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Influence of piperacillin on pharmacokinetics of etimicin in healthy volunteers

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KEY WORDS etimicin; piperacillin; pharmacokinetics; microbiological techniques

ABSTRACT

AIM: To investigate the influence of piperacillin on the pharmacokinetics of etimicin. **METHODS**: Ten healthy male volunteers subjects were administered randomly with 200 mg of etimicin alone or in combination with 2000 mg of piperacillin. After two weeks washout period, the subjects were crossed over to the second regimen. Blood and urinary samples were collected at specified time intervals. Etimicin concentration was analyzed using microbioassay method with *Bacillus pumillus* as the tested strain. Pharmacokinetic parameters were determined from serum concentration-time data with the 3p87-software package. **RESULTS**: Maximum serum concentrations of etimicin alone was (21 ± 5) mg/L compared with (19 ± 4) mg/L for the combination. The elimination half-lives were (1.9 ± 0.4) h and (1.9 ± 0.2) h for etimicin alone and in combination, respectively. The area under the concentration-time curve of etimicin alone was (38 ± 7) $mg \cdot h \cdot L^{-1}$ as opposed to (41 ± 8) $mg \cdot h \cdot L^{-1}$ in combination. Twelve hours after administration, urinary recovery rates of etimicin were (56 ± 8) % and (56 ± 6) % for etimicin alone and with piperacillin, respectively. **CONCLUTION**: The results indicated that the pharmacokinetics of etimicin was not affected by concurrent administration of piperacillin in healthy male volunteers. No modification in dosing regimen is necessary when two drugs were co-administered.

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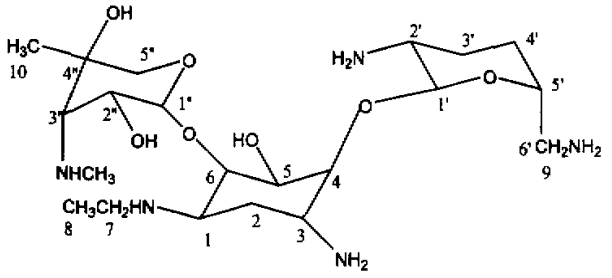
INTRODUCTION

Etimicin (ETI, antibiotic 89-07) is a new semi-synthetic parenteral aminoglycoside antibiotic in China[1]. ETI has highly potent activity against most of gram-negative bacillus compared with other aminoglycosides, such as gentamicin, amikacin, tobromicin, and netimicin[2,3]. In addition, the new drug exhibits lower ototoxicity and nephrotoxicity than other aminoglycosides[4,5]. Therefore, it has significant potential advantages over other aminoglycosides in the treatment of serious infection caused by gram-negative aerobic bacteria.

The treatment of serious pseudomonal infections often requires the use of aminoglycosides in combination with beta-lactam antibiotics. The standard combination therapy can exert synergistic activity against the invading pathogens and can also delay the emergence of resistant strains of bacteria[6,7]. However, pharmacokinetic interaction of etimicin between these two classes of antibiotics has been reported in patients with normal and impaired renal functions[8]. The ototoxicity and nephrotoxicity caused by aminoglycoside also could be further enhanced when co-administered[9]. Since ETI is frequently administrated in combination with beta-lactams, the present study was designed to determine whether piperacillin (PIP) has a potential influence on the pharmacokinetics of etimicin when given in combination. PIP was a representative of beta-lactam and was chosen as the test drug in our study.

MATERIALS AND METHODS

Materials ETI (white, purity = 586 mg/g) was provided by Jiangsu Institute of Microbiology. Injection of ETI was provided by the No 4 Pharmaceutics Factory of Wuxi. PIP was purchased from Qilu Pharmaceutics Factory. Peptone was a product of Oxide Limited



Etimicin

Basingstoke Hampshire (England). *Bacillus pumillus* was a generous gift from Prof Zeng Yan-Lin, Shanghai Institute of Materia Medica, Chinese Academy of Sciences.

Volunteers Approval for this study was obtained from the Ethics Committee on Human Research of the Henan Medical University. Ten healthy male subjects with no known allergies to penicillin or other beta-lactam agents participated in the study. Physical examinations and laboratory tests including blood, urine, liver, kidney, and electrocardiogram showed no abnormal findings. The mean age of the subjects was (20.5 ± 0.9) a, and the mean body weight was (60 ± 6) kg. Informed written consents in according with the Helsinki Declaration (Somerset West Amendment, 1996) were obtained from all volunteers. None of the volunteers took other antimicrobial agents during the two weeks preceding the study. Cigarette and alcohol were forbidden on the study days.

