·新冠肺炎专栏·

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新型冠状病毒肺炎治疗药物监测研究进展

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摘 要: 新型冠状病毒肺炎(简称“新冠肺炎”)在全球持续蔓延, 其治疗用药均为老药新用。但这些药物在新的适应症中的药代动力学参数缺乏, 且很多患者需要使用血透和人工肺等可能影响药物浓度的治疗手段, 因此急需对患者用药进行治疗药物监测(therapeutic drug monitoring, TDM), 以提高临床用药的有效性, 并降低其毒副作用。本研究对新冠肺炎患者使用的羟基氯喹、替考拉宁、阿比朵尔、克立芝(洛匹那韦 / 利托那韦, LPV/RTV)和万古霉素的治疗药物监测进行综述, 包括各药在老适应症患者中的 TDM 研究进展、药物浓度检测的方法(主要是液相色谱串联质谱法)、血药浓度治疗窗以及这些药物在新冠肺炎患者中的 TDM 研究进展, 以期为新冠肺炎 TDM 研究提供方法学的支持, 为患者个体化用药提供理论依据。

关键词: 新型冠状病毒肺炎(COVID-19); 治疗药物监测(TDM); 羟基氯喹; 替考拉宁; 液相色谱串联质谱法(LC-MS/MS)
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Progress in Therapeutic Drug Monitoring of 2019 Novel Coronavirus Pneumonia

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Abstract: The corona virus disease 2019 (COVID-19) is spreading all over the world. The current clinical treatment is dependent on old drugs. However, the pharmacokinetic parameters of all these drugs in COVID-19 treatment are very limited, and furthermore, there are some therapeutic factors (such as hemodialysis, and extracorporeal membrane oxygenation (ECMO)) affecting pharmacokinetic parameters. It is necessary to perform therapeutic drug monitoring (TDM) to improve clinical efficacy and decrease drug adverse reactions. In this work, we reviewed the TDM development of hydroxychloroquine, teicoplanin, arbidol, Klitsch (lopinavir/ritonavir, LPV/RTV), and vancomycin used in COVID-19 patients, including the TDM progress of these drugs in other diseases, concentration detection methods (mainly liquid chromatograph tandem mass spectrometry), therapeutic window range, and the TDM development of these drugs in COVID-19 patients. This review may provide methodological support for TDM research, and provide theoretical basis for individualized medication of COVID-19.

Key words: corona virus disease 2019 (COVID-19); therapeutic drug monitoring (TDM); hydroxychloroquine; teicoplanin; liquid chromatograph tandem mass spectrometry (LC-MS/MS)

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自 2019 年 12 月发现首例新型冠状病毒肺炎(简称“新冠肺炎”; corona virus disease 2019, COVID-19)患者以来[1~2], 疫情迅速蔓延至全球。截至 2020 年 4 月 23 日, 我国累计确诊病例 84 305 例, 死亡 4 642 例, 现有确诊病例 1 470 例; 全球累计确诊病例 254 万例, 现有确诊病例 175 万例(https://www.who.int/emergencies/diseases/novel-coronavirus-2019; 2020-04-24)。

面对这种突发传染病, 如何科学有效治疗成为摆在广大医务工作者面前的迫切任务。新药开发周期长, 老药新用是目前治疗的首选。当前, 已用于治疗新冠肺炎的药物有羟基氯喹(hydroxychloroquine, HCQ)、替考拉宁(teicoplanin)、阿比朵尔(arbidol)和洛匹那韦/利托那韦(lopinavir/ritonavir, LPV/RTV)等[3~4]。然而, 在新的适应症中, 这些药物的药代动力学参数均缺乏, 且抗病毒药物均有其两面性, 药物浓度低时不能起到抗病毒的作用, 而浓度高时则会出现毒副作用。因此, 开展治疗药物监测(therapeutic drug monitoring, TDM)已成为抗病毒/抗菌治疗的个体化用药的有效手段之一。TDM 采用现代化的分析技术测定患者的血液或其他体液中的药物浓度, 从而协助临床制定合理用药方案, 指导剂量调整, 以提高药物疗效, 降低不良反应。目前, 常用的 TDM 方法有高效液相色谱法(high performance liquid chromatography, HPLC)、免疫学方法(如酶联免疫法和荧光免疫法)、液相色谱串联质谱法(liquid chromatograph tandem mass spectrometry, LC-MS/MS)[5]。本文从新冠肺炎药物在老适应症中的 TDM 研究进展、药物浓度检测的方法、血药浓度治疗范围以及这些药物在新冠肺炎患者中的 TDM 研究进展几个方面详细介绍了羟基氯喹、替考拉宁、阿比朵尔、克立芝和万古霉素。

