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利奈唑胺对肾功能不全 G⁺ 感染患者血小板减少的相关性研究 *

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摘要 目的:分析利奈唑胺对肾功能不全 G⁺ 患者血小板减少的关系。**方法:**回顾性分析 92 例应用利奈唑胺治疗的革兰阳性球菌感染患者的临床资料,根据是否伴有肾功能不全分为肾功能不全组(33 例),正常组(59 例),检测用药前、用药后血小板计数,观察停药后血小板计数恢复正常时间及不良反应发生情况。**结果:**肾功能不全组治疗后血小板计数显著低于治疗前及正常组($P<0.01$),正常组治疗前、后血小板计数比较无统计学意义($P>0.05$);肾功能不全组血小板减少发生率高于正常组($P<0.05$);停药后正常组血小板恢复正常时间短于肾功能不全组($P<0.01$);肾功能不全组血红蛋白下降率高于正常组($P<0.05$),其余不良反应发生率比较差异无统计学意义($P>0.05$)。**结论:**感染患者肾功能可影响利奈唑胺所致血小板减少发生率,肾功能不全患者在应用利奈唑胺时应定期监测血小板计数。

关键词:利奈唑胺;肾功能不全;血小板减少

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Correlation of Linezolid with Thrombocytopenia in Patients with Renal Dysfunction*

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ABSTRACT Objective: To analyze the relationship of renal dysfunction and linezolid-induced thrombocytopenia. **Methods:** A retrospective analysis was performed on the clinical data of 92 cases of linezolid-treated patients with Gram-positive bacterial infections. 33 patients with renal dysfunction were designed into the renal dysfunction group, and 59 other patients were assigned as normal group. Detected the platelet before and after treatment, and observe the time for platelet count recovering to normal after treatment and the occurrence of adverse reactions. **Results:** After treatment, platelet count of renal dysfunction group was significantly lower than before treatment and normal group ($P<0.01$). There was no statistical difference in platelet count between before and after treatment in the normal group ($P>0.05$). In renal dysfunction group, the incidence of thrombocytopenia was higher than in the normal group($P<0.05$). After treatment, the normal group took shorter time to have the platelet recovered than the renal dysfunction group($P<0.01$). Hemoglobin decreased greater in renal dysfunction group than in the normal group ($P<0.05$). The other incidences of adverse reactions showed no significant differences ($P>0.05$). **Conclusion:** The kidney function of infected patients can affect their linezolid-induced thrombocytopenia. Patients with renal dysfunction should have regular monitor on platelet counts when taking linezolid.

Key words: Linezolid; Renal dysfunction; Thrombocytopenia

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前言

利奈唑胺是新一代恶唑烷酮类抗菌药物,其对多重耐药的革兰阳性球菌的抗菌作用良好,加之其肾毒性轻微,常用作万古霉素的替代药物^[1]。但近年研究发现,利奈唑胺可引发血小板减少,影响预后。临床利奈唑胺引发血小板减少的机制尚未明确,但有研究指出,利奈唑胺导致血小板减少与感染患者肾功能相关,而且具有明显的血药浓度依赖性。本文回顾性分析给予利奈唑胺治疗的肾功能不全患者及肾功能正常患者的临床资料,分析感染患者肾功能与利奈唑胺致血小板减少的关系。

1 资料与方法

1.1 一般资料

选取本院应用利奈唑胺治疗的革兰阳性球菌感染患者 92 例。入选标准:①符合《感染病学》中肺部感染诊断标准^[2];②痰细菌培养检出革兰阳性球菌,且为利奈唑胺抗菌谱范围内;③血肌酐 $>10^4 \mu\text{mol/L}$;④单独给予利奈唑胺治疗,治疗时间 ≥ 3 d。排除标准:①严重贫血者,即血红蛋白 $<60 \text{ g/L}$ 者;②有出血倾向者;③利奈唑胺过敏者;④严重肝功能异常者。

