

西他沙星抗菌活性、药代动力学及临床应用研究现状

Research status on antibacterial activity, pharmacokinetics and clinical applications of sitafloxacin

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要从事药物代谢动力学方向的研究

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摘要: 西他沙星作为第四代氟喹诺酮类抗菌药物, 对革兰氏阴性菌、革兰氏阳性菌、非典型病原菌及厌氧菌等均具有良好的抗菌活性, 对氟喹诺酮类耐药菌株、耐甲氧西林金黄色葡萄球菌、青霉素不敏感肺炎链球菌以及肠球菌等也具有抑制作用, 在临床上广泛用于上呼吸道和下呼吸道感染、泌尿生殖系统感染、口腔感染和中耳炎等疾病的治疗。西他沙星在 50 ~ 200 mg 剂量范围内呈现线性药代动力学特征, 口服后吸收迅速, 在全身各组织器官广泛分布, 并主要以原型药物从尿液排出, 腹泻、恶心、肝功能异常是其常见药物不良反应。近年来, 有临床研究表明, 西他沙星对多重耐药菌引起的呼吸机相关性肺炎、医院获得性肺炎、肺结核、男性生殖支原体感染、脓肿分枝杆菌感染、牙源性感染、幽门螺杆菌感染、难治性分枝杆菌皮肤感染也有效, 但仍需更多临床研究评估其疗效和安全性, 同时需要开展在老年、肝功能不全等特殊人群中的药代动力学研究。本文系统综述了西他沙星的药理作用机制、抗菌活性、药代动力学/药效学特征及临床应用研究现状, 旨在为临床安全有效地使用西他沙星提供参考依据。

关键词: 西他沙星; 抗菌活性; 药代动力学/药效学; 临床应用

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Abstract: Sitafloxacin, a fourth - generation fluoroquinolone antibacterial agent, exerts potent antibacterial activity against gram - negative and gram - positive bacteria, atypical pathogens and anaerobic bacteria. It also remains effective against fluoroquinolone - resistant strains, methicillin - resistant *Staphylococcus aureus*, penicillin - insensitive *Streptococcus pneumoniae* and *Enterococcus*. It is widely used clinically for treating infectious diseases such as upper and lower respiratory tract infections, genitourinary infections, oral infections and otitis media. Sitafloxacin shows linear pharmacokinetic characteristics within the dose range of 50 - 200 mg. It is rapidly absorbed after oral administration, widely distributed in various tissues and organs throughout the body, and mainly excreted in the urine as unchanged form. Commonly reported adverse events include diarrhea, nausea and abnormal liver function. In recent years, studies have found that sitafloxacin is also effective against multidrug - resistant pathogens causing ventilator - associated pneumonia, hospital - acquired pneumonia, tuberculosis, *Mycoplasma genitalium* infections in men, *Mycobacterium abscessus* infection periodontal infection, *Helicobacter pylori* infections and refractory *Mycobacterium* skin infections. However,

further clinical studies are still needed to evaluate its efficacy and safety, and pharmacokinetic studies should be conducted in special populations such as the elderly and those with hepatic impairment. This article systematically reviews the pharmacological mechanism, antibacterial activity, pharmacokinetic/pharmacodynamic characteristics and recent advances in clinical research of sitafloxacin, aiming to provide a reference basis for the safe and effective clinical use of sitafloxacin.

Key words: sitafloxacin; antibacterial activity; pharmacokinetics/pharmacodynamics; clinical application