1 治疗药物监测的研究进展

1.1 羟基氯喹

羟基氯喹(HCQ)是 1946 年在氯喹的基础上被开发出来的抗疟药。除了抗疟之外, 羟基氯喹的药理作用还有很多, 如免疫调节、抗病毒、抗菌等[6~8]。在临床上羟基氯喹主要用于治疗系统性红斑狼疮和类风湿性关节炎。对于羟基氯喹的抗病毒作用, 相关研究显示其能抑制登革热病毒[9], 可以阻断寨卡病毒的母婴传播[10], 此外还可以抑制严重急性呼吸综合征冠状病毒(severe acute respiratory syndrome coronavirus, SARS-CoV)的体外活性[11]。

研究表明, 羟基氯喹的疗效和它的血药浓度在一定范围内呈正相关, 浓度过低的羟基氯喹无法达到满意的治疗效果, 而过高又会产生毒副作用。在治疗红斑狼疮时, 当羟基氯喹的全血浓度为 1 000 ng/mL 时能达到比较好的临床效果[12~13], 而当羟基氯喹的全血浓度小于 100 ng/mL 时则疗效较差, 且患者依从性差[14]。Frances 等[15]对羟基氯喹的药物浓度与皮肤红斑狼疮的临床疗效进行了分析, 发现羟基氯喹的血药浓度在完全缓解的患者中明显高于部分缓解和未缓解的患者, 全血浓度小于 200 ng/mL 时患者不仅依从性差, 治疗效果也不理想。Chasset 等[16]对 34 例服用羟基氯喹的皮肤红斑狼疮患者进行 TDM, 将羟基氯喹的剂量从 400 mg/d 增加至 9.8 mg/(kg·d), 结果显示羟基氯喹的血药浓度从小于 750 ng/mL 升高至平均 1 187 ng/mL, 患者病情也得到改善, 而当剂量降低时, 症状又会再次出现。目前, 关于羟基氯喹的血药浓度没有统一标准, 有研究表明 500 ng/mL 的全血浓度可作为最小有效剂量[17]; 血浆/血清中的谷浓度(C_{min})范围是 100~130 μg/mL, 峰浓度(C_{max})为 170~300 μg/mL[18~19]。通常, 羟基氯喹剂量不超过 6.5 mg/(kg·d)或 400 mg/d, 其中眼科指南建议不超过 5 mg/(kg·d), 病情稳定后以最小剂量维持[20]。

自从羟基氯喹在体外被发现对 SARS-CoV-2 有活性(EC_{50}=0.72 μmol/L)[19]后, 很快被用于 COVID-19 患者的临床试验[21~22]和临床治疗[23~24]。然而, HCQ 对 COVID-19 的疗效仍存在争议, 需要通过临床试验进一步证实[25]。目前对羟基氯喹的 TDM 报道只有 Perinel 等[24]的工作, 他们对 13 例 COVID-19 患者的 161 份全血标本进行了药物代谢动力学(pharmacokinetics, PK)分析, 发现只有 61.5% (8/13)的患者的药物浓度达到了最低治疗水平(1 mg/L)。PK-PD (pharmacokinetics-pharmacodynamics)模型结果推荐羟基氯喹的临床使用剂量为: 第 1 天 800 mg (单剂), 然后每天 2 次, 每次 200 mg, 连续 7 d。本课题组采用 LC-MS 方法对 12 例使用羟基氯喹的新冠肺炎患者进行了 TDM 研究, 发现有 31% (10/32 标本)的患者的血药浓度在治疗窗之外(数据未发表) (表 1)。以上文献和本课题组对羟基氯喹进行 TDM 时, 其血药浓度主要采用 HPLC 法[26]和 LC-MS 法[24, 27]进行检测。

