目的：探讨三七总皂甙(PNS)的脑保护作用机制. **方法**：体外培养鸡胚脑神经细胞，用氰化钠造成缺氧，作为试验PNS作用的模型，细胞内三磷酸腺苷(ATP)和培养液中肌酸激酶浓度作为观察指标，分别用HPLC-UV和全自动生化分析仪定量. **结果**：缺氧前30 min将PNS 50和100 mg L^{-1}加入到培养液中能明显延缓缺氧2 h细胞内ATP的耗竭(分别为11.3 ± 1.5和12.8 ± 2.2 μmol/g protein)，促进再给氧30 min时细胞内ATP的恢复(分别为21.0 ± 2.0和22.7 ± 2.6 μmol/g protein). PNS于缺氧开始或再给氧时给予，仍能促进再给氧期细胞内ATP的恢复，减少神经细胞内肌酸激酶的释放.
结论：PNS对培养神经细胞缺氧性损伤具有保护作用，其机制可能与改善能量代谢，保护细胞结构完整性有关.

关键词 三七；人参；皂苷类；培养的细胞；神经元；缺氧症；腺苷三磷酸；肌酸激酶

BIBLID: ISSN 0253-9756 Acta Pharmacologica Sinica 中国药理学报 1995 Sep; 16 (5): 402—404

Pharmacokinetics of ceftizoxime in renal failure patients without dialysis

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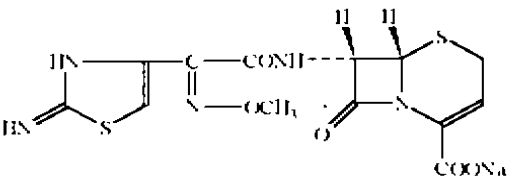
AIM: To investigate the pharmacokinetics of ceftizoxime (Cef) in renal failure patients without any dialysis and supply the basis for a suitable clinical regimen. **METHODS**: Cef in plasma and urine was assayed by HPLC. **RESULTS**: After injecting Cef 16.7 mg kg^{-1}, Cef concentration in blood was described as a 2-compartment open model. The main pharmacokinetic parameters were V_d 0.55 ± 0.17 L kg^{-1}; AUC 879 ± 460 mg L^{-1} h; Cl 27 ± 11 mL kg^{-1} h^{-1}. $T_{\frac{1}{2}\beta}$ was 15 ± 4 h. **CONCLUSION**: $T_{\frac{1}{2}\beta}$ in renal failure patients was about 10 times longer than that in normal volunteers. The clinical regimen should be adjusted in renal failure patients with infection, either prolonging the interval between Cef administration, or decreasing Cef dosage.

KEY WORDS ceftizoxime; kidney failure; pharmacokinetics

Ceftizoxime (Cef) is a potent, β-lactamase stable cephalosporin of the 3rd generation, against a wide spectrum of *Gram*-positive and -negative bacteria[1]. Since Cef is eliminated mainly through urinary route, renal function plays a major role in its elimination[2]. This study was to investigate the pharmacokinetics of Cef in renal failure patients without any dialysis and to design a



Ceftizoxime sodium

Received 1994-01-04 Accepted 1994-11-21

suitable clinical regimen.

MATERIALS AND METHODS

Drugs and instruments Cef powder of 1 g per injection vial (batch № 901101) was supplied by Fujisawa Pharmaceutical Co, Japan. The assaying instruments consisted of a set of Hitachi 655 HPLC system equipped with a model 655-12 pump, a 655-22 wavelength adjustable uv detector, a 655-71B data processor, and a Rheodyne 7125 sample injector. The analytical column (150 mm × 5 mm) was packed with YWG-C_{18}(size 5 μm).

Men Four renal failure patients without any dialysis or infection, aged 55±s 5 (48−58) a, were selected with the medical history of 13±6 (9−20) a and body weight of 61±3 (58−62) kg. Their main laboratory data were blood urea nitrogen 25±10 (13−36) mmol L^{-1}; serum creatinine 568±268 (275−851) mmol L^{-1}, and creatinine clearance 0.30±0.12 mL s^{-1}. All the patients consented to join the study. No drug was used 72 h prior to and only Cef was injected during the study.

Protocol A single dose of Cef 16.7 mg kg^{-1} was injected iv. Blood samples were collected into heparinized tubes at 0, 3, 7, 12, 24, and 48 h. Plasma was immediately obtained by centrifugation (1000 × g). Urine was collected at 6-h intervals. Samples were kept at −20 ℃ until analysis.

Drug analysis Cef in plasma and urine was assayed by RP-HPLC, which was done on a C_{18} column with a mobile phase of acetonitrile : water : phosphoric acid : diethylamine = 1 : 9 : 0.2 : 0.25 (vol : vol, pH 3.0)[3]. The uv detector wavelengths were 254 nm for plasma and 290 nm for urine. The regression was linear within 1−160 mg L^{-1} (1, 5, 10, 20, 40, 80, and 160 mg L^{-1}) for plasma and 10−1600 mg L^{-1} (10, 50, 100, 200, 400, 800, and 1600 mg L^{-1}) for urine. The recovery rate of Cef was 99 %−103 % with a coefficient of variation <5 %.

Pharmacokinetic analysis The data of plasma concentrations were analyzed with MCPKP[4] on an IBM-PC computer. Compartment model of Cef disposition was fitted automatically and then pharmacokinetic parameters were calculated.

RESULTS

The time course of Cef concentrations in plasma of 4 patients was shown in Fig 1.