环丙沙星、左氧氟沙星、莫西沙星等氟喹诺酮类抗菌药物自上世纪 60 年代上市以来,在感染性疾病中广泛应用。然而,随着耐药菌株在全球范围内的广泛传播,使该类药物的临床应用面临严峻挑战^[1]。西他沙星作为第四代氟喹诺酮类新药,2019 年我国批准片剂在国内上市,用于治疗上呼吸道和下呼吸道感染、泌尿生殖系统感染、口腔感染和中耳炎等疾病^[2-3],其通过抑制细菌脱氧核糖核酸(deoxyribonucleic acid, DNA)旋转酶及拓扑异构酶Ⅳ的活性发挥杀菌作用,且对部分其他氟喹诺酮类药物耐药菌株仍表现出较好的抗菌活性。近年来,西他沙星也被用于治疗幽门螺杆菌感染、肺结核、分枝杆菌皮肤感染、男性生殖支原体感染。常规给药剂量为 50 mg, *bid* 或 100 mg, *qd*,口服后吸收迅速,在全身各组织器官广泛分布,主要以原型药物从尿液排出。血药峰浓度/最低抑菌浓度(minimal inhibit concentration, C_{max}/MIC)和 24 h 血药浓度-时间曲线下面积/最低抑菌浓度(area under concentration-time curve/minimal inhibit concentration, AUC_{24}/MIC)是西他沙星主要的药代动力学/药效学(pharmacokinetics/pharmacodynamics, PK/PD)参数。本文通过检索近年来中文数据库中国知网和英文数据库 PubMed 相关文献,系统综述了西他沙星的药理作用机制、抗菌活性、PK/PD 特征以及在不同感染治疗中的临床应用现状,旨在为临床安全有效地使用西他沙星提供参考依据。

1 西他沙星药理作用机制和抗菌活性

1.1 化学结构

西他沙星化学结构中 C-6 位氟原子的引入,增加了其对细菌 DNA 旋转酶的抑制作用,提高了对细菌细胞膜的渗透性,进而增强抗菌活性。C-7 位氮杂双环结构的引入,显著增强其分子疏水性,提高了跨膜渗透效率^[3]。同时, C-8 位氯原子的修饰,进一步提高其抗菌活性, N-1 位氟环丙氨基加强了其与 DNA 旋转酶复合物的结合能力,见图 1。

1.2 作用机制

西他沙星在腺嘌呤核苷三磷酸(adenosine triphosphate, ATP)存在下,通过与细菌 DNA 旋转酶及拓扑

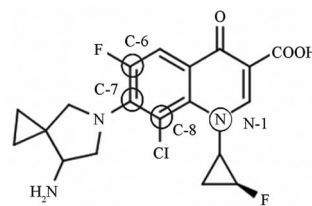


图 1 西他沙星的化学结构式^[3]

Figure 1 The chemical structural formula of sitafloxacin

异构酶Ⅳ共价结合,形成稳定的酶-DNA-药物三元复合物,从而不可逆地抑制上述 2 种酶介导的 DNA 超螺旋化调控与解环连反应^[3],最终导致细菌死亡。此外,西他沙星对肺炎链球菌 DNA 旋转酶与拓扑异构酶Ⅳ的半数抑制浓度(inhibition concentration 50, IC_{50})比值为 1.40,表明其对 2 种酶具有近似等效的抑制作用^[4]。相较于左氧氟沙星、环丙沙星及莫西沙星等同类药物,西他沙星对上述靶酶的抑制作用更强。

1.3 抗菌活性

西他沙星对葡萄球菌属、链球菌属、肠球菌属、肠杆菌属、枸橼酸杆菌属、梭杆菌属、流感嗜血杆菌、铜绿假单胞菌、嗜肺军团菌、消化链球菌属、沙眼衣原体、肺炎衣原体及肺炎支原体等均有抗菌活性,且表现为浓度依赖性杀菌特性^[5]。由于临床与实验室标准研究所(Clinical and Laboratory Standards Institute, CLSI)药敏试验标准中无西他沙星的折点,目前推荐其敏感性结果判读可以参照其他氟喹诺酮类药物^[6-7]。

编码细菌 DNA 旋转酶(*gyr A* 和 *gyr B*)和拓扑异构酶Ⅳ(*par C* 和 *par E*)基因的耐药决定区域发生突变,会降低酶与氟喹诺酮类药物的亲和力,从而发生耐药。*Par C* 和 *Par E* 亚基分别与 *Gyr A* 和 *Gyr B* 相同,预示这 2 种酶有相似的耐药突变。编码细菌膜外排泵基因突变也会增加氟喹诺酮类药物的外排,导致胞内药物浓度降低^[8]。西他沙星同时作用于 DNA 旋转酶和拓扑异构酶Ⅳ来抑制细菌生长,因此,除非细菌的 DNA 旋转酶和拓扑异构酶Ⅳ均发生突变,否则不会对西他沙星产生高水平耐药^[9]。与其他氟喹诺酮类药物相比,肺炎链球菌对西他沙星不易产生耐药性,即便是携带 *Gyr A* 和 *Par C* 突变基因,或是对其他