Microbioassay method ETI levels in serum were determined by a validated agar diffusion microbioassay method[10]. *Bacillus pumillus* was used as the test strain. The standard curve was performed in human normal serum or phosphate buffer solution (PBS, pH 7.4). The linear relation was determinated at the concentration of 64, 32, 8, 4, 2, 1, 0.5 mg/L. PIP was added into the standard solution with 10-fold concentration of ETI as the combination *in vitro*. Ten μL sample was used to quantity the antibacterial loop diameter as the characterization of the antibacterial activity of ETI alone and in combination with PIP. The intra- and inter-day coefficients of variation were assayed by 5 serum samples with different concentrations for 5 times in a day or in 5 consecutive days.

Influence of PIP on the pharmacokinetics of ETI The study was designed in a randomized cross-over study. The subjects firstly received administration of 200 mg of ETI alone or in combination with 2 g of PIP. ETI was administrated in 200 mL of 0.9 % sodium chloride for 30 min via intravenous infusions using a constant-rate infusion pump. PIP in 20 mL of 5 % glucose was infused into forearm less than 5 min prior to medication of ETI. After two weeks washout period, the subjects were crossed over to the second regimen. Blood was sampled by puncture the finger with a 22-gauge needle for determination of the antibacterial activity against *Bacillus pumillus* at the following time points: 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, and 8 h after administration. Serum containing ETI was separated and stored at −20 ℃ until assayed. The urine output of each of subjects was collected from 0 to 3, 3 to 6, and 6 to 12 h after administration. The volume of the voided urine were recorded and 3 mL portion was diluted with PBS (pH 7.4) into 1∶8, 1∶16, and 1∶32 for the high concentration of ETI in urine sample. These processed samples were stored at −20 ℃ pending analysis. Ten μL of serum or processed urine was used to quantity the antibacterial loop diameter as the characterization of the antibacterial activity to *Bacillus pumillus*. The highest observed concentration, which occurred at the end of intravenous infusion, was defined as C_{max}. Pharmacokinetic parameters of ETI were calculated and analyzed by 3p87 software package. The weighting function was determined as $1/C^2$. Urine recovery of ETI was calculated as the product of EMI concentration and the total volume of urine for a given interval for 12 h.

Statistical analysis Statistical analysis of the concentration and pharmacokinetic parameters were performed using paired Student-*t* test (SPSS software package, USA, 1997) in ETI alone and in combination with PIP. Correlation analyses were performed by least square linear regression. *P* value less than 0.05 was considered statistically significant.

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RESULTS

Influence of PIP on ETI serum concentration *in vitro* The standard curves for ETI in serum and urine samples were linear within the concentration ranges of 0.5 to 64 mg/L for etimicin alone and in combination with PIP *in vitro*. The limit of sensitivity of the assay was 0.5 mg/L in both serum and urine samples. Antibacterial loop diameter as the characterization of the antibacterial activity has no difference between etimicin alone and in combination (Tab 1). The mean intra- and inter-day coefficients of variation were less than 6 %.

Influence of PIP on pharmacokinetics of ETI The mean serum concentration-time curves for ETI alone and in combination with PIP were shown in Fig 1.

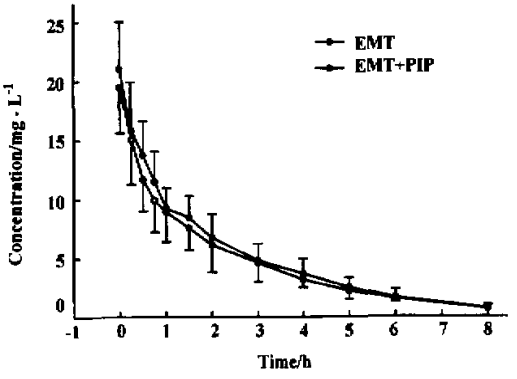

Fig 1. Serum concentration-time plots for etimicin (200 mg) alone and in combination with piperacillin (2 g) adminstered intravenously in healthy male volunteers. $n = 10$. $\bar{x} \pm s$.

Maximum serum concentrations of etimicin alone was (21 ± 50) mg/L compared with (19 ± 4) mg/L for the combination. Urine excretion amount and urinary recovery rates of etimicin were (111 ± 16) mg *vs* (112 ± 12) mg and (56 ± 8) % *vs* (56 ± 6) % for etimicin alone and with piperacillin, respectively.

The concentration-time curves of ETI alone and combination with PIP in healthy male volunteers were fitted with two-compartment open model. The concentration-time equations of ETI alone and in combination with PIP were $C = 6.7091e^{-3.9373t} + 12.9921e^{-0.3610t}$ and $C = 6.7215e^{-3.5298t} + 14.37357e^{-0.3637t}$, respectively. Pharmacokinetic parameters were shown in Tab 2. The area under the concentration-time curve (AUC) was calculated by the log-trapezoidal rule with extrapolation to infinity. The elimination half-life ($T_{\frac{1}{2}\beta}$) were eliminated as $(\ln 2)/b$, where b is the absolute value of the slope of the least-square regression line for n-terminal datum points. There was no difference on these pharmacokinetic parameters in ETI alone and in combination with piperacillin.

