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Short review

Influence of fever on the pharmacokinetics of ciprofloxacin

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Abstract

The influence of fever on the pharmacokinetics of ciprofloxacin was investigated in seven patients with acute febrile diseases. Antibiotic serum concentrations were determined using high-performance liquid chromatograpy (HPLC). The analog computer and the Simulink™ software package were used to identify the pharmacokinetic model and Penoclin™ software package to obtain the secondary parameters. During fever, higher maximum serum concentrations (C_{max}) of ciprofloxacin were observed in six out of seven patients. The result suggests that the influence of fever on the pharmacodynamics of ciprofloxacin is favorable. © 1999 Published by Elsevier Science B.V. and International Society of Chemotherapy. All rights reserved.

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1. Introduction

Fever may affect the absorption, distribution, and elimination of drugs. Changes in pharmacokinetics vary with the animal species, antibiotic and agent used to induce a febrile reaction. Very few studies have been done on humans. In etiocholanolone-induced fever and during acute febrile disease, serum concentration of gentamicin was lower than in afebrile persons [1]. Pharmacokinetics of cefotaxime in fever seems not to be altered [1], but ceftazidime and ceftriaxone showed larger volumes of distribution and higher clearance [2,3]. In febrile neutropenic patients, higher clearance of teicoplanin was observed [4].

2. Materials and methods

Patients enrolled in the study were hospitalized at the Department of Infectious Diseases, University Medical Center Ljubljana because of acute febrile diseases. The enrolment criteria included axillary temperature of $>$ 38°C at the beginning of antibiotic treatment, age >15 years and absence of underlying conditions or an underlying condition which did not deteriorate during the intercurrent febrile disease. No concurrent medications were allowed with the exception of the drugs taken chronically in an unchanged dosing regimen. All patients provided written informed consent. The study was approved by the Medical Ethics Committee.

Ciprofloxacin was given at a dosage of 200 mg every 12 h as an i.v. infusion over 30 min, the volume of the infusion being 100 ml.

Blood samples were drawn immediately predose, immediately after the end of the infusion, and at 1, 5, 3, 6,

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Table 1
Demographic data of patients studied, their diagnoses and the day of defervescence

Patient no.	Age (years)	Sex	Weight (kg)	Height (cm)	Diagnosis	Day of defervescence
1	39	M	83	179	Pyelonephritis	2
2	53	F	77	174	Pyelonephritis	4
3	51	F	88	166	Pyelonephritis	2
4	63	M	66	168	Pyelonephritis	5
5	51	F	62	158	Pyelonephritis	2
6	68	F	60	167	Pyelonephritis	4
7	63	F	95	170	Pyelonephritis, arterial hypertension	3

9 and 12 h after the initiation of the first infusion. Another series of blood specimens were taken following the same schedule during a period of up to 2 days after defervescence. Basic laboratory tests were performed at the beginning of the treatment and repeated after defervescence. Vital signs were recorded prior to, in the middle and at the end of the dosing interval under investigation, and twice daily between the two dosing intervals. The day of defervescence was defined as the first day when axillary temperature remained below 37.2°C in the morning and in the afternoon and did not relapse. Patients were considered to be evaluable for pharmacokinetic analysis if they became afebrile while on the same antibiotic regimen.

The blood samples were centrifuged and stored at −20°C.

Ciprofloxacin total serum concentrations were measured by using a high-performance liquid chromatographic assay. The analysis were carried out using a ConstaMetric III G pump (LDC Milton Roy), a flow-rate of 1 ml/min, a SpectroMonitor D LDC Milton Roy UV detector, $\lambda = 274$ nm, or a Shimadzu RF-535 fluorescence detector at excitation wavelength 277 nm and emission wavelength 451 nm, and a CI 4000 Milton Roy integrator. A Rheodyne 7125 injector with a 20- or 46-μl sample loop and a LiChroCART 250 × 4 mm column with LiChristopher 100 RP-18 packing material, 5 μm, were used. The mobile phase used for HPLC consisted of acetonitrile and 0.01 M phosphoric acid (20:80, v/v). Samples were prepared either with ultrafiltration or dialysis. One milliliter of serum sample was ultrafiltrated with the use of Amicon ultrafiltration system with 10000-Da molecular cut-off filter, then 20 μl of ultrafiltrate were injected in the column. For the dialysis, 0.01 ml of the standard solution of ciprofloxacin ($c = 0.66$ μg/ml) was added to 1 ml of serum sample diluted with equal volume of deionised water. The dialysis was performed using a Gilson ASTED system with cellulose–acetate membrane with molecular cut-off 10000 Da. During 10 min of dialysis the donor was moving (flow rate, 0.26 ml/min) and the acceptor was stagnant. For the acceptor solution the mobile phase was used. After 10 min, 46 μl of dialysate were injected in the column. With both methods the detection limit was found to be about 30 ng/ml and the linear range was between 20 ng/ml and 20 μg/ml. In all cases for the serum standards, serum was spiked with appropriate amount of standard ciprofloxacin solution and prepared in the same way as the samples.

