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肾脏移植病人静脉滴注环孢素 A 的药物动力学

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Pharmacokinetics of cyclosporin A in renal transplant patients after infusion

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ABSTRACT Seventeen patients after renal transplantion were infused iv cyclosporin A (CsA) 0.65 ± 0.13 mg · kg^{-1} · h^{-1}. Blood CsA was determined by fluorescence polarization immunoassay (FPIA). Pharmacokinetic parameters were calculated from micro-computer pharmacokinetic programme $T_{\frac{1}{2}\beta} = 8.6 \pm 3.4$ h, $V_d = 3.2 \pm 1.3$ L · kg^{-1}. No significant difference was found between sexes and between age groups.

KEY WORDS cyclosporins; pharmacokinetics; kidney transplantation; intravenous infusions

提要 17 例肾脏移植病人术后 2-4 d，iv 输注环孢素 A 0.65 ± 0.13 mg · kg^{-1} · h^{-1}，荧光偏振免疫法测定全血环孢素 A 浓度，非线性最小二乘法计算动力学参数。环孢素 A 药物动力学过程符合二房室开放模型。V_d: 3.2 ± 1.3 L · kg^{-1}, $T_{\frac{1}{2}\beta}$: 8.6 ± 3.4 h.

关键词 环孢素类；药物动力学；肾移植；静脉内输注

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免疫抑制剂环孢素 A (cyclosporin A, CsA)可用于多种器官移植及治疗某些免疫性疾病。iv 输注 CsA 适用于肾移植初期及口服 CsA 吸收较差的病人。开展各种给药途径下 CsA 临床药物动力学研究及治疗药物监测有助于提高其临床疗效[1]。国内尚未见有关 CsA iv 给药动力学研究报道。本文研究 17 例肾移植初期病人 iv 输注 CsA 的临床药物动力学，并分析病人性别、年龄对动力学过程的影响。

MATERIALS AND METHODS

1 CsA 血药浓度测定 荧光偏振免疫法 (FPIA)多抗试剂在荧光偏振免疫分析仪(TDx Analyzer)上测定 CsA 全血浓度[2]。

2 观察对象及给药方法 肾移植病人 17 例(M 11, F 6)，年龄 22-56 a (40.4 ± 8.4 a)，体重 57.1 ± 6.4 kg。术后 2-4 d 将 CsA 250 mg

用 5%等渗葡萄糖注射液稀释成 50% (wt / vol)的 iv 输注液，以 0.65 ± 0.13 mg · $kg^{-1} \cdot h^{-1}$ 速率 iv 输注.

3 取血及数据处理 在 iv 输注 CsA 前，输注 CsA 过程中 1,3 h，停止 iv 输注 CsA 后 0，0.25，1，3，5，14 h 取静脉血 1.0 ml 于肝素抗凝试管中，FPIA 法测定 CsA 浓度. 并用 MCPKP 药物动力学程序(中国农业科学院中兽医研究所 中国兰州)[3]计算 CsA 药物动力学参数. t 检验比较性别、年龄在动力学参数上的差异.

RESULTS

肾移植病人 iv 输注 CsA 的药物动力学过程符合二房室开放模型. CsA $T_{\frac{1}{2}\beta} = 8.6 \pm 3.4$ h，$V_d = 3.2 \pm 1.3$ L · kg^{-1}. 动力学参数见 Tab 1. 研究结果表明不同性别、年龄组病人动力学参数无显著性差异($P > 0.05$).

DISCUSSION

CsA 的药物动力学过程符合二房室开放模型，与文献[4]报道一致. CsA 快速分布相 $T_{\frac{1}{2}\alpha}$ 较短(0.27 ± 0.16 h)，表明CsA可很快从血液分布到其它组织器官中. CsA $K_{el} = 0.36 \pm 0.13$ h 与文献[4](0.31 ± 0.11 h)报道相近，CsA 的 $T_{\frac{1}{2}\beta}$ 较长(8.6 ± 3.4 h). 由于其主要通过肝脏代谢消除，CsA 对肝脏有一定毒副作用、临床常与 CsA 合并使用的药物如甲基强的松龙、强的松、酮康唑可与 CsA 竞争肝脏代谢酶并对肝脏 P-450 代谢酶有损伤作用. 因此当病人长期使用 CsA 及合并用药较多时，CsA $T_{\frac{1}{2}\beta}$ 可延长并易导致CsA体内蓄积. 在 CsA 监测过程中发现一些病人在停止使用 CsA 2-5 d，CsA 在血中仍可维持一定浓度水平. 这除与代谢物干扰有关外，$T_{\frac{1}{2}\beta}$ 延长也是导致这种现象产生的重要因素. CsA $T_{\frac{1}{2}\beta}$ 可长达 43.31 h[4]，而且其它动力学参数也可随用药时间而改变[5]. 虽然男、女病人；40 a 以上、40 a 以下病人的动力学参数无显著差异、但 CsA 治疗药物监测中发现当使用相同剂量时，CsA 在男病人、年轻病人血中浓度低于女病人、年老病人，而且文献[6]也认为年龄可影响 CsA 的动力学过程. 也许因观察例数不够，本文尚无法说明性别、年龄对 CsA 动力学过程的影响.