1.2 替考拉宁

替考拉宁是由壁胞酶游动放线菌发酵制成的

一种糖肽类抗生素, 在临床上主要用于治疗各种由革兰氏阳性菌引起的感染, 例如呼吸道感染、骨和关节感染、尿路感染、皮肤和软组织感染等, 也可用于其他抗生素如青霉素类、头孢菌素类治疗无效或耐药的葡萄球菌引起的感染[28]。研究发现, 替考拉宁在体外对 SARS-CoV 有抑制作用[29]。Baron 等[30]建议将替考拉宁作为一种治疗 SARS-CoV-2 的潜在选择。

替考拉宁的杀菌效应与其血药浓度超过最低抑菌浓度(minimum inhibitory concentration, MIC)的时间有关[31], 因此, 在使用替考拉宁时常需要进行治疗药物监测。目前, 对替考拉宁开展 TDM 的领域有多重耐药菌感染、重症肺炎、骨关节感染、骨髓炎、中性粒细胞减少症伴发热和全身性感染等。替考拉宁的 TDM 指标有体内药物暴露量($AUC_{0\text{-}24h}$)、游离谷浓度和谷浓度(C_{min})[32]。对于大部分革兰氏阳性菌感染, 替考拉宁的 C_{min}>10 mg/L, 对于心内膜炎或其他重度感染, 替考拉宁的 C_{min} 应至少达到 15~30 mg/L。Sato 等[33]在一项针对耐甲氧西林金黄色葡萄球菌(methicillin resistant *Staphylococcus aureus*, MRSA)感染的肺炎患者研究中发现, 替考拉宁的血清浓度及疗效与治疗期间前 3 天的平均起始给药剂量(mean initial dose, MID)有关。MID为 266.7 mg [(负荷剂量 400 mg+第 2 日剂量 200 mg+第 3 日剂量 200 mg)/3]或以下时, 患者在第 4 天给药前的 C_{min} 均未超过 10 mg/L, 而 MID>533.3 mg 时, C_{min} 显著提高并达到靶浓度, 而且治疗效果得到改善。Matthews 等[34]研究发现替考拉宁给药方案为负荷剂量(600 mg, 1 日 2 次)+维持剂量(600 mg, 1日 1 次)时, 比单一剂量(400 mg, 1 日 1 次)更易达到 20~60 mg/L 的目标 C_{min}。Zhao 等[35]研究了儿童血液肿瘤患者中的替考拉宁药动学情况, 结果显示, 剂量 10 mg/kg 不足以达到目标血药浓度(C_{min}, 10 mg/L), 而婴儿 18 mg/kg、幼儿 14 mg/kg 和青少年 12 mg/kg 的剂量方案可达到目标血药浓度[AUC=750 mg/(L·h)]。

目前, 替考拉宁在 COVID-19 中的报道较少[30, 36~37]。Zhang 等[37]研究发现替考拉宁对 SARS-CoV-2 的抑制活性是保守的, 体外抑制 50%的病毒所需浓度(IC_{50})为 1.66 μmol/L, 远低于人体血液中达到的浓度 8.78 μmol/L (每日 400 mg)。