A two-compartment pharmacokinetic model was fitted to the obtained data. The model structure was based on the previous knowledge of pharmacokinetic behaviour of ciprofloxacin [5]. The curve-fitting procedure using adaptive model scheme identification was applied. For this purpose a combination of the analog computer and digital simulation technique using Matlab™ with Simulink™ software was used. The equipment applied included a parallel processor EAI-2000 (Electronic Associates, West Long Branch, NJ, USA) and an IBM-compatible personal computer equipped with Matlab™ with Simulink™ software (The Mathworks, Natick, MA, USA). The first fitting of the model response to the measured concentrations was accomplished by manually changing the above-mentioned four parameters on the analog computer. These estimates were additionally tuned by means of Simulink™ yielding fits of acceptable quality. Since in the multiple dosage scheme the cumulation of ciprofloxacin in plasma was negligible, the data obtained in febrile and afebrile stages were treated as if they had been collected after a single dose.

In order to obtain secondary pharmacokinetic parameters, data were analyzed also by the use of software package Pcnonlin™ ver. 4.2 (Statistical Consultants, Lexington, USA). For this purpose, the built-in model 9 (two-compartment model with constant i.v. input and first-order output) from the Pcnonlin's pharmacokinetic library was used. For each patient distribution rate constant (a), elimination rate constant (b), AUC, Cl, and volume of distribution at steady state were calculated in the febrile stage and after defervescence.

Statistical analysis was performed using the Wilcoxon signed-rank test.

3. Results

Seven patients (five females and two males) completed the study. Their mean age was 55.4 years, S.D. 9.4 years.

Demographic data, the diagnoses and the day of defervescence are presented in Table 1. A comparison of basic laboratory data during fever and after defervescence showed significantly higher white blood cell count, packed cell volume, and blood urea nitrogen concentrations, and significantly lower serum potassium concentrations in febrile patients (Wilcoxon signed rank test, $P < 0.05$). Microparameters of the pharmacokinetic models of ciprofloxacin and secondary pharmacokinetic parameters are shown in Table 2. No significant difference was found between microparameters obtained during fever and after defervescence. In three patients [1,3,7] a one-compartment pharmacokinetic model was obtained by the fitting procedure in both periods. In the other three patients [2,4,6] a two-compartment model was obtained during both periods, and a second compartment was identified in one patient only during afebrile period [5]. Secondary parameters of ciprofloxacin calculated by the use of Pcnonlin™ are presented in Table 2. Excluding patient 7, in whom very different pharmacokinetic parameters were measured on the basis of very low serum ciprofloxacin concentration, C_{max} was higher during fever than after defervescence in the other six febrile patients ($P < 0.05$, Wilcoxon signed-rank test). A comparison of other parameters did not show any significant difference between the two periods.

4. Discussion

In our study, serum concentrations of ciprofloxacin and the derived pharmacokinetic parameters showed great interpatient variability, previously shown for many other drugs. Serum concentration of ciprofloxacin was especially low in patient 7, probably reflecting her body mass and composition.

Although not reaching statistical significance, V_1 of ciprofloxacin decreased during fever in six of the seven patients. Although different volumes of distribution were calculated in different studies, enlargement of the volumes during fever was reported in most studies on the pharmacokinetics of β-lactam antibiotics, aminoglycosides and trimethoprim [1–3,6–8]. Smaller V_1 values during fever was only found for sulphadimidine in dogs and tobramycin in rats [1,9]. Lower average k_d and k_{-d} associated with pyrexia in patients with a two-compartment model of ciprofloxacin suggest that the shift of the drug from one compartment to the other was slower during fever than after defervescence. The results are in contradiction with some animal and human studies of pharmacokinetics in which greater shift towards the peripheral compartments was observed, or suspected during fever [1,6]. An opposite transfer towards the central compartment was observed for moxalactam in rabbits [6] and gentamicin in ewes [1]. Limited distribution during fever was found for rifamycin [1].