根据肾小球滤过率(GFR)检查结果分为肾功能不全组

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(GFR≤ 60 mL/min)33 例,其中男 21 例,女 12 例;年龄 29~74 岁,平均(56.5± 11.4)岁;利奈唑胺治疗时间 3~14 d,平均(5.6± 2.2) d;慢性肾功能不全 16 例,急性肾小球肾炎 9 例,急性肾功能不全 5 例,肾衰竭 2 例,尿毒症 1 例。肾功能正常组(GFR>60 mL/min)59 例,男 39 例,女 20 例;年龄 27~72 岁,平均(57.3± 10.6)岁;利奈唑胺治疗时间 3~13 d,平均(5.3± 1.9) d。两组性别、年龄、治疗时间比较差异无统计学意义(P>0.05),具有可比性。

1.2 给药方法

两组均给予利奈唑胺注射液(美国辉瑞公司生产,批号 165800033),600 mg/次,12 h/次,2 次/d,疗程 3~14 d。

1.3 观察指标

测量两组用药前、后血小板计数;统计血小板计数减少发生率;记录停药后血小板计数恢复正常时间。

1.4 血小板减少评定标准

血小板减少为血小板计数较用药前下降≥ 75%或血小板

计数<100.0× 10⁹/L。分级标准^[3]:以Ⅰ级,血小板计数>75.0× 10⁹/L,但<100.0× 10⁹/L;②Ⅱ级,血小板计数为 50.1× 10⁹/L~75.0× 10⁹/L;③Ⅲ级,血小板计数为 25.0× 10⁹/L~50.0× 10⁹/L;④Ⅳ级,血小板计数<25.0× 10⁹/L。

1.5 统计学方法

计量资料用($\bar{x} \pm s$)表示,采用 t 检验;计数资料采用 χ^2 检验,P<0.05 为差异有统计学意义。

2 结果

2.1 用药前、后血小板计数及血小板减少发生率

两组用药前血小板计数比较差异无统计学意义(P>0.05);用药后两组血小板计数均低于用药前,但肾功能不全组显著低于正常组,差异比较有统计学意义(P<0.01);肾功能不全组用药后血小板计数 22.6× 10⁹/L~147.5× 10⁹/L,血小板计数减少发生率高于对照组,差异比较有统计学意义(P<0.05)(表 1)。

表 1 两组用药前、后血小板计数及血小板减少发生率比较

Table 1 The platelet count before and after treatment and platelet reduction incidence between two groups

Groups	n	Platelet count(× 10 ⁹ /L)		Platelet reduction incidence [n (%)]				
		Before treatment	After treatment	Grade I	Grade II	Grade III	Grade IV	Total incidence
Renal dysfunction group	33	183.9± 47.9	116.6± 34.9***	7(21.21)	10(30.30)	5(15.15)	2(6.06)	24(72.73) [△]
Normal group	59	185.6± 49.6	151.4± 50.3*	10(16.95)	8(16.95)	1(1.69)	0(0)	19(32.20)

Note: Comparison between before and after having drugs in the same group, *P<0.05, P<0.01**, comparison between group after having drugs, #P<0.01, △P<0.05.

2.2 血小板计数恢复正常时间

肾功能不全组 12 例需要输注血小板,停药后血小板计数恢复到基线值需要 4~16 d,平均(7.4± 2.9) d。肾功能正常组无 1 例需要输注血小板,停药后血小板计数恢复到基线值需要 2~9 d,平均(4.2± 1.6) d。两组停药后血小板计数恢复到基线值时间比较差异有统计学意义(P<0.01)。

2.3 不良反应发生情况

两组用药前、后肌酐、尿素氮比较差异无统计学意义(P>0.05);肾功能不全组用药后 3 例轻度头痛、5 例恶心、3 例轻度腹泻、7 例伴有血红蛋白下降、2 例伴有白细胞下降;正常组 2 例轻度头痛、3 例恶心、2 例伴有血红蛋白下降、1 例伴有白细胞下降。两组血红蛋白下降比例比较差异有统计学意义(P<0.05),其他不良反应发生率比较差异无统计学意义(P>0.05),见表 2。

表 2 两组不良反应发生情况比较

Table 2 Incidence of adverse events compares between two groups

Groups	Cases (n)	anhydride(μ mol/L)		Urea nitrogen(mmol/L)		Adverse events				
		Before treatment	After treatment	Before treatment	After treatment	Headache	Nausea	Diarrhea	Decrease of Hemoglobin	Decrease of leukocyte
Renal dysfunction group	33	275.43± 123.67	281.27± 107.89	22.34± 9.76	24.31± 10.02	3(9.09)	5(15.15)	3(9.09)	7(21.21)	2(6.06)
Normal group	59	64.98± 17.56	66.74± 18.05	5.78± 2.01	6.04± 1.87	2(3.39)	3(5.08)	0(0.00)	2(3.39)	1(1.69)

Note: comparison between groups, $\chi^2=5.09$, P<0.05.

