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The PK/PD index for ciprofloxacin in critically ill patients

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Summary

Introduction. The aim of the study was an analysis of pharmacokinetics and PK/PD parameters C_{max}/MIC and AUC/MIC for ciprofloxacin in intensive care unit patients. ***Material and methods.*** Patients (n=3) received ciprofloxacin intravenously at 400 mg/ 8 h. Blood samples were collected on day 1st of the ciprofloxacin therapy. Plasma drug concentrations were measured by HPLC-UV method. ***Results.*** The mean maximum concentration after the first dose was C_{max}^{1} = 3.26 (± 2.41) μg/ml. The mean C_{max}^{1}/MIC and AUC/MIC ratio were: 10.48 (± 4.72) and 192.1 (± 134.8), respectively. ***Conclusions.*** Big inter-subject variability for PK/PD parameters in ICU patients requires systematic monitoring. *AAnestezjologia i Ratownictwo 2010; 4: 409-413.*

Keywords: ciprofloxacin, pharmacokinetics, pharmacodynamics, critically ill patients

Introduction

Antibiotics are the most commonly used drugs in intensive care unit (ICU) patients and intensivists have to accept the new recommended dosing strategies determined by the patient's clinical condition. The changes that occur in the patients who are critically ill or septic may be responsible for subtherapeutic antibiotic concentrations leading to poorer clinical outcomes and bacterial resistance. Critical illness and therapeutic interventions (e.g., haemodynamically active drugs, mechanical ventilation, renal replacement therapy) alters antibiotic pharmacokinetics mainly through an increase in the volume of distribution (V_d) and altered drug clearance. Increased V_d is caused by fluid extravasation (sepsis, trauma, severe hypoalbuminaemia, fluid therapy, parenteral nutrition, increased cardiac output), fluid loss (post surgical drainage, burns in early phase) and compartmental fluid accumulation (pleural effusion, ascites, mediastinitis) [1]. The renal clearance of most hydrophilic and moderately lipophilic antimicrobials is significantly increased in burns (late phase), acute leukaemia, hyperdynamic sepsis phase, but it is reduced in renal failure and age >75 years [1].

For an appropriate antibiotic therapy, the intensivist must be familiar with pharmacokinetic/pharmacodynamic concepts that integrate an antibiotic's microbiological activity and pharmacokinetic properties. Pharmacokinetics relates to absorption, distribution and elimination (metabolism and excretion) of antimicrobials. Pharmacodynamics determines the relationship between concentrations at sites of infection and the antimicrobial effects predicted by MIC (*minimal inhibitory concentration*). Three basic PK/PD parameters were established for most antibiotics. C_{max}/MIC for antibiotic with pronounced

concentration–dependent killing, such as aminoglycosides, T>MIC for antibiotics with time-dependent killing and minimal or moderate post-antibiotic effect (PAE) (b-lactams and conventional macrolides). The third pattern (AUC/MIC) is characterised by time-dependent killing and prolonged PAE (tetracyclines, azithromycin, glycopeptides, linezolid) [2-4].

For fluoroquinolones with concentration-dependent killing and prolonged PAE the best PK/PD parameters strongly linked to the outcome are the C_{max}/MIC and AUC/MIC ratio. Ciprofloxacin is a quinolone with broad spectrum activity determined by C_{max}/MIC >10 and AUC/MIC: 100-125 [5-7]. The monitoring of the abovementioned parameters is also one of the methods to reduce the process of increasing resistance to antibiotics, which is currently a serious problem, reported also by the WHO. The deficit of new antibacterial drugs (since 2006 only one antibiotic has been registered in the USA – doripenem) forces rational use of currently applied chemotherapeutics. The fluoroquinolones are a good example of where underdosing of antibiotics has led to rapid development of bacterial resistance [8].

The aim of the study was an analysis of ciprofloxacin pharmacokinetics and PK/PD: C_{max}/MIC and AUC/MIC indexes in intensive care unit patients.