已经报道的和本课题组开展的替考拉宁药物浓度检测方法主要有 HPLC 法[38]、LC-MS/MS 法[39](具体信息见表 1)。

1.3 阿比朵尔

阿比朵尔是一种广谱抗病毒化合物, 于 1993 年首次投放市场, 用于预防与治疗甲型和乙型流感病毒[40]。现有研究已经扩展了阿比朵尔的抗病毒作用, 其可广泛作用于乙型和丙型肝炎病毒、呼吸道合胞病毒、鼻病毒、基孔肯雅病毒、汉坦病毒等[41~42]。该药物通过干扰网格蛋白通路阻断病毒进入的过程[43]。阿比朵尔对冠状病毒活性的抑制作用早有报道, 主要研究对象是 SARS-CoV, 研究显示阿比朵尔的终浓度为 50 μmol/L 时, SARS-CoV 被显著抑制[44]。当前, 阿比朵尔治疗 SARS-CoV-2 的临床试验已经启动[21, 45], Wang 等[46]对武汉市 69 例新冠肺炎患者进行了抗病毒治疗, 其中阿比朵尔的治疗显示出提高出院率和降低死亡率的趋势。目前, 测定阿比朵尔血药浓度的方法有 HPLC 法[47]和 LC-MS 法[48], 本课题组在结合文献报道的基础上, 开发了阿比朵尔的 LC-MS 检测方法(具体信息见表 1), 并对 30 多例新冠肺炎患者的血浆样品进行了检测。

1.4 克立芝

克立芝是一种蛋白酶抑制剂, 全称为洛匹那韦/利托那韦(lopinavir/ritonavir, LPV/RTV), 主要用于治疗艾滋病。其中, 洛匹那韦属于 HIV 蛋白酶抑制剂, 利托那韦是一种针对天冬氨酰蛋白酶的活性拟肽类抑制剂。

克立芝在临床上多与其他药物联用, 它无论是对成人还是儿童(2 岁以上)都可以有效治疗HIV感染。虽然克立芝不易产生耐药性, 但是胃肠道不良反应和代谢紊乱仍很常见[49], 所以对克立芝实行治疗药物监测是有必要的。数据显示, 怀孕期间 20%的 HIV 孕妇患者 LPV 浓度低于治疗水平[50]。Lambert 等[50]发现标准剂量的 LPV/RTV (400/100 mg, 每天 2 次)在怀孕期间使用是合适的。Rabie 等[51]开展了一项针对 HIV 感染儿童的研究, 他们将 LPV/RTV 给药从每天 2 次调整为每 8 h 一次, 结果显示 64%的儿童达到了 LPV 的靶浓度(≥1 mg/L); 如果将剂量增加 1 倍, 仍然每天 2 次, 那么只有 40%的儿童能达到 LPV 的靶浓度。研究报道, 用 LPV/RTV 治疗 HIV 时 LPV 的血药浓度范围是 8~24 μmol/L[52]。

在疫情发生初期, 有学者提出 LPV/RTV 可用于新型冠状病毒肺炎的治疗[53~54], 而 LPV/RTV 也确实被纳入我国第三版新型冠状病毒肺炎的诊疗方案中。LPV/RTV 可以显著降低病毒载量, 减轻

临床症状[55]; 同时也可以降低新型冠状病毒肺炎从重症到危重症的转化率[56]。然而, LPV/RTV 对新冠肺炎的临床疗效尚有争议, Cao 等[57]在 199 例重症 COVID-19 住院患者中对 LPV/RTV 进行了一项随机试验, 发现洛匹那韦/利托那韦不能缩短临床症状缓解的时间。

目前, 检测 LPV/RTV 血药浓度的主要方法是 HPLC-MS 法[58]。本课题组在结合文献报道的基础上, 开发了 LPV/RTV 的 LC-MS 方法, 具体信息见表 1。

1.5 万古霉素

万古霉素是一种三环糖肽类抗生素, 同替考拉宁适应症相似, 在临床上主要用于治疗由革兰氏阳性菌引起的感染。它是治疗耐甲氧西林金黄色葡萄球菌和耐甲氧西林凝固酶阴性葡萄球菌感染的一线药物[59], 同时还可以用于骨髓炎、皮肤和软组织感染、心内膜炎等重症感染的治疗, 是目前抗感染的主要药品[60]。

