparin from multiple perspectives, both of which are polysaccharide antithrombotic drugs, and to provide recommendations for regulation. **Methods:** Starting from the structure-activity relationship, we explored the basic requirements for quality control, comprehensively sorted out the mechanism of action, clinical application, adverse reactions, and other aspects, and compared the anticoagulation, antithrombotic strength, and clinical application value of the two. **Results and Conclusion:** As antithrombotic drugs, sulodexide and low molecular weight heparin have similar antithrombotic effects. The anticoagulant effect of sulodexide is stronger than that of low molecular weight heparin, and there is no risk of bleeding. Due to the difficulty in quality control of multi-component polysaccharide drugs, this article proposes that the supervision of APIs and preparations should start from the source of starting materials, and refer to the entire production process quality control of biosimilars to ensure the stability, safety and effectiveness of the quality of polysaccharide drugs.

Keywords: sulodexide; low molecular weight heparin; anticoagulation; antithrombotic; quality control

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舒洛地特 (Sulodexide) 与低分子肝素 (Low Molecular Weight Heparin, LMWH) 都是源自猪肠粘膜提取的糖胺聚糖 (Glycosaminoglycan, GAG), 属于多糖类, 作为抗血栓药物有超过30多年的临床用药历史^[1-6]。LMWH由肝素解聚得到, 根据生产工艺、末端结构和分子量等进行分类分级。已有依诺肝素钠、达肝素钠、那曲肝素钠、贝米肝素钠、低分子量肝素钠等LMWH类产品获准进口中国。除贝米肝素钠外, 其他LMWH均有多家国内企业仿制药获准上市^[7-9]。舒洛地特由意大利ALFA WASSERMANN S.p.A. (现更名为ALFA SIGMA S.p.A.) 研发生产, 2003年获准进口中国, 国内有多家单位正在仿制中^[10-12]。舒洛地特与低分子肝素相比在抗血栓及临床应用方面有哪些异同? 对其质量控制等监管有哪些要求? 本文从构效关系入手, 探讨质控基本要求, 对作用机理、临床应用、不良反应等多方位进行全面梳理并比较二者的抗凝、抗血栓强度及临床应用价值, 论证二者的差异和各自特点, 对质量控制提出建议。

1 构效关系

糖胺聚糖 (GAG) 的糖链是由己糖醛酸或半乳糖与糖醛胺连接的重复二糖单元组成的长链多糖, 包括肝素、硫酸皮肤素 (Dermatan Sulfate, DS) 等。肝素也叫未分级肝素 (Unfractionated Heparin, UFH), 分子量5~40 kDa, 平均15~19 kDa^[13], 经过各种化学法或酶法降解得到的LMWH^[14], 分子量在8 kDa以下, 保留了肝素糖链的核心五糖特定位点, 与抗凝血酶Ⅲ (Antithrombin Ⅲ, AT-Ⅲ) 结合而抑制活化X因子 (FXa), 产生抗血栓作用, 而与糖链长度无关。只有当肝素糖链长度大于18个糖单元, 分子量大于5 kDa时, 即与AT-Ⅲ结合同时又与活化Ⅱ因子 (FⅡa) 也叫凝血酶非特异性结合在同一糖链上而抑制FⅡa, 具有抗凝作用, 因此UFH的抗FXa因子与抗FⅡa活性比为1:1, 抗凝作用强^[15-16]; 而LMWH糖链片断较短, 大部分长度均低于18个单糖, 抗FXa/抗FⅡa之比 >1.5 ^[16], 抗凝作用弱。如依诺肝素, 平均分子量4.5 kDa, 抗FXa/抗FⅡa之比为3.8^[14]; 贝米肝素平均分子量3.6 kDa, 抗FXa/抗FⅡa之比高达8.0, 具有最低分子量、最高抗FXa/抗FⅡa活性比之称^[17], 因此抗FXa/抗FⅡa之比是考量LMWH抗血栓作用和质量标准中的重要指

标之一, 比值越高表明其抗凝作用越弱而抗血栓作用越强; 同时糖链长短、分子量大小都与抗血栓作用密切相关, 也是质控的重要项目之一。

舒洛地特是多组分、纯天然、高纯度GAG药物, 含80%快速迁移肝素 (Fast Moving Heparin, FMH) (基于电泳迁移率)^[18], 平均分子量7 kDa, 糖链结构与LMWH一样, 但硫酸化程度较低, 部分硫酸根被乙酰基替代, 也被称为低分子量的硫酸乙酰肝素 (Heparan Sulfate, HS), 可与AT-Ⅲ结合而抑制FXa具有抗血栓作用, 同时因糖链长度大于18个糖单元片段, 比LMWH多, 抗FⅡa即抗凝作用比LMWH强; 另外还含有20%硫酸皮肤素 (Dermatan Sulfate, DS), 可与肝素辅因子Ⅱ (Heparin Cofactor Ⅱ, HCⅡ) 结合, 快速抑制凝血酶活性, FMH促进DS与HCⅡ的结合, 由于同时存在对AT-Ⅲ有亲和力的FMH和对HCⅡ有亲和力的DS, 二者协同增效^[19-22], 理论上抗血栓作用舒洛地特应比LMWH更强^[23]。由于多一组分DS, 质控要求更高, 对FMH和DS的结构确认、含量、相对分子量及其分布、抗FXa活性等都是质量监控的主要项目。