Materials and methods

The research, after approval of the Institutional Review Board at Poznan University of Medical Sciences, was carried out at the Clinical Department of Anaesthesiology, Intensive Care and Pain Treatment, Heliodor Święcicki Clinical Hospital, University of Medical Sciences, Poznan and at the Department and Unit of Clinical Pharmacy and Biopharmacy, University of Medical Sciences, Poznan. Three patients (3 females) were included in the study. An intravenous chemotherapeutic was applied in the dose of 400 mg three times a day. Patients with identified microbiological factor were qualified for the investigation. Table 1 presents the characteristics of the researched group.

Four blood samples were drawn at various time point (t=0, t=0.5 hours, t=6 hours, t=8 hours after infusion of 400 mg of ciprofloxacin) to determine plasma concentrations of ciprofloxacin. The measurement of ciprofloxacin concentration in the blood plasma was made by means of the HPLC method with UV detection, which was an adaptation of the method developed by May M. et al [9]. The parameters of chromatographic separation were: XTerra®RP column 18 3.5µm 4.6×150 mm (Waters), mobile phase: acetic acid (5%) – methanol – acetonitrile (90 : 5 : 5), mobile phase flow speed 1 ml/min, UV detector wave length 280 nm.

Table 1. Patient characteristics of 3 ICU patients treated with ciprofloxacin

Patient characteristics	Mean ±SD
Sex (male-female)	0:3
Age [y]	38.3 ± 8.5
Weight [kg]	65.0 ± 5.0
Serum creatinine [mg/dL]	0.42 ± 0.20
Procalcitonine [mg/L] at the beginning of therapy	3.13 ± 2.22
Procalcitonine [mg/L] at the end of therapy	0.69 ± 0.56

The infection was determined based on clinical symptoms, procalcitonine level (> 0.5 ng/mL) and bacterial organisms growth in a normally sterile sites (bronchoalveolar lavage - BAL, blood).

PK/PD model

MICs were determined by using the Etest®. MIC is the minimum inhibitory concentration for the organism/antibiotic combination (micrograms/milliliters). For ciprofloxacin, the measurement of peak serum concentrations and division of the concentration by the MIC of the infecting organism resulted in C_{max}/MIC ratios. AUC/MIC ratios were estimated mathematically based on the equation AUC/MIC = [Dose/(Vd*MIC]*[$t_{0,5}$/0.693]*[24/DI]*f, where *Vd* is the apparent volume of distribution in the central compartment [L], *DI* is the dosing interval [h], $t_{0,5}$ is the half-life [h], *f* is the fraction of unbound drug [10].

Results

Positive cultures were found in BAL and blood in our patients. *Pseudomonas* species were found in 2 of 3 patients. *Acinetobacter baumannii* in 1 and *Klebsiella oxytoca* in 1 patient. The MIC values that would represent the 90th percentile of values for these pathogens (MIC_{90}) in our ICU patients are shown in Table 2. Table 3 presents the mean values of ciprofloxacin concentrations in the plasma (C) after the first dose of ciprofloxacin (C_{max}^{1}) was administered to the analysed

Table 2. Minimal inhibitory concentrations (90th percentile) of cultured pathogens in the analysed ICU patients

Patient's number	Pathogens	Biological material	MIC_{90} (mg/l)
1	*Acinetobacter baumannii*	BAL	0.19
	Pseudomonas aeruginosa	BAL	0.38
2	*Klebsiella oxytoca*	blood	0.094
3	*Pseudomonas aeruginosa*	BAL	0.75

Table 3. The individual values of ciprofloxacin concentration in the plasma *C* [μg/ml] in 0.5, 6 and 8 hours after the end of intravenous infusion of the first dose of ciprofloxacin, C_{max}/MIC and AUC/MIC in the analysed ICU patients (n=3); S – arithmetic mean; SD –standard deviation;