万古霉素的治疗效果及其产生的毒性大小与发生不良反应的概率等都和它的血药浓度有关[61], 基于这一点, 目前临床上使用万古霉素时一般都要对其进行治疗药物监测。最低抑菌浓度(MIC)≤1 mg/L 时, AUC/MIC>400 有良好的细菌清除性能[62~63]。Zelenitsky 等[64]以 AUC/MIC 为靶标, 将其目标值从>451 增加到>578, 发现 MRSA 感染性休克患者的生存率从 70.0%增加到 81.8%。由于 AUC 数据获取较难, 万古霉素 TDM 一般也以谷浓度或峰浓度为靶标[65]。中国万古霉素 TDM 指南中建议, 以谷浓度为靶标时, 要把给药 3 d 后的谷浓度作为监测指标, 目标浓度维持在 10~15 mg/L, 严重感染时维持在 10~20 mg/L[66]。以峰浓度为靶标时, 峰浓度(给药后 0.5~1.0 h 采血标本)为 30~40 mg/L[65]。张迎迎等[67]将 1 例食管穿孔患者的给药剂量从 1 g、12 h 一次调整为 1 g、8 h 一次, 结果显示万古霉素谷浓度从 7.20 mg/L 上升到 12.38 mg/L, 达到万古霉素目标谷浓度 10~20 mg/L。此外, Ye 等[68]通过荟萃分析发现, 万古霉素 TDM 能显著提高治疗的有效率, 降低肾毒性的产生率。以上研究中万古霉素血药浓度检测的方法主要有 HPLC 法、LC-MS/MS 法[69]和荧光偏振免疫法[70]等。

对于危重的新冠肺炎患者, 大多需要采用有创呼吸机, 而研究显示 31%的患者可能会导致二次感染[71]。革兰氏阳性菌(包括耐甲氧西林金黄色葡萄球菌和肠球菌属)是医院感染的主要病原菌, 尤其是呼吸机相关性肺炎[72]。因此, 危重的新冠肺炎患者需要使用万古霉素, 但 PubMed 数据库(https://pubmed.ncbi.nlm.nih.gov/)中尚未检索到 vancomycin (万古霉素)与 COVID-19 的报道。本课题组参考文献资料, 开发了基于 LC-MS 的万古霉素血清浓度检测方法(表 1), 对 8 例使用万古霉素的新冠肺炎患者进行了 TDM 研究, 发现 50%的个体在首次检测万古霉素时血药浓度低于治疗窗, PK-PD 模型分析显示 8 个患者的 AUC/MIC 均不在 400~900 范围内(数据未发表)。

表 1 治疗药物监测中抗新型冠状病毒药物在血浆/血清中的部分参数汇总

Table 1 Summary of partial parameters of anti-novel coronavirus drugs in plasma/serum in TDM

Compounds	Concentration	Ion pairs (m/z)
Teicoplanin	10~20 μg/mL	940.4→316.2
Vancomycin	10~15 μg/mL (C_{min})	725.8→143.9
	20~40 μg/mL (C_{max})	
HCQ	100~130 ng/mL (C_{min})	336→247
	170~300 ng/mL (C_{max})	
Arbidol	10 μmol/L	479→434
LPV/RTV	8~24 μmol/L	LPV: 629.4→429.1
		RTV: 721.4→295.9

2 总结

本研究全面综述了羟基氯喹、替考拉宁、阿比朵尔、克立芝(LPV/RTV)和万古霉素 5 种药物在其老适应症中的治疗药物监测进展, 且对这些药物在新冠肺炎患者中的有限研究进行了简述。由于这些药物在新冠肺炎患者中的 TDM 研究较少, 所以 PK 数据的适用性有待在更大的人群中进行验证。但是本课题组(研究数据尚未发表)和国际的研究[24]均显示: 治疗药物监测能为新发传染病尽快提供最佳给药方案。

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