2 作用机理的异同

2.1 LMWH

2.1.1 抗血栓作用

LMWH与AT-Ⅲ结合, 引起AT-Ⅲ局部构象变化, 又与FXa特异结合使FXa自溶, 抑制FXa活性并阻止了FXa进一步催活凝血酶, 发挥抗血栓作用; LMWH还可增加血细胞表面及血管壁负电荷, 防止血小板聚集, 预防血栓形成^[24-25]。

2.1.2 抗凝作用

LMWH中少量糖链大于18个单糖的部分, 与AT-Ⅲ结合同时与FⅡa非特异结合使凝血酶灭活; 同时通过抑制FXa继而抑制凝血酶的生成途径, 对已产生的凝血酶没有抑制作用, 因此LMWH抗凝作用弱。人体试验测得依诺肝素的活化部分凝血酶时间 (Activated Partial Thromboplastin Time, APTT) 仅为UFH的1/4^[26], 表明其抗FⅡa抗凝作用远低于UFH, 并且不能被鱼精蛋白中和。

2.2 舒洛地特

2.2.1 抗血栓作用

舒洛地特与LMWH相似, 同为与AT-Ⅲ结合, 抑制FXa活性, 发挥抗血栓作用。质量标准中的抗

FXa活性：依诺肝素为 $100 \text{ IU} \cdot \text{mg}^{-1}$ ，舒洛地特为 $70 \sim 100 \text{ IU} \cdot \text{mg}^{-1}$ ，两者的抗FXa活性即抗血栓作用几乎相等。由于舒洛地特的FMH组分为低分子硫酸乙酰肝素，对血管内皮细胞有高度亲和力，可抑制血小板聚集和粘附，降低血浆纤维蛋白原浓度，增加组织纤溶酶原激活因子（Tissue Plasminogen Activator, t-PA）以及全身纤溶和溶栓活性^[27-28]；舒洛地特还含有DS成分，已证实可抑制基质金属蛋白酶（Matrix Metalloproteinase, MMP）家族尤其是MMP 9的表达，MMP 9可增加血管内皮细胞的通透性，降解细胞外基质（Extracellular Matrix, ECM）和糖萼，加速细胞凋亡，影响血管和微血管张力^[29]。在一项体外细胞培养的试验中，显示在人全血中舒洛地特呈剂量依赖性显著抑制MMP 9的表达，并且这种抑制作用仅有FMH无效，含有DS成分才有效^[30-32]。MMPs抑制剂已成为预防和治疗动脉粥样硬化、心血管病的新靶点^[33]。舒洛地特溶栓作用在大鼠静脉血栓模型（腔静脉结扎）动物试验中得到证实，对6 h前形成血栓的大鼠注射 $2 \text{ mg} \cdot \text{kg}^{-1}$ 舒洛地特，结果显示血栓重量显著减少，2 h后血栓减小了70%^[34]。舒洛地特的多重机制抗栓、溶栓及其两个成分协同增效作用都预示抗血栓作用舒洛地特比LMWH强。

2.2.2 抗凝作用

舒洛地特比LMWH具有更强的抗凝和抑制血小板聚集的作用，一方面糖链长度大于LMWH，大于18个单糖的部分多，可直接与AT-III和F II a同时结合而抑制凝血酶，另一方面舒洛地特从内皮中动员内源性组织因子（Tissue Factor, TF）抑制血小板活化、聚集。舒洛地特含有20%DS与HC II结合，快速抑制凝血酶活性，协同增效，进一步增强其抗凝作用。体外试验证实舒洛地特比依诺肝素的APTT延长1倍（ $p < 0.01$ ），血小板聚集形成率仅是其1/5，表明抗凝作用舒洛地特强于依诺肝素，并可被鱼精蛋白中和，可作为肝素的替代品^[35-36]。

2.2.3 对血管内皮修复、糖萼的保护作用

内皮糖萼（Endothelial Glycocalyx, EG）是一层网状苔藓样组织，覆盖于血管内皮细胞管腔面，由GAG、蛋白聚糖（Proteoglycans）和膜糖蛋白（Glycoproteins）等构成，GAG侧链为透明质酸、硫酸软骨素、HS等，维持血管内皮细胞的屏障和