氟喹诺酮类药物耐药的肺炎链球菌,西他沙星仍能表现出良好的抗菌活性^[10]。西他沙星对耐甲氧西林金黄色葡萄球菌敏感率达82.8%,对甲氧西林敏感凝固酶阴性葡萄球菌敏感率为97.5%,对耐青霉素肺炎链球菌敏感率达98.2%^[9]。KONG等^[11]对比了氧氟沙星、左氧氟沙星、莫西沙星、西他沙星、非那沙星和地拉沙星对结核分枝杆菌的体外抗菌活性,发现西他沙星对结核分枝杆菌的抗菌活性最强($MIC_{90} = 0.25 \mu\text{g} \cdot \text{mL}^{-1}$),且与莫西沙星交叉耐药率仅为40.6%。FUJIWARA等^[12]对比了西他沙星与莫西沙星对非结核分枝杆菌的敏感性,结果表明51株(59.3%)非结核分枝杆菌对西他沙星的 MIC 低于 $1 \mu\text{g} \cdot \text{mL}^{-1}$ 。此外,西他沙星对多重耐药结核分枝杆菌的活性优于左氧氟沙星与莫西沙星,对耐氟喹诺酮类结核分枝杆菌也有效^[13]。

2 西他沙星的药代动力学特征

2.1 健康受试者

西他沙星在50~200 mg剂量范围内呈现线性药代动力学特征。健康受试者单次口服西他沙星50 mg或100 mg后,约1.2 h达到 $C_{\max}$ $0.51 \sim 1.4 \mu\text{g} \cdot \text{mL}^{-1}$, $AUC_{0-\infty}$ 为 $2.62 \sim 8.19 \mu\text{g} \cdot \text{h} \cdot \text{mL}^{-1}$,血浆蛋白结合率为46%~55%,给药后,在中耳黏膜、上颌窦黏膜、牙龈组织等均有分布,表观分布容积(V_d)为 $2.5 \sim 2.8 \text{ L} \cdot \text{kg}^{-1}$ 。西他沙星在体内基本不被代谢,72 h内约80%的给药量以原型药物经肾排泄,约20%的给药量从粪便中排出,消除半衰期($t_{1/2}$)为 $5.7 \sim 6.2 \text{ h}$,肾清除率(CL_r)约为 $165.83 \text{ mL} \cdot \text{min}^{-1}$,总清除率(CL)为 $327 \sim 313 \text{ mL} \cdot \text{min}^{-1}$ ^[14]。与日本健康受试者相比,中国健康受试者口服西他沙星后体内暴露量略微增加,消除速率稍慢,但清除率在统计学上差异无统计学意义。体外研究表明,人肝微粒体中的葡萄糖醛酸基转移酶($\text{udp} - \text{glucuronosyltransferases}$, $UGTs$) 1A1和 $UGT1A9$ 酶参与了西他沙星的葡萄糖醛酸化代谢过程。西他沙星对细胞色素P450酶($\text{cytochrome p450 proteins}$, CYP)的选择性较弱,仅对 $CYP1A1$ 和 $CYP1A2$ 有较弱的抑制作用,而对 $CYP2C9$ 、 $CYP2D6$ 及 $CYP3A4$ 等未见明显抑制作用^[15]。 $UGT1A1$ 、 $UGT1A9$ 和ATP结合盒亚家族B成员(ATP-binding cassette sub-family B member, $ABCB$)1的基因多态性会影响西他沙星体内药代动力学过程^[16]。因此,西他沙星和其他合并用药发生药物相互作用的风险较低。饮食不影响西他沙星吸收过程,空腹和餐后服药其PK参数无明显变化^[17]。此外,西他沙星体内PK过程也没有表现出性别差异,男性与女性的 $C_{\max}$ 比值