The discrepancy between the results of the abovementioned studies and our data can be attributed to the different species studied, different causes of febrile disease, and in the case of ciprofloxacin, to its different pharmacokinetic properties in comparison with aminoglycosides and β-lactams. To some extent, this difference can be related to the choice of the control group. In animal studies, febrile and afebrile animals were compared. Most human studies compared volunteers and patients, or there was a long interval between the febrile episode and the control period. In our patients, the control period followed immediately after defervescence, and it may be that the so-called 'acute phase' had not yet completely passed off by that time.

Different pharmacokinetic models observed in our patients and a change of the pharmacokinetic model after defervescence in one patient suggest that in some febrile patients the drug is distributed more evenly, i.e. in one (central) compartment, while in other patients, distribution of the drug is uneven and limited. The patients, in whom a one-compartment pharmacokinetic model of ciprofloxacin was observed during fever, probably reflecting an even distribution of the drug in the body, became afebrile within 3 days of the initiation of treatment. Fever lasted longer in patients 2, 4 and 6, in whom a two-compartment distribution of ciprofloxacin was observed during acute febrile disease. The difference in distribution can be attributed to the differences in protein binding, but ciprofloxacin does not belong to the highly protein-bound antibiotic. Another reason for varying drug distribution patterns in febrile patients may be the difference in haemodynamic responses of patients to fever. It is known that cardiac output increases during endotoxin-induced fever and that blood flow to many organs and tissues is enhanced [1]. A more even distribution of drugs would hence be expected. A question arises, however, whether all patients are able to meet the demands of the hyperdynamic circulation during fever, especially when dehydrated.

From the pharmacodynamic point of view, serum concentrations of ciprofloxacin and $AUC_{0\rightarrow 24}$ measured in our patients were very low. Nevertheless the treatment outcome was good in all patients, suggesting low MICs of the causative microorganisms, and good penetration of ciprofloxacin into the kidneys. Since the maximum serum concentration of ciprofloxacin is established to be relevant for the efficacy of the treatment [10], the significantly higher C_{max} of ciprofloxacin during fever observed in six of the seven patients, suggest a better pharmacokinetic/pharmacodynamic relationship for ciprofloxacin in febrile patients.

Table 2
Pharmacokinetic parameters for ciprofloxacin during fever and after defervescence

Patient no.	V_1 (l)		k_d (h^{-1})		k_{-d} (h^{-1})		AUC (μgh/ml)		k_{el} (h^{-1})		$t_{1/2\alpha}$ (h)		$t_{1/2\beta}$ (h)		C_{max} (μg/ml)		Cl (l/h)		V_{ss} (liter)	
	F	AF	F	AF	F	AF	F	AF	F	AF	F	AF	F	AF	F	AF	F	AF	F	AF
1	19.23	28.57	0.0	0.0	0.0	0.0	24.27	15.90	0,5	0,45	0.10	1.58	3.68	386.02	8.90	6.25	8.24	12.58	39.19	44.80
2	20.62	20.62	0.92	2.0	0.44	0.9	6.22	17.74	1,3	0,8	0.17	0.21	1.45	8.39	5.62	5.13	32.14	11.27	45.64	118.39
3	28.57	41.67	0.0	0.0	0.0	0.0	10.51	27.05	0,7	0,19	0.13	0.05	1.17	4.44	5.51	4.49	19.03	7.39	31.97	46.98
4	31.25	35.71	2.1	2.5	0.69	1.7	26.35	10.76	0,17	0,77	0.20	0.09	11.37	5.10	3.92	3.05	7.59	18.58	117.64	125.54
5	27.03	27.03	0.0	0.54	0.0	0.79	18.01	19.46	0,45	0,4	1.78	0.22	298.76	3.94	6.34	5.90	11.10	10.28	43.44	53.15
6	27.03	29.85	0.83	0.66	0.2	0.25	34.43	5.52	0,3	0,9	0.63	0.23	23.64	2.21	5.45	3.73	5.81	36.26	167.74	84.19
7	200	117.7	0.0	0.0	0.0	0.0	3.20	9.95	0,3	0,2	0.01	0.14	2.34	4.64	0.92	1.53	62.52	20.10	209.67	133.69
Average	50.53	43.01	0.55	0.81	0.19	0.52	17.57	15.20	0,53	0,53	0.43	0.36	48.92	59.25	5.24	4.30	20.92	16.64	93.61	86.68
SD	66.05	33.58	0.80	1.03	0.28	0.64	11.49	7.15	0,38	0,29	0.62	0.54	110.47	144.11	2.42	1.67	20.51	9.76	72.02	39.13

F, during fever; AF, after defervescence.

In conclusion, our data do not support the adjustment of ciprofloxacin dosage during fever, but caution is needed in patients infected with less-sensitive microorganisms. Besides, artificial lowering of fever seems not to be warranted.

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