DISCUSSION

In the study, a potent and rapid bactericidal effect of ETI was observed against *Bacillus pumillus*. The antibacterial activity of ETI alone and in combination with PIP (5 – 640 mg/L) were quite similar. Unlike the previously interactions with beta-lactams and aminoglycosides, our results documented that PIP does not affect the antibacterial activity to *Bacillus pumillus in vitro*.

Tab 1. The antibacterial loop diameter (mm) of ETI alone and in combination with PIP (10-fold) against *Bacillus pumillus* at the indicated concentration (mg/L) *in vitro*. $n = 5$. $\bar{x} \pm s$. $^aP > 0.05$ *vs* ETI.

	32	16	8	4	2	1	0.5	γ
ETI	16.3 ± 0.4	14.4 ± 0.3	13.31 ± 0.28	11.46 ± 0.27	9.69 ± 0.22	8.06 ± 0.11	6.45 ± 0.18	0.9969
ET + PIP	16.4 ± 0.6	14.5 ± 0.3[a]	13.4 ± 0.3[a]	11.28 ± 0.25[a]	9.6 ± 0.3[a]	8.18 ± 0.27[a]	6.52 ± 0.09[a]	0.9980

Tab 2. Influence of PIP on the pharmacokinetic parameters of ETI on healthy male volunteers. $n = 10$. $\bar{x} \pm s$. $^aP > 0.05$ *vs* ETI.

	C_{max}/mg·L^{-1}	$T_{\frac{1}{2}\alpha}$/h	$T_{\frac{1}{2}\beta}$/h	K_{10}/h^{-1}	AUC/mg·h·L^{-1}
ETI	21 ± 5	0.18 ± 0.07	1.92 ± 0.39	0.52 ± 0.18	38 ± 7
ETI + PIP	19 ± 4[a]	0.20 ± 0.07[a]	1.90 ± 0.22[a]	0.51 ± 0.17[a]	41 ± 8[a]

Furthermore, no difference of intra- and inter-day coefficients of variation indicated the microbiology method was credible and accurate to measure the concentration of EMI alone or in combination with PIP. This method was not only as accurate as high-pressure liquid chromatography (HPLC) for determining the concentration of antimicrobial agents, but also can assay the antimicrobiotical activity to tested strain[11-13].

Pharmacokinetic interactions between beta-lactam agents and aminoglycoside antibiotics have been studied extensively[14-16]. Concurrent administration of penicillin and an aminoglycoside significantly shortens the $T_{1/2}$ of the latter group of antibiotic[17], particularly in patients with renal impairment. In the contrary, cefoperazone can increase the maximum concentration of tobramycin in patients and extend the $T_{1/2}$ of tobramycin[9], as a result, the ototoxicity and nephrotoxicity caused by tobramycin would be increased when two drugs combined. Since ETI is minimally metabolized and excreted primarily in urine by the glomerular filtration process[18], and poorly bound to serum proteins, it was expected that concurrent administration of PIP would not affect the pharmacokinetics of ETI. In the current study, pharmacokinetic parameters of ETI were not affected by concurrent administration of PIP in healthy male volunteers. Therefore, No modification in dosing regimen is necessary when ETI was co-administered with PIP.

ETI, as a new aminoglycoside, has much advantage in the treatment of serious infectious caused by Gram-negative aerobic bacteria. However, the safety and interaction when ETI was co-administered with beta-lactams in patients, especially in old and neonatal, or liver or renal dysfunction, and when was given as twice a day or more and continuously remains unclear. Therefore, further studying the interaction of pharmacokinetics and pharmacodynamics with other beta-lactam antibiotics will be important.

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哌拉西林对健康男性志愿者依替米星药动学的影响

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关键词 依替米星；哌拉西林；药物动力学；微生物学技术

目的：探讨哌拉西林(piperacilin，PIP)对依替米星(etimicin，ETI)健康男性志愿者健康药动学的影响．**方法**：采用自身交叉试验．单用组：ETI 200 mg，静脉滴注；合用组：静脉推注 PIP 2 g 后，继之给予 ETI 200 mg，静脉滴注．血、尿中 ETI 浓度测定采用微生物法，检测菌为短小芽胞杆菌．**结果**：单用组和合用组的药时曲线均符合二房室开放模型，主要药动学参数如 $T_{1/2\beta}$、AUC 分别为(1.9±0.4)和(1.9±0.2) h；(38±7)和(41±8) mg·h·L^{-1}；12 h 尿药回收率分别为(56±8) %和(56±6) %．经统计学处理均无显著性差异($P>0.05$)．**结论**：两药合用时 PIP 对 ETI 健康男性志愿者药动学无明显影响．为临床两种药物合用提供了药代动力学依据．

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