为92.7% (90% CI : 9.6% ~ 105.8%, $P = 0.152$)^[18],连续10 d多次给药也未观察到药物蓄积。

2.2 特殊人群

西他沙星体内药物暴露量随肾功能减退而增加。临床研究表明,单次口服西他沙星50 mg后,轻度($CL_{CR} \geq 60$ 且 $< 90 \text{ mL} \cdot \text{min}^{-1}$)、中度($CL_{CR} \geq 30$ 且 $< 60 \text{ mL} \cdot \text{min}^{-1}$)和重度($CL_{CR} \geq 10$ 且 $< 30 \text{ mL} \cdot \text{min}^{-1}$)肾功能不全患者的 AUC_{24} 分别为4.18、6.29和6.33 $\mu\text{g} \cdot \text{h} \cdot \text{mL}^{-1}$ 。因此,肾功能不全患者服用西他沙星时需根据肌酐清除率进行剂量调整, CL_{CR} 在 $30 \sim 49 \text{ mL} \cdot \text{min}^{-1}$ 者每日给药50 mg, CL_{CR} 低于 $30 \text{ mL} \cdot \text{min}^{-1}$ 者每48 h给药50 mg^[19]。老年受试者(67~80岁)与健康受试者相比,单次服用西他沙星100 mg后, AUC_{24} 增加30.7%,达峰时间($t_{\max}$)延长313.0%, $t_{1/2}$ 延长83.3%, $C_{\max}$ 则降低33.0%,然而针对老年或肝功能减退患者的剂量调整尚未明确,此类特殊人群使用西他沙星时需密切监测是否有药物蓄积^[20]。另外,西他沙星在新生儿、儿童及妊娠期妇女中缺乏安全性数据,不推荐用于这些人群^[3]。

2.3 PK/PD研究

$C_{\max}/MIC$ 和 AUC_{24}/MIC 是预测氟喹诺酮类药物抗菌疗效的PK/PD参数^[21],当革兰氏阳性菌 AUC_{24}/MIC 比值大于25~30,革兰氏阴性菌 AUC_{24}/MIC 比值大于100~125时,西他沙星可以有效清除细菌^[22]。对于呼吸道感染患者,口服西他沙星(50 mg, bid 或100 mg, qd)的疗效与PK/PD参数相关,当 $C_{\max}/MIC \leq 5$ 且 $AUC_{24}/MIC \leq 100$ 时,50 mg组和100 mg组患者的细菌清除率分别为33.3%和40.0%;而当 $C_{\max}/MIC > 5$ 且 $AUC_{24}/MIC > 100$ 时,2组患者的细菌清除率显著提升至96.3%^[17];当 $AUC_{24}/MIC > 30 \sim 40$ 时,肺炎链球菌几乎能被完全清除^[10]。

3 西他沙星的临床应用

西他沙星的临床适应症包括肺炎、咽喉炎、扁桃体炎、急性支气管炎、膀胱炎、尿道炎、肾盂肾炎、宫颈炎、牙周炎、中耳炎、鼻窦炎、冠周炎及颌骨骨髓炎等感染性疾病,近年来还被用于治疗多重耐药菌感染、结核杆菌感染、幽门螺杆菌感染等。与其他氟喹诺酮类药物相比,西他沙星有相似或更好的临床疗效。

3.1 呼吸系统感染

多项随机、双盲、多中心非劣效性试验结果表明,在治疗社区获得性肺炎($\text{community} - \text{acquired pneumonia}$, CAP)或慢性呼吸道疾病感染加重时,口服西他沙星的疗效不劣于口服左氧氟沙星、莫西沙星或妥舒沙星。MIYAZAKI等^[23]在120例老年肺炎患者

中进行的随机对照研究显示,西他沙星组(100 mg, *qd*)与加雷沙星组(400 mg, *qd*)的临床有效率分别为88.5% (95% CI: 76.6 ~ 95.6) 和 88.9% (95% CI: 77.4 ~ 95.8), 且药物相关不良事件发生率在统计学上差异无统计学意义。在另一项临床研究中, LI 等^[24] 纳入了345例中国成人CAP患者以对比口服西他沙星与莫西沙星的疗效, 结果显示, 西他沙星100 mg组和200 mg组的临床有效率分别为94.8%和96.8%, 莫西沙星400 mg组的临床治愈率为95.0%, 3组的细菌清除率分别为97.0%、97.1%和94.9%。对于多重耐药鲍曼不动杆菌引起的呼吸机相关性肺炎/医院获得性肺炎, 采用西他沙星联合多黏菌素及美罗培南的治疗方案, 可实现47.5%的7日细菌清除率^[25]。