渗透性^[37-39]。当糖萼层变薄、脱落时，会导致血管通透性增加、炎症细胞迁移、降低抗凝机制等，体外试验和人体试验都证实之，而舒洛地特可显著增加细胞活力，减少细胞凋亡^[40]，及可测量到糖尿病患者的舌下及视网膜血管糖萼层厚度显著增加^[41]。糖萼的恢复需要HS的生物合成参与，外源性补充糖萼成分可有效帮助修复受损的糖萼，而舒洛地特80%组分为低分子HS，是提供HS前体制剂，可为糖萼修复提供物质来源，起到对血管内皮修复、糖萼的保护作用。

2.2.4 多效性

舒洛地特具有多种生物活性，包括脂肪酶活性 $\geq 10 \text{ LRU} \cdot \text{mg}^{-1}$ 、抗F II a活性 $< 100 \text{ IU} \cdot \text{mg}^{-1}$ 、抗FXa活性 $70 \sim 100 \text{ IU} \cdot \text{mg}^{-1}$ 、HC II $\approx 180 \text{ U} \cdot \text{mg}^{-1}$ 、APTT $< 50 \text{ U} \cdot \text{mg}^{-1}$ 等^[27]，这种多效性和广谱性是LMWH所没有的。随着研究深入，更多报道舒洛地特的多效性，尤其作为修复血管内皮靶点的潜在药物，可改善微循环、抑制炎症因子异常释放等在临床应用重新焕发活力^[42-43]。

3 临床应用

3.1 LMWH

自1980s上市以来LMWH临床应用最多的是预防和治理静脉血栓栓塞（Venous Thromboembolism, VTE），已逐渐取代肝素。VTE临床表现为深静脉血栓（Deep Vein Thrombosis, DVT）或肺栓塞（Pulmonary Embolism, PE）死亡率较高。2019年对全球580个LMWH的临床试验进行总结分析，其中DVT的临床试验研究占42%，其次是癌症22%，冠状动脉疾病10%，流产和妊娠9%，肾功能不全8%^[14]。因癌症与高凝状态有关，LMWH可预防和治理癌症相关血栓形成^[44-45]。心肌梗死是缺血性心脏疾病，主要是由于冠状动脉供血严重不足或者完全性闭塞所造成，引发心绞痛，LMWH可治疗不稳定型冠状动脉疾病，包括不稳定型心绞痛和非Q波型心肌梗死^[46-47]。妊娠期的易栓症可致反复自然流产，因LMWH不能穿过胎盘，因此不会导致胎儿出血或畸形，是妊娠期PE的首选药物^[48-49]。肾功能不全是由肾小球内凝血损伤肾小球，采用LMWH抗凝抗血栓治疗^[50-51]。因LMWH只能静脉和皮下注射，因此方便的直接口服抗凝剂已逐渐取而代之成为首选，LMWH的临床应用价值

受到挑战^[52-53]。

3.2 舒洛地特

舒洛地特除可静脉和肌肉注射外还可以口服,比LMWH有更长的半衰期,口服生物利用度40%,肌肉注射生物利用度90%^[19]。临床主要应用于抗静脉和动脉血栓^[54-55],对复发性VTE的二级预防,首选药是舒洛地特^[56-57]。2019年欧洲心脏病学会(European Society of Cardiology, ESC)发布的急性肺栓塞的诊断治疗指南,舒洛地特是延伸治疗的首选项^[54-58]。慢性静脉疾病(Chronic Venous Disease, CVD)、慢性静脉机能不全(Chronic Venous Insufficiency, CVI)是由于静脉高压、微循环淤滞、形成毛细血管微血栓,损害了血管内皮糖萼,引起促炎反应涉及各种细胞因子和MMPs等的释放,造成静脉壁和静脉瓣膜功能改变,引发静脉曲张、下肢静脉性溃疡等。舒洛地特的治疗有效,正是依靠其血管内皮修复、重建糖萼功能,抑制炎症因子释放,改善毛细血管通透性以及纤溶抗栓作用,恢复微循环^[59-60],已得到大量临床研究证实^[61-62]。

舒洛地特在治疗动脉疾病方面也有显著疗效。糖尿病肾病(DN)临床标志是尿蛋白增加,是由于血管内皮功能不全引发肾脏的血流动力学改变,舒洛地特具有修复血管内皮、抗栓功能,可显著减少糖尿病人的尿蛋白,治疗由肾小球内凝血损伤肾小球引起的肾功能不全,预防糖尿病引起的残疾,已得到临床验证^[63-64]。

当COVID-19肆虐时,重症和死亡主要原因为多器官功能障碍、广泛性炎症和全升高凝导致的血栓^[65-66],因新型冠状病毒(SARS-CoV-2)感染引发广泛和严重的血管内皮功能紊乱,因此血管内皮成为防治COVID-19的靶点^[67-69]。2022年国际血栓和止血学会(ISTH)将抗血栓药物纳入最新治疗COVID-19指南^[70],认为COVID-19患者可获得额外益处,可降低重症患者的血栓栓塞风险,尤其推荐非住院病人服用舒洛地特,舒洛地特可替代LMWH防治COVID-19引起的栓塞并发症^[67]。临床试验表明舒洛地特可防止重症,减少患者住院天数,是有效的血管内皮保护剂^[71-73]。