	$1_{A. baumanii}$	$1_{P. aeruginosa}$	2	3	S ± SD	CV %
C_{max} [1] /MIC	11.53	5.76	16.59	8.03	10.48 ± 4.72	45.0
AUC/MIC	352.6	176.3	214.6	24.7	192.1 ± 134.8	70.2
$C_{0,5h}$	6.02		2.19	1.56	3.26 ± 2.41	73,9
C_{6h}	1.65		0.48	0.87	1.00 ± 0.59	59,0
C_{8h}	1.45		0.35	0.22	0.67 ± 0.68	101,5

patients. The mean C_{max}/MIC value for ciprofloxacin after the first dose is: 10.48 (± 4.72) (Table 3). The mean AUC/MIC value for ciprofloxacin after the first dose is: 192.1 (± 134.8) (Table 3). On the basis of the measured ciprofloxacin concentrations the pharmacokinetic parameters of the drug were calculated: volume of distribution Vd [l], half-life $t_{0.5}$ [h], ciprofloxacin clearance Cl [l/h], mean residence time MRT [h] (Table 4). We observed large (CV>30%) interpatient variations in Vd and Cl values.

Table 4. Pharmacokinetic variables of 3 ICU patients treated with *i.v.* ciprofloxacin

PK parameters	S ± SD	CV %
Vd [l]	142.23 ± 70.93	49.8
Vd/kg [l/kg]	2.24 ± 1.17	52.2
$t_{0,5}$ [h]	3.09 ± 0.36	11.6
Cl [l/h]	33.16 ± 17.98	54.2
MRT [h]	4.46 ± 0.52	11.6

Discussion

In many cases the application of the recognised PK/PD properties of antibiotics enables a preliminary forecast of the efficacy of the applied treatment. Aminoglycosides belong to (C_{max}/MIC) concentration-dependent antibiotics. As results from clinical research, the C_{max}/MIC ratio for aminoglycosides should be 4-10 [2,11,12]. Therefore, concentration-dependent antibiotics should be administered in large doses once a day, which guarantees obtaining high C_{max}/MIC values [13]. The time of high concentration persistence is of secondary importance due to the *postantibiotic effect - PAE* in this group of drugs [2,8]. The efficacy of beta-lactams (penicillin, cephalosporin, monobactam, carbapenem), macrolides, clindamycin is determined by the concentration time over MIC (T>MIC). In the case of time-dependent antibiotics the effective concentration time over MIC (*T > MIC*) should be 30–40% for G (+) microorganisms and for G (–) microorganisms: at least 60–70% of the period between the doses. The maximum killing effect of these antibiotics was observed when the time was close to 100% and such *T>MIC* is recommended to patients in severe general state. Improved efficacy in the treatment with time-dependent antibiotics is obtained by increasing their concentration 4-5 times more than the MIC, whereas further increase in C_{max} brings no benefit. Thus, in practice a therapy with time-dependent antibiotics consists in increasing the dosage frequency (3-6×/d) [11], or applying a continuous intravenous infusion [14]. According to many authors, the best predictor of the efficacy of fluoroquinolones is AUC_{24}/MIC and Cmax/MIC. In clinical research for fluoroquinolones it was proved that the AUC_{24}/MIC value higher than

100 gives a big chance of clinical and bacteriological success. The C_{max}/MIC for fluoroquinolones should be larger than 10. In practice, in order to obtain the aforementioned values of PK/PD indexes large doses of fluoroquinolones with long biological half-life $t_{0.5}$ must be applied or to increase the frequency of dosage. In comparison with the AUC_{24}/MIC the C_{max}/MIC has an undoubted advantage, namely it is possible to collect only one blood sample from the patient [15]. In some situations the C_{max}/MIC parameter seems to be more credible than the AUC_{24}/MIC. Nawarro et al. [5] compared the usual dosage regimen of 250 mg/12 h versus 500 mg/24 h of ciprofloxacin for the treatment of urinary infections. The AUC_{24} was the same for the same daily dose (250 mg/12 h or 500 mg/24h). The proposed regimen of 500 mg once a day administered in the morning, which produces higher values of Cmax/MIC values, is probably more advantageous than 250 mg/12h.