西他沙星也被用于肺结核(pulmonary tuberculosis, TB)的治疗。一项纳入30例初治涂片阳性的肺结核患者的随机对照研究评估了每日口服西他沙星(200 mg)、左氧氟沙星(500 mg)或异烟肼(300 mg)治疗7 d的早期杀菌活性(early bactericidal activity, EBA), 结果显示, 治疗0 ~ 2 d 异烟肼组 EBA (0.39 ± 0.22) $\log_{10}\text{CFU} \cdot \text{mL}^{-1} \cdot \text{d}^{-1}$ 高于左氧氟沙星组 (0.26 ± 0.27) $\log_{10}\text{CFU} \cdot \text{mL}^{-1} \cdot \text{d}^{-1}$ 和西他沙星组 (0.22 ± 0.25) $\log_{10}\text{CFU} \cdot \text{mL}^{-1} \cdot \text{d}^{-1}$, 但组间在统计学上差异无统计学意义 ($P=0.08$); 治疗2 ~ 7 d 西他沙星组 EBA (0.26 ± 0.31) $\log_{10}\text{CFU} \cdot \text{mL}^{-1} \cdot \text{d}^{-1}$ 高于异烟肼组 (0.17 ± 0.16) $\log_{10}\text{CFU} \cdot \text{mL}^{-1} \cdot \text{d}^{-1}$ 和左氧氟沙星组 (0.14 ± 0.10) $\log_{10}\text{CFU} \cdot \text{mL}^{-1} \cdot \text{d}^{-1}$, 在统计学上差异无统计学意义 ($P=0.59$), 所有患者均完成治疗且未发生严重不良事件, 表明西他沙星与左氧氟沙星早期杀菌活性相当, 且持续杀菌活性更优、安全性更好, 这为肺结核临床治疗提供了新选择^[26]。另有1例广泛耐药肺结核患者的病例报道表明, 患者在接受西他沙星、利奈唑胺、贝达喹啉、环丝氨酸以及氯法齐明联合治疗2个月后, 痰涂片、痰培养转阴, 治疗3个月后, 胸部CT显示双肺多发散在结节斑片影明显缩小、部分空洞闭合, 治疗24个月后停药。在治疗难治性脓肿分枝杆菌感染及系统性硬化相关间质性肺病患者的继发性/自发性气胸时, 联合西他沙星抗感染治疗后, 3周内可实现症状缓解^[27]。因此, 对于脓肿分枝杆菌引起的难治性肺部或肺外感染, 可以联合使用西他沙星治疗^[28]。

3.2 泌尿生殖系统感染

西他沙星在治疗复杂性尿路感染(urinary tract infection, UTI)时的疗效不劣于口服左氧氟沙星。有临床研究对比了西他沙星与左氧氟沙星在中国成人

急性非复杂性或复杂性UTI的疗效, 结果显示, 在非复杂性UTI治疗中, 西他沙星组(100 mg, *qd*)与左氧氟沙星组(500 mg, *qd*)的临床有效率分别为89.2%和97.1%, 细菌清除率分别为97.1%和97.6%; 对于复杂性UTI, 西他沙星组(100 mg, *bid*)与左氧氟沙星组(500 mg, *qd*)的临床有效率分别为81.8%和76.9%, 细菌清除率分别为93.3%和63.6%^[29]。在另一项针对289例UTI及急性肾盂肾炎(acute pyelonephritis, APN)患者的非劣效性临床研究中, 口服西他沙星(100 mg, *bid*)治疗7 ~ 14 d后的临床有效率达97.2%, 细菌清除率为61.1%, 显著优于头孢菌素对照组^[30]。