4 两者的不良反应差异

LMWH比UFH安全性高,出血副作用小,较少产生肝素诱导的血小板减少症,但仍有不良反应

报道^[74]。有报道患者在注射了依诺肝素后,出现腹膜后血肿和腹腔室综合征、肝素诱导的血小板增多症、肝素诱导的皮肤坏死、大疱性出血性皮炎等,仍需要监测FXa水平^[75-77]。

舒洛地特不仅可以注射还可口服,无需监测FXa水平,几乎没有出血风险^[78],具有良好的安全性,尚无报告非预期的严重不良反应,没有发现新的安全性风险信息,也未见监管机构暂停或限制销售,因此安全性优于LMWH。

5 质量控制异同

LMWH类细分有10余个品种,欧洲药典收载5个^[79],分别为达肝素钠(Dalteparin Sodium)、依诺肝素钠(Enoxaparin Sodium)、那曲肝素钙(Nadroparin Calcium)、帕肝素钠(Parnaparin Sodium)和汀肝素钠(Tinzaparin Sodium),美国药典收载2个^[80],分别为达肝素钠和依诺肝素钠。不同生产工艺的产品体现出各自的结构特点,具有独特的药理和生物学特征。2010年美国FDA批准了第一个依诺肝素注射液的仿制药^[81],而欧洲药品管理局(European Medicines Agency, EMA)把LMWH归于生物类似药(Biosimilars)^[82]。我国国家药品监督管理局药品审评中心也制定出新策,对生物来源的肝素类新药按生物制品管理,而LMWH仿制药按化药管理,需与原研药对比进行质量一致性评价,并要求历史遗留的国内10余个具有有效批准文号但未细分品种的LMWH产品,结合工艺和关键质量指标,确定其具体分类后,完善相关的质量研究,完成质量一致性评价,以保证产品的安全有效^[9,83]。

舒洛地特是含80%FMH和20%DS的混合物,糖链结构复杂,国内虽有多家在研发或仿制,但目前为止仍无成功申报的企业。舒洛地特质量控制应与LMWH类似,包括对原料药和制剂的监管,原料药制备工艺、结构确证、原料药杂质分析和质量控制、制剂工艺和质量控制等。原料药质量标准中应有糖组成分析、结构确认,相对分子质量及相对分子质量分布,杂质谱分析包括来源于原料的、有可能人为掺入的、工艺杂质、降解产物等^[84-85]。由于是多糖多组分,为不均一的混合物,其制剂质量标准可参照生物类似药对分离的组分要求:FMH含量80%±8%,DS含量20%±8%,慢速移动肝素(Slow Moving Heparin, SMH)不得过4%^[10,18]等,

同时对多组分采用生物效价测定,以效价进行含量表征。由于舒洛地特具有多种生物活性,但因是抗血栓药,因此建议采用抗血栓活性测定方法即生色底物法测定抗FXa效价,该方法比用动物血浆或全血法测定血凝等试验更为专属和简便,自动化程度更高^[8,86]。脂肪酶活性测定方法是测定动物体内活性方法,存在繁琐、耗费动物、误差大等弊病^[87],并且不能完全代表舒洛地特的活性,不能体现抗血栓特性,建议取消。

6 思考与建议

舒洛地特与LMWH同是来源于猪肠黏膜,都是GAG的长链多糖,是有效的抗血栓药物,两者的抗血栓作用即抗FXa活性相近,由于舒洛地特除FMH组分外多一个DS组分,两个成分的抗血栓能力有协同增效作用,理论上应比LMWH作用强,期望进一步临床验证。由于舒洛地特原研生产企业小众,国际上仿制药少,故文献报道的临床数据远少于LMWH,但其安全有效、多机制抗栓、保护血管内皮等功效不可质疑。舒洛地特与LMWH都有多组分不均一的特性,因此建议参照生物类似药的监管,从起始物料源头开始进行控制,明确动物种属来源,保证检验检疫合格,同时对生产工艺步骤进行病毒灭活验证,保证药品的病毒安全,对提取、分离纯化、结构修饰、结构鉴定、相对分子质量及相对分子质量分布、含量及活性测定等环节进行严格的管理和控制,实现全过程、全方位质量控制体系,保证多糖类药物的质量稳定、可靠、安全、有效,最终达到产品质量的一致性。

参考文献:

[1] Bignamini AA, Chebil A, Gambaro G, et al. Sulodexide for Diabetic-Induced Disabilities: A Systematic Review and Meta-analysis[J]. *Adv Ther*, 2021, 38 (3): 1483-1513.

[2] Pompilio G, Nicolaidis A, Kakkos SK, et al. Systematic Literature Review and Network Meta-analysis of Sulodexide and Other Drugs in Chronic Venous Disease[J]. *Phlebology*, 2021, 36 (9): 695-709.