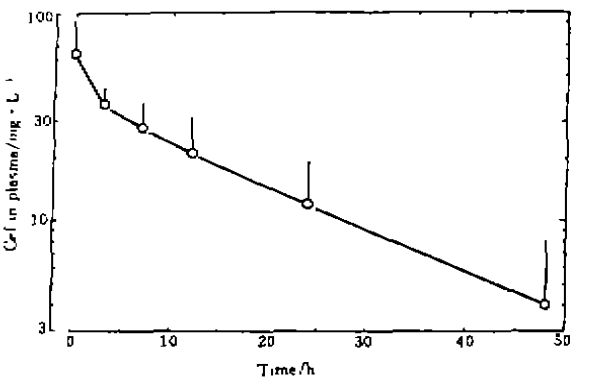


Fig 1. Cef in plasma after iv 16.7 mg kg^{-1} in 4 patients with kidney failure. $\bar{x}\pm s$.

The concentration of Cef in blood was described as a 2-compartment open model. The main pharmacokinetic parameters of Cef after iv 16.7 mg kg^{-1} were C_0 63±27 mg L^{-1}; V_d 0.55±0.17 L kg^{-1}; $T_{\frac{1}{2}\beta}$ 15 ±4 h; AUC 879 ±461 mg L^{-1} h; and Cl 27±11 mL kg^{-1} h^{-1} (Tab 1).

Tab 1. Pharmacokinetic parameters of ceftizoxime after iv 16.7 mg kg^{-1} in 4 patients with kidney failure.

Patient	1	2	3	4	$\bar{x}\pm s$
C_0/mg L^{-1}	30	90	78	53	63±27
$T_{\frac{1}{2}\beta}$/h	15	13	12	20	15±4
V_d/L kg^{-1}	0.66	0.73	0.42	0.38	0.55±0.17
Cl/mL kg^{-1} h^{-1}	31	39	25	13	27±11
AUC/mg L^{-1} h	642	518	811	1 546	879±461

Total Cef excreted in urine within 48 h was 36.5 %±9.8 % of the dose (Tab 2).

DISSCUSION

The investigation showed Cef disposition had no significant changes in the renal failure patients without any dialysis treatment, but its elimination was much slower. $T_{\frac{1}{2}\beta}$ in this study was 15±4 h, about 10 times longer

Tab 2. Ceftizoxime excreted in urine after iv 16.7 mg kg^{-1} in 4 patients with kidney failure. $\bar{x}\pm s$.

Time/h	Cef/mg	% of dose
0—6	88±37	8.8±3.7
6—12	85±33	8.5±3.3
12—18	57±26	5.7±2.6
18—24	53±29	5.3±2.9
24—30	20±7	2.0±0.7
30—36	30±16	3.0±1.6
36—42	19±15	1.9±1.5
42—48	13±11	1.3±1.1
Total	365±98	36.5±9.8

than that in normal volunteers[5]. Cef excreted in urine reached 90 %—100 % in normal volunteers within 24 h, which only 36.5 % in renal failure patients within 48 h. For normal renal function patients with infection Cef was injected iv 1 g every 8—12 h generally, and 2 g every 4 h for those severely infected[1]. In this study, plasma concentration remained still at 5.0 mg L^{-1} 48 h after the injection in renal failure patients without any dialysis treatment. Considering that MIC_{90} of Cef to *Gram*-negative bateria was 2.0 mg L^{-1}, the clinical regimen should be adjusted in renal failure patients with infection (either prolonging the interval between Cef adminstration, or decreasing the dosage), especially in those without any dialysis treatment so as to ensure the therapeutic effects and avoid adverse reactions.

ACKNOWLEGMENTS To Dr ZHANG Gou-Zhao and other doctors and nurses in the Department of Kidney Diseases, Changhai Hospital for their support and cooperation.

REFERENCES

1 Richards DM, Heel RC. Ceftizoxime. A review of its antibacterial activity, pharmacokinetic properties and therapeutic use. Drugs 1985; **29**: 281—329.

2 Kowalsky SF, Echols RM, Venezia AR, Andrews EA. Pharmacokinetics of ceftizoxime in subjects with various degrees of renal function. Antimicrob Agents Chemother 1983; **24**: 151—5.

3 Gao S, Li P, Liu GL, Wang SX. Analysis of ceftizoxime in plasma and urine by HPLC. Chin J Hosp Pharm 1992; **12**: 149—51.

4 Xia WJ, Cheng ZR. MCPKP — a microcomputer program specialized for pharmacokinetic compartment analysis. Acta Pharmacol Sin 1988; **9**: 188—92.

5 Li XT, Wang QN, Jiang YF. Pharmacokinetics of ceftizoxime in humans. Chin J Antibiot 1989; **14**: 425—32.

402-404 4

头孢唑肟在未透析肾衰病人的药物动力学

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目的: 研究头孢唑肟(Cef)在未透析肾衰病人的药物动力学, 为临床合理用药提供依据. **方法**: HPLC 法测定血浆和尿中 Cef 的浓度, **结果**: 单剂量 iv Cef 16.7 mg kg^{-1}, 病人血药浓度变化呈二室开放模型, 主要药物动力学参数: V_d 0.55±0.17 L kg^{-1}; AUC 879±461 mg L^{-1} h; Cl 27±11 mL kg^{-1} h^{-1}. $T_{\frac{1}{2}\beta}$为15±4 h. **结论**: 肾衰患者 $T_{\frac{1}{2}\beta}$约是正常志愿者的 11 倍, 感染时用药方案需调整, 或延长用药间隔, 或减少用药剂量.

关键词 头孢唑肟; 肾功能衰竭; 药物动力学

药动力学