3 讨论

利奈唑胺是全球第一个人工合成的恶唑烷酮类抗菌药物,其对葡萄球菌属、肠球菌属、肺炎链球菌属等革兰阳性球菌具有高效抗菌作用,尤其是对目前困扰临床的耐万古霉素肠球

菌、耐甲氧西林金黄色葡萄球菌等多重耐药菌属也有高效抗菌活性^[4]。国内外文献报道的应用利奈唑胺致血小板减少发生率从 20%~52%不等^[4-6]。而特殊人群应用利奈唑胺所致的血小板减少发生率也有所差异。国内有小样本研究报道^[5],老年感染者应用利奈唑胺后血小板减少发生率高于青年组及新生儿组,

差异比较有统计学意义($P<0.05$)。董海燕等^[9]研究发现,不同疾病患者应用利奈唑胺后血小板发生率也有差异。本研究中肾功能正常组应用利奈唑胺后血小板减少发生率为 32.20%,与文献报道基本相符,但肾功能不全组血小板减少发生率为 72.73%,显著高于文献报道水平,提示肾功能可能对利奈唑胺所致的血小板减少有一定的影响。

目前对于利奈唑胺引发血小板减少的机制尚未明确。刘晓等^[7]进行多因素 Logistic 回归分析发现,利奈唑胺致血小板减少症的危险因素包括利奈唑胺用药剂量、用药时间、肌酐清除率。国外学者 Morata 等^[8]也得到相同的研究结果,其报道成年肾功能不全的感染患者在应用利奈唑胺后,不同时间点利奈唑胺的血药浓度不同。根据 Cockcroft-Gault 公式计算肌酐清除率发现,肌酐清除率决定着利奈唑胺的清除率,而且血小板计数减少呈利奈唑胺血药浓度依赖性。由此可知,肾功能不全使利奈唑胺在一定时间内保持较高的血药浓度,进而增加血小板减少发生率。Nukui 等^[9]研究发现,肺部耐甲氧西林金黄色葡萄球菌感染伴有严重肾功能不全患者,在多次应用利奈唑胺后,利奈唑胺的主要代谢产物 PNU-142300 与 PNU-142586 的蓄积是肾功能正常患者的 10 倍,这可能是肾功能不全患者影响利奈唑胺所致血小板减少的原因之一^[10-13]。本研究中,用药后肾功能不全组血小板计数显著低于肾功能正常组($P<0.01$),而停药后肾功能不全组血小板计数恢复到基线值所需的时间长于肾功能正常组($P<0.01$),这可能与肾功能不全组肌酐清除率下降,而停药后对于利奈唑胺的清除能力减弱有关,与刘晓、Morata 等研究得出的肌酐清除率决定着利奈唑胺的清除率相符^[14-16]。

临床对于肾功能不全患者应用利奈唑胺后血小板减少的处理存在一定争议。Pea 等^[17]研究认为,无论是肾功能不全患者还是肾功能正常患者,在应用利奈唑胺治疗后,血肌酐水平并无显著变化,肾功能不全患者用药后并未加重肾功能损害,反而有 19 例患者肾功能好转。

因此其主张无论患者肾功能如何,用药后利奈唑胺血药浓度无显著差异,无需对肾功能不全患者调低剂量。对于肾功能不全患者,调整利奈唑胺剂量,使其 C_{min} 与 AUC_{0-24 h} 分别维持在 2~7 $\mu\text{g/mL}$ 和 160~300 $\text{mg}\cdot\text{h/L}$ 时,可使血小板计数恢复正常,减少不良反应^[18-20]。本研究中,笔者并未对利奈唑胺的剂量进行调整。但笔者认为,利奈唑胺属于时间依赖性抗菌药物,应尽量减少利奈唑胺使用时间。

综上所述,革兰阳性球菌感染患者肾功能可影响利奈唑胺所致血小板减少发生率,但其机制有待进一步研究。肾功能不全患者在应用利奈唑胺时应定期监测血小板计数,尽量缩短利奈唑胺使用时间。

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