[3] Bignamini AA, Matuška. Sulodexide for the Symptoms and Signs of Chronic Venous Disease: A Systematic Review and Meta-analysis[J]. *Adv Ther*, 2020, 37 (3): 1013-1033.

[4] Their ZT, Drake-Lavelle K, Prest PJ, et al. Progression of Intracranial Hemorrhage After Chemical Prophylaxis Using

Low-Molecular-Weight Heparin in Patients with Traumatic Brain Injury[J]. *Am Surgeon*, 2022, 88 (5): 894-900.

- [5] Fernando SM, Tran A, Cheng W. VTE Prophylaxis in Critically Ill Adults: A Systematic Review and Network Meta-analysis[J]. *Chest*, 2022, 161 (2): 418-428.
- [6] Tran A, Fernando SM, Carrier M. Efficacy and Safety of Low Molecular Weight Heparin Versus Unfractionated Heparin for Prevention of Venous Thromboembolism in Trauma Patients: A Systematic Review and Meta-analysis[J]. *Ann Surg*, 2022, 275 (1): 19-28.
- [7] 李京, 龚益妮, 邓利娟, 等. 达肝素钠注射液质量评价[J]. *药物评价研究*, 2022, 45 (8): 1584-1591.
- [8] 王悦, 范慧红. 多糖类生化药物的质控策略与质控技术研究进展[J]. *中国药学杂志*, 2021, 56 (1): 8-12.
- [9] 石靖, 陈思. 低分子量肝素仿制研究技术要求和监管理念的进展[J]. *国际药学研究杂志*, 2018, 45 (11): 852-857.
- [10] 王亚敏. 舒洛地特研究进展及临床应用[J]. *中国临床药理学与治疗学*, 2010, 15 (1): 109-114.
- [11] 张娟, 冷佳蔚, 李水仙, 等. 舒洛地特注射液非临床安全性评价[J]. *中国药业*, 2021, 30 (6): 28-31.
- [12] 张娟, 魏霞, 李水仙, 等. 舒洛地特原料药安全性检查法研究[J]. *中国药业*, 2019, 28 (14): 22-24.
- [13] 国家药典委员会. 肝素钠[S]/中华人民共和国药典: 二部, 北京: 中国医药科技出版社, 2020: 637-638.
- [14] Hao C, Sun M, Wang H, et al. Low Molecular Weight Heparins and Their Clinical Applications[J]. *Prog Mol Biol Transl*, 2019, 163: 21-39.
- [15] Hemker HC, Al Dieri R, Béguin S. Heparins: A Shift of Paradigm[J]. *Front Med (Lausanne)*, 2019, 6: 254.
- [16] Guerrini M, Bisio A. Low-Molecular-Weight Heparins: Differential Characterization/Physical Characterization[J]. *Handb Exp Pharmacol*, 2012, 207: 127-157.
- [17] Mart í nez-Gonz á lez J, Rodr í guez C. New Challenges for a Second-Generation Low-Molecular-Weight Heparin: Focus on Bemiparin[J]. *Expert Rev Cardiovas*, 2010, 8 (5): 625-634.
- [18] Veraldi N, Guerrini M, Urso E, et al. Fine Structural Characterization of Sulodexide[J]. *J Pharmaceut Biomed*, 2018, 156: 67-79.
- [19] Coccheri S, Mannello F. Development and Use of Sulodexide in Vascular Diseases: Implications for Treatment[J]. *Drug*