生殖支原体是可导致性传播感染的病原体, 其引发的临床疾病在男性中主要表现为尿道炎, 在女性中则包括宫颈炎和盆腔炎。近年来, 携带耐药相关突变基因的生殖支原体菌株在亚洲、澳大利亚、新西兰、日本等国家流行, 携带大环内酯类耐药相关突变基因和喹诺酮类耐药相关突变基因的生殖支原体菌株流行率分别高达66.4% ~ 89.6%和19.0% ~ 77.7%。*Par C*(如S83、D87位点)和*Gyr A*(如M95、G93、D99位点)的突变, 分别与莫西沙星和西他沙星治疗失败相关, 但西他沙星对携带耐药相关突变基因的生殖支原体感染疗效仍显著优于莫西沙星^[31]。一项开放、前瞻性队列研究评估了西他沙星(200 mg, *qd*)7 d疗程对男男性行为者直肠和泌尿生殖道感染的疗效, 发现西他沙星中位治愈检测时间为21 d, 总体微生物学治愈率达87.8%, 在*Par C*突变高流行而*Gyr A*突变低流行的地区, 可以作为生殖支原体感染的一线治疗方案^[32]。SAMRA等^[33]回顾性研究分析了229例大环内酯类耐药的生殖支原体感染病例, 结果显示, 采用多西环素(100 mg, *bid*)联合西他沙星(100 mg, *bid*)治疗方案的细菌清除率可达80.6%, 同时该联合方案还可以用于治疗莫西沙星治疗无效的患者。21 d持续给予西他沙星和多西环素可以作为治疗高耐药性生殖型分枝杆菌的挽救疗法, 总治愈率达77.8%^[34]。此外, 西他沙星在治疗沙眼衣原体宫颈炎方面也显示出良好疗效^[35]。

3.3 幽门螺杆菌感染

近年来, 幽门螺杆菌(*helicobacter pylori*, Hp)对克拉霉素、甲硝唑和左氧氟沙等抗菌药物耐药率增加, 导致Hp根除率下降^[36]。西他沙星的耐药率低于其他氟喹诺酮类抗菌药物, 且对发生*Gyr A*突变的Hp菌株也保持良好抗菌活性, 因此逐渐被用于Hp感染的补救治疗^[37]。

西他沙星对幽门螺杆菌表现出相较于左氧氟沙星、环丙沙星更好的抗菌疗效^[38]。一项纳入17例青霉

素过敏且 Hp 根除失败患者的临床研究显示,采用伏诺拉生(20 mg, *bid*)联合甲硝唑(250 mg, *bid*)及西他沙星(100 mg, *bid*)治疗 7 d 后, Hp 根除率达 88.2% (95% CI: 63.6% ~ 98.5%), 且耐受性良好^[39]。对于接受一线 Hp 治疗方案失败的患者,采用含西他沙星的补救治疗方案仍可以表现出较高的细菌清除率。对于二线治疗失败的患者, WASAKI 等^[40]提出了伏诺拉生(10 mg, *bid*) - 阿莫西林(125 mg, *qid*) - 西他沙星(50 mg, *bid*)的三线治疗方案,治疗 7 d 后 Hp 的总体根除率达 94.4%, 对于携带 *Gyr A* 耐药相关突变基因的幽门螺杆菌该方案也同样有效。近年来,由于 7 d 三联 Hp 治疗方案(西他沙星 - 阿莫西林 - 兰索拉唑)明显比左氧氟沙星 - 阿莫西林 - 兰索拉唑三联疗法更有效(70.0% *vs.* 43.1%), 日本已不再使用左氧氟沙星治疗 Hp^[41]。