FPIA 法多抗试剂测定 CsA 血中浓度要较液相色谱法(HPLC)、放射免疫法(RIA)单抗试剂的测定结果高，这与 CsA 体内代谢物交叉干扰有关，这种干扰可达 1%-110%[7]. FPIA 法和 RIA 法、HPLC 法的测定结果具有良好相关性. 对单个病人来说这种相关性更好[7-8]. 肾移植初期病人单剂量 iv 输注 CsA

Tab 1. Pharmacokinetic parameters of CsA after iv infusion in renal transplantation patients. $\bar{x} \pm s$. * $P > 0.05$.

	Sex		Age		Total
	Women / $n = 6$	Men / $n = 11$	< 40 a / $n = 6$	> 40 a / $n = 11$	/ $n = 17$
K_{12}, h^{-1}	2.2 ± 1.4	2.3 ± 1.3*	2.1 ± 1.0	2.3 ± 1.5*	2.3 ± 1.3
K_{21}, h^{-1}	1.0 ± 0.8	0.9 ± 0.4*	0.9 ± 0.4	0.9 ± 0.6*	0.9 ± 0.6
K_{el}, h^{-1}	0.31 ± 0.12	0.39 ± 0.13*	0.37 ± 0.07	0.36 ± 0.16*	0.36 ± 0.13
$T_{\frac{1}{2}\alpha}$, h	0.33 ± 0.24	0.24 ± 0.09*	0.27 ± 0.13	0.27 ± 0.18*	0.27 ± 0.16
$T_{\frac{1}{2}\beta}$, h	9.8 ± 4.9	7.8 ± 2.0*	7.8 ± 2.0	8.9 ± 4.0*	8.6 ± 3.4
V_d, L · kg^{-1}	3.8 ± 1.5	2.8 ± 1.0*	3.0 ± 1.3	3.2 ± 1.2*	3.2 ± 1.3
V_c, L · kg^{-1}	1.0 ± 0.4	0.69 ± 0.19*	0.73 ± 0.21	0.9 ± 0.4*	0.8 ± 0.3

时血中仍以原型药物为主，而且根据 FPIA 法测定 CsA 全血中浓度计算出的主要动力学参数和采用 HPLC 法测定计算出的参数相近[4].

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α-二甲胺基-环己氧基二甲基镓对红内期伯氏和约氏疟原虫超微结构的影响

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Effects of α-dimethylamino-cyclohexoxyl-dimethyl gallium on ultrastructure of erythrocytic stage of *Plasmodium berghei* and *P yoelii*

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ABSTRACT The effects of α-dimethylamino-cyclohexoxyl-dimethyl gallium (DCDG), a new antimalarial drug developed in China, on the ultrastructure of murine malaria parasites *in vivo* was studied in comparison with those of chloroquine (CQ) and artemisinin (Art). All these 3 antimalarials were administered ig to mice at dosages of 1-3, 40-80, and 200-400 mg · kg^{-1} for DCDG, CQ, and Art respectively, based on a similar intensity of morphological changes in the parasites. Blood samples were collected for electron microscopy from 15 min to 48 h after medication. The results showed that DCDG killed the malaria parasites (both asexual and sexual forms) rapidly. The most prominent changes in DCDG-treated parasites were serious dilation of perinuclear space, endoplasmic reticulum, mitochondrion and some other vesicles or intermembranous spaces. These led to the formation of large autophagic vacuoles containing some membranous materials, which were subsequently extruded. Then the parasite cells became more concentrated, finally pyknotic and died. The mode of action was very different from that of CQ and Art.

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