- Des Devel Ther, 2013, 8: 49–65.
- [20] Nenci GG. Dermatan Sulphate as an Antithrombotic Drug[J]. Pathophysiol Haemost Thromb, 2002, 32 (5–6) : 303–307.
- [21] Cosmi B, Cini M, Legnani C, et al. Additive Thrombin Inhibition by Fast Moving Heparin and Dermatan Sulfate Explains the Anticoagulant Effect of Sulodexide, a Natural Mixture of Glycosaminoglycans[J]. Thromb Res, 2003, 109 (5–6) : 333–339.
- [22] Cosmi B, Agnelli G, Young E, et al. The Additive Effect of Low Molecular Weight Heparins on Thrombin Inhibition by Dermatan Sulfate[J]. Thromb Haemost, 1993, 70 (3) : 443–447.
- [23] Bendayan P, Boccalon H, Dupouy D, et al. Dermatan Sulfate is a More Potent Inhibitor of Clot-Bound Thrombin than Unfractionated and Low Molecular Weight Heparins[J]. Thromb Haemost, 1994, 71 (5) : 576–80.
- [24] Kher A, Bara L, Samama M. Low Molecular Weight Heparins[J]. Pathol Biol, 1986, 34 (1) : 61–69.
- [25] Bianchini P, Bergonzini GL, Parma B, et al. Relationship between Plasma Antifactor Xa Activity and the Antithrombotic Activity of Heparins of Different Molecular Mass[J]. Haemostasis, 1995, 25 (6) : 288–298.
- [26] Bratt G, Törnebohm E, Lockner D. A Human Pharmacological Study Comparing Conventional Heparin and a Low Molecular Weight Heparin Fragment[J]. Thromb Haemost, 1985, 53 (2) : 208–211.
- [27] Hoppensteadt DA, Fareed J. Pharmacological Profile of Sulodexide[J]. Int Angiol, 2014, 33 (3) : 229–235.
- [28] Coccheri S. Biological and Clinical Effects of Sulodexide in Arterial Disorders and Diseases[J]. Int Angiol, 2014, 33 (3) : 263–274.
- [29] Newby AC. Matrix Metalloproteinase Inhibition Therapy for Vascular Diseases[J]. Vasc Pharmacol, 2012, 56 (5–6) : 232–244.
- [30] Raffetto JD, Yu W, Wang X, et al. Sulodexide Improves Contraction and Decreases Matrix Metalloproteinase-2 and -9 in Veins Under Prolonged Stretch[J]. J Cardiovasc Pharm, 2020, 75 (3) : 211–221.
- [31] Mannello F, Medda V, Ligi D, et al. Glycosaminoglycan Sulodexide Inhibition of MMP-9 Gelatinase Secretion and Activity: Possible Pharmacological Role Against Collagen Degradation in Vascular Chronic Diseases[J]. Curr Vasc Pharmacol, 2013, 11 (3) : 354–365.
- [32] Jguirim-Souissi I, Jelassi A, Najah M, et al. Metalloproteinases: Therapeutic Target in Atherosclerosis[J]. Tunis Med, 2008, 86 (5) : 490–496.
- [33] Barbanti M, Guizzardi S, Calanni F, et al. Antithrombotic and Thrombolytic Activity of Sulodexide in Rats[J]. Int J Clin Lab Res, 1992, 22 (3) : 179–184.
- [34] Adiguzel C, Iqbal O, Hoppensteadt D, et al. Comparative Anticoagulant and Platelet Modulatory Effects of Enoxaparin and Sulodexide[J]. Clin Appl Thromb Hemost, 2009, 15 (5) : 501–511.
- [35] Siddiqui F, Hoppensteadt D, Bontekoe E, et al. Comparative Anticoagulant and Thrombin Generation Inhibitory Profile of Heparin, Sulodexide and Its Components[J]. Clin Appl Thromb-Hem, 2020, 26: 1076029620954913.
- [36] Jedlicka J, Becker BF, Chappell D. Endothelial Glycocalyx[J]. Crit Care Clin, 2020, 36 (2) : 217–232.
- [37] Barry M, Pati S. Targeting Repair of the Vascular Endothelium and Glycocalyx after Traumatic Injury with Plasma and Platelet Resuscitation[J]. Matrix Biol Plus, 2022, 14: 100107.
- [38] Abassi Z, Armaly Z, Heyman SN. Glycocalyx Degradation in Ischemia-Reperfusion Injury[J]. Am J Pathol, 2020, 190 (4) : 752–767.
- [39] Milusev A, Rieben R, Sorvillo N. The Endothelial Glycocalyx: A Possible Therapeutic Target in Cardiovascular Disorders[J]. Front Cardiovasc Med, 2022, 9: 897087.
- [40] Gabryel B, Jarzabek K, Machnik G, et al. Superoxide Dismutase 1 and Glutathione Peroxidase 1 are Involved in the Protective Effect of Sulodexide on Vascular Endothelial Cells Exposed to Oxygen-Glucose Deprivation[J]. Microvasc Res, 2016, 103: 26–35.
- [41] Broekhuizen LN, Lemkes BA, Mooij HL, et al. Effect of Sulodexide on Endothelial Glycocalyx and Vascular Permeability in Patients with Type 2 Diabetes Mellitus[J]. Diabetologia, 2010, 53 (12) : 2646–2655.
- [42] Ligi D, Maniscalco R, Mannello F. New Frontiers for an Old Drug: What Is New on the Pleiotropic Effect of Sulodexide in Chronic Venous Disease[J]. J Cardiovasc Pharm, 2020, 75 (3) : 208–210.
- [43] Andreozzi GM. Editorial: Sulodexide, an Old Drug with