3.4 牙周感染

口服西他沙星能够有效改善牙周治疗期间的牙周健康状况,对于无法接受麻醉或存在组织损伤风险的老年患者,可作为替代治疗方案。一项纳入 44 名老年牙周病患者的研究评估了西他沙星(100 mg, 疗程 5 d)试验组与对照组(局麻下接受龈下刮治和根面平整术)对接受支持性牙周治疗老年患者牙周袋的临床疗效,结果表明,2 组治疗后 1 个月,牙龈卟啉单胞菌、福赛坦氏菌以及齿垢密螺旋体的检出率均显著降低,基线至 1 个月的细菌降幅中位数分别为 3.08% 和 2.54%^[42]。活动性牙周炎患者口服西他沙星(200 mg, 疗程 5 d)后 1 个月,牙周致病菌红色复合菌的占比(包括牙龈卟啉单胞菌、齿垢密螺旋体和福赛坦氏菌)显著降低,且该抑菌效果可持续 12 个月,这进一步证实了对于不适合接受侵入性治疗的牙周炎患者,口服西他沙星可以作为支持性牙周治疗期间的替代方案^[43]。此外,使用西他沙星进行全身抗生素治疗和机械清创能有效防止牙周手术后复发口腔溃疡^[44]。MORIKAWA 等^[45]在常规洗牙和根面平整失败后,针对龈下牙周致病菌水平较高的患者制定了全口消毒与口服西他沙星(100 mg, *qd*, 治疗 7 d)相结合的方案,结果显示,探诊袋深度、探诊出血量和发炎的牙周表面积都有明显改善,红色复合菌也大幅减少,表明此方案可用于替代牙周手术治疗细菌量大的严重牙周炎。

3.5 皮肤感染

西他沙星也是难治性分枝杆菌皮肤感染的治疗新选择。1 例由龟分枝杆菌引起下肢皮肤感染的老年患者,在接受利福平、乙胺丁醇、克拉霉素、左氧氟沙星治疗无效后,换用西他沙星(200 mg)联合克拉霉素(800 mg)治疗 6 个月后,病灶改善且无复发^[46]。

4 西他沙星的安全性及药物不良反应

西他沙星药物不良反应包括腹泻、稀便、头痛、皮疹及转氨酶升高,其中以胃肠道反应最为常见^[47]。过敏性休克、急性全身性过敏反应、眼 - 粘膜 - 皮肤综合征(stevens - johnson syndrome, SJS)、急性肾损伤、血小板减少症及低血糖等严重药物不良反应虽罕见但需警惕。氟喹诺酮类药物最严重的药物不良反应为心脏毒性和光毒性,但西他沙星引起心律失常、光毒性的风险较小^[48-49]。

文献报道,西他沙星在治疗呼吸道感染与尿路感染治疗中总体不良事件发生率显著高于左氧氟沙星(分别为 29.8% *vs.* 25.9% 及 24.6% *vs.* 11.6%)^[50]。然而,在 CAP 成年患者中,西他沙星(100 mg, *qd*)与莫西沙星(400 mg, *qd*)的不良事件发生率在统计学上差异无统计学意义(29.8% *vs.* 28.2%), 药物不良反应主要表现为头晕、恶心、腹泻等^[24]。这表明,西他沙星的安全性与其他氟喹诺酮类药物相似,但在特定适应症及特定人群中,仍需个体化评估其引发药物不良反应的风险。

5 结语

西他沙星作为第四代氟喹诺酮类抗菌药物,抗菌谱广,对其他氟喹诺酮耐药的菌株也有较强的抗菌作用。西他沙星在 50 ~ 200 mg 剂量范围内呈现线性药代动力学特征,口服给药后吸收迅速,有良好的组织渗透性,饮食不影响西他沙星吸收过程,每日多次给药也未见体内蓄积。多项随机、双盲、多中心、非劣效性临床试验表明,在治疗社区获得性肺炎或慢性呼吸道疾病感染加重时,口服西他沙星的疗效不劣于口服左氧氟沙星或莫西沙星,在治疗复杂性尿路感染时不劣于口服左氧氟沙星。近年来,西他沙星也被用于多重耐药菌引起的呼吸机相关性肺炎、医院获得性肺炎、肺结核、男性生殖支原体感染、脓肿分枝杆菌感染、牙源性感染、幽门螺杆菌感染、难治性分枝杆菌皮肤感染的治疗。腹泻、恶心、肝功能异常是其常见药物不良反应。然而,西他沙星在特殊人群中的研究不足,目前,西他沙星不推荐用于儿童、妊娠期妇女及哺乳期妇女,也缺少在老年、肝功能不全患者中的药代动力学数据,临床用药剂量调整缺乏循证依据。因此,未来仍需开展大量相关研究,评价西他沙星的疗效与安全性,为临床使用提供参考依据。

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