- Recent Renewed Interest[J]. *Curr Vasc Pharmacol*, 2013, 11 (3) : 352–353.
- [44] Hindr é R, Hamdan A, Pastr é J, et al. Treatment of Cancer Associated Thrombosis[J]. *B Cancer*, 2022, 109 (5) : 528–536.
- [45] Christopoulou A, Ardavanis A, Papandreou C, et al. Prophylaxis of Cancer–Associated Venous Thromboembolism with Low–Molecular–Weight Heparin–Tinzaparin: Real world Evidence[J]. *Oncol Lett*, 2022, 23 (4) : 115.
- [46] Zed PJ, Tisdale JE, Borzak S. Low–Molecular–Weight Heparins in the Management of Acute Coronary Syndromes[J]. *Arch Intern Med*, 1999, 159 (16) : 1849–1857.
- [47] Galli M, Andreotti F, D'Amario D, et al. Antithrombotic Therapy in the Early Phase of Non–ST–Elevation Acute Coronary Syndromes: A Systematic Review and Meta–Analysis[J]. *Eur Heart J–Card Pha*, 2020, 6 (1) : 43–56.
- [48] Dias ATB, Modesto TB, Oliveira SA. Effectiveness of the Use of Low Molecular Heparin in Patients with Repetition Abortion History: Systematic Review and Meta–Analysis[J]. *JBRA Assist Reprod*, 2021, 25 (1) : 10–27.
- [49] Zhao L, Bi S, Fu J, et al. Retrospective Analysis of Fondaparinux and Low–Molecular–Weight Heparin in the Treatment of Women with Recurrent Spontaneous Abortion[J]. *Front Endocrinol (Lausanne)*, 2021, 12: 717630.
- [50] Symes J. Low Molecular Weight Heparins in Patients with Renal Insufficiency[J]. *Cannt J*, 2008, 18 (2) : 55–61.
- [51] Atiq F, van den Bemt PM, Leebeek FW, et al. A Systematic Review on the Accumulation of Prophylactic Dosages of Low–Molecular–Weight Heparins (LMWHs) in Patients with Renal Insufficiency[J]. *Eur J Clin Pharmacol*, 2015, 71 (8) : 921–929.
- [52] Tritschler T, Castellucci LA, Van Es N, et al. Treatment of Venous Thromboembolism in Elderly Patients in the Era of Direct Oral Anticoagulants[J]. *Pol Arch Intern Med*, 2020, 130 (6) : 529–538.
- [53] Marcucci M, Etxeandia–Ikobaltzeta I, Yang S, et al. Benefits and Harms of Direct Oral Anticoagulation and Low Molecular Weight Heparin for Thromboprophylaxis in Patients Undergoing Non–Cardiac Surgery: Systematic Review and Network Meta–Analysis of Randomised Trials[J]. *BMJ*, 2022, 376: e066785.
- [54] Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the Diagnosis and Management of Acute Pulmonary Embolism Developed in Collaboration with the European Respiratory Society (ERS): The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC) [J]. *Eur Respir J*, 2019, 54 (3) : 1–68.
- [55] Pompilio G, Integlia D, Raffetto J, et al. Comparative Efficacy and Safety of Sulodexide and Other Extended Anticoagulation Treatments for Prevention of Recurrent Venous Thromboembolism: A Bayesian Network Meta–analysis[J]. *TH Open*, 2020, 4 (2) : e80–e93.
- [56] Elmi G, Pizzini AM, Silingardi M. The Secondary Prevention of Venous Thromboembolism: Towards an Individual Therapeutic Strategy[J]. *Vascular*, 2018, 26 (6) : 670–682.
- [57] Luzzi R, Belcaro G, Dugall M, et al. The Efficacy of Sulodexide in the Prevention of Postthrombotic Syndrome[J]. *Clin Appl Thromb–Hem*, 2014, 20 (6) : 594–599.
- [58] Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the Diagnosis and Management of Acute Pulmonary Embolism Developed in Collaboration with the European Respiratory Society(ERS) [J]. *Eur Heart J*, 2020, 41 (4) : 543–603.
- [59] Andreozzi GM. Role of Sulodexide in the Treatment of CVD[J]. *Int Angiol*, 2014, 33 (3) : 255–262.
- [60] Mannello F, Ligi D, Raffetto JD. Glycosaminoglycan Sulodexide Modulates Inflammatory Pathways in Chronic Venous Disease[J]. *Int Angiol*, 2014, 33 (3) : 236–242.
- [61] Bignamini AA, Matuška J. Sulodexide for the Symptoms and Signs of Chronic Venous Disease: A Systematic Review and Meta–analysis[J]. *Adv Ther*, 2020, 37 (3) : 1013–1033.
- [62] Pompilio G, Nicolaides A, Kakkos SK, et al. Systematic Literature Review and Network Meta–Analysis of Sulodexide and Other Drugs in Chronic Venous Disease[J]. *Phlebology*, 2021, 36 (9) : 695–709.
- [63] Bignamini AA, Chebil A, Gambaro G, et al. Sulodexide for Diabetic–Induced Disabilities: A Systematic Review and Meta–Analysis[J]. *Adv Ther*, 2021, 38 (3) : 1483–1513.
- [64] Li R, Xing J, Mu X, et al. Sulodexide Therapy for the Treatment of Diabetic Nephropathy, a Meta–Analysis and

- Literature Review[J]. *Drug Des Devel Ther*, 2015, 9: 6275–6283.
- [65] Teuwen LA, Geldhof V, Pasut A. COVID-19: The Vasculature Unleashed[J]. *Nat Rev Immunol*, 2020, 20 (7): 389–391.
- [66] Higashikuni Y, Liu W, Obana T, et al. Pathogenic Basis of Thromboinflammation and Endothelial Injury in COVID-19: Current Findings and Therapeutic Implications[J]. *Int J Mol Sci*, 2021, 22 (21): 12081.
- [67] Szolnoky G. Sulodexide may be a Real Alternative to Low Molecular Weight Heparins in the Prevention of COVID-19 Induced Vascular Complications[J]. *Dermatol Ther*, 2020, 33 (6): e14437.
- [68] Tarnawski AS, Ahluwalia A. Endothelial Cells and Blood Vessels are Major Targets for COVID-19-Induced Tissue Injury and Spreading to Various Organs[J]. *World J Gastroentero*, 2022, 28 (3): 275–289.
- [69] Okada H, Yoshida S, Hara A, et al. Vascular Endothelial Injury Exacerbates Coronavirus Disease 2019: The Role of Endothelial Glycocalyx Protection[J]. *Microcirculation*, 2021, 28 (3): e12654.
- [70] Schulman S, Sholzberg M, Spyropoulos AC, et al. ISTH Guidelines for Antithrombotic Treatment in COVID-19: Reply[J]. *J Thromb Haemost*, 2022, 20 (11): 2710–2711.
- [71] Gonzalez-Ochoa AJ, Raffetto JD, Hernández AG, et al. Sulodexide in the Treatment of Patients with Early Stages of COVID-19: A Randomized Controlled Trial[J]. *Thromb Haemost*, 2021, 121 (7): 944–954.
- [72] Charfeddine S, Ibnhadjamor H, Jdidi J, et al. Sulodexide Significantly Improves Endothelial Dysfunction and Alleviates Chest Pain and Palpitations in Patients with Long-COVID-19: Insights from TUN-EndCOV Study[J]. *Front Cardiovasc Med*, 2022, 9: 866113.
- [73] Murchu EO, Spillane S, Byrne P, et al. Interventions in an Ambulatory Setting to Prevent Progression to Severe Disease in Patients with COVID-19: A Systematic Review[J]. *Ann Pharmacother*, 2022, 56 (3): 309–318.
- [74] Smetana KS, Counts J, Sodhi A, et al. Review of Target-Specific Anticoagulation Reversal Agents[J]. *Crit Care Nurs Q*, 2022, 45 (2): 180–188.
- [75] Dabney A, Bastani B. Enoxaparin-Associated Severe Retroperitoneal Bleeding and Abdominal Compartment Syndrome: A Report of Two Cases[J]. *Intensive Care Med*, 2001, 27 (12): 1954–1957.
- [76] Xiang T, Cheng M. Enoxaparin-Induced Reactive Thrombocytosis: A Case Report[J]. *Thromb J*, 2021, 19 (1): 34.
- [77] Uceda-Martin M, Lambert A, Miremont G, et al. Bullous Haemorrhagic Dermatitis Induced by Heparins and Other Anticoagulants: 94 Cases from French Pharmacovigilance Centres and a Literature Review[J]. *Ann Dermatol Vener*, 2022, 149 (1): 45–50.
- [78] Bikdeli B, Chatterjee S, Kirtane AJ, et al. Sulodexide Versus Control and the Risk of Thrombotic and Hemorrhagic Events: Meta-Analysis of Randomized Trials[J]. *Semin Thromb Hemost*, 2020, 46 (8): 908–918.
- [79] EP 11.0[S]. 2022: 2460, 2634, 3467, 3640, 4229.
- [80] USP-NF2022 Issue 1[S]. 2022.
- [81] Ofosu FA. The United States Food and Drugs Administration Approves a Generic Enoxaparin[J]. *Clin Appl Thromb-Hem*, 2011, 17 (1): 5–8.
- [82] Harenberg J, Cimminiello C, Agnelli G, et al. Biosimilars of Low-Molecular-Weight Heparin Products: Fostering Competition or Reducing 'Biodiversity'[J]. *J Thromb Haemost*, 2016, 14 (3): 421–426.
- [83] 陈思, 石靖. 低分子肝素类药品的质量控制[J]. *中国新药杂志*, 2018, 27 (3): 285–289.
- [84] Lauren E Pepi, Patience Sanderson, Morgan Stickney, et al. Developments in Mass Spectrometry for Glycosaminoglycan Analysis: A Review[J]. *Mol Cell Proteomics*, 2021, 20: 100025.
- [85] Sheng A, Chen Q, Yu M, et al. Coupling Liquid Chromatography and Tandem Mass Spectrometry to Electrophoresis for In-Depth Analysis of Glycosaminoglycan Drugs: Heparin and the Multicomponent Sulodexide[J]. *Anal Chem*, 2021, 93 (3): 1433–1442.
- [86] 李京, 龚益妮, 张佟, 等. 全自动血凝仪测定肝素类药物抗Xa因子和抗IIa因子效价 [J]. *中国药理学杂志*, 2021, 56 (21): 1755–1763.
- [87] 李湛军, 邓利娟, 范慧红. 舒洛地特生物活性研究[J]. *药物分析杂志*, 2010, 30 (6): 1045–1047.

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