Individualised antibiotic therapy in critically ill patients is a big challenge. In this group of patients different pharmacokinetics of drugs can be observed due to the pathophysiological changes, which are typical of them. Hydrophilic antibiotics (e.g., aminoglycosides, beta-lactams, glycopeptides, and colistin) have increased volume of distribution and altered drug clearance and lipophilic antibiotics (e.g., fluoroquinolones, macrolides, tigecycline, and lincosamides) show lesser volume of distribution changes, but may develop altered drug clearances [12]. Additionally, coadministered haemodynamically active drugs (e.g., dobutamine, dopamine, furosemide, mannitol) may cause enhanced elimination of antibiotics by increased renal blood flow, which determines enhanced glomerular filtration and tubular secretion, and finally, renal clearance [1,16]. Fluoroquinolones are widely used drugs in the management of moderate to severe infections in critically ill patients. Numerous pharmacokinetic/pharmacodynamic studies aimed at defining optimal dosing regimens for ciprofloxacin revealed good predictors of clinical outcome: Cmax/MIC and AUC/MIC.

In the analysed patients the antibacterial therapy included intravenous administration of ciprofloxacin in the dose of 400 mg/8h. Patients with identified microbiological factor were analysed in the research. Patient No. 1 (septic shock due to the Crohn disease and peritonitis because of multiple bowel perforation, complicated by massive bleeding from esophageal varices and nosocomial pneumonia; many laparotomies; multiorgan dysfunction syndrome) had ciprofloxacin included empirically. Before the antibiotic was included, BAL had been collected for microbiological investigation due to the clinical symptoms of inflammation in the lower respiratory tract. From the BAL two bacterial strains were cultured - *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. Both strains were sensitive to ciprofloxacin. From patient No. 2 (severe abdominal sepsis due to the iatrogenic biliary ducts injury after cholecystectomy; many laparotomies, respiratory insufficiency) specimens for microbiological investigations were also collected and ciprofloxacin was included empirically. *Klebsiella oxytoca* with MIC 0.094 was cultured from the blood. The patient was receiving the antibiotic only for 3 days together with linezolid. On the second day of ciprofloxacin administration imipenem was also included due to the patient's critical condition and infection exponents. In patient No. 3 (intracranial hemorrhage; severe sepsis due to nosocomial pneumonia) ciprofloxacin was included after the result of the BAL had been obtained from the culture. The aetiological factor of the infection in the respiratory tract was *Pseudomonas aeruginosa* with the MIC of 0.75 relative to ciprofloxacin. According to the recommendations, in the case of an infection with such aetiology the antibiotic must be administered for about 2 weeks. Simultaneously amikacin was also administered to reinforce the effect and to prevent the development of immune mechanism. The high values of the variability coefficient (CV>30%) for the values of measured concentrations (Table 3) and pharmacokinetic parameters (Table 4) of ciprofloxacin in the analysed patients point to big inter-subject variability, which is typical of critically ill patients. The mean values of the calculated parameters correspond to the data from the literature. The individual values of the Cmax/MIC parameter are high in the analysed patients (Table 3). Only in the case of infection with *Pseudomonas aeruginosa* the obtained Cmax/MIC is significantly lower due to the high MIC. However, probably after reaching the stationary state (min. 3 - 5 $t_{0.5}$) the C^{ss}_{max}/MIC parameter will be higher. Very high AUC/MIC values (> 125) (Table 3) may be caused by calculation based on only three ciprofloxacin concentrations (0.5 h, 6 h, 8 h). Probably the number of samples is too limited to be fully representative and the research to be continued with higher number of samples.

Conclusion

Because of PK/PD changes during sepsis, blood concentrations of antibiotics are unpredictable and suggest the need for drug level monitoring. The application of PK/PD parameters in forecasting the result of an antibiotic therapy in an individual patient undoubtedly requires the knowledge of the rules of pharmacokinetics. It also requires the possibility to monitor the drug concentration in the biological material and to mark the actual MIC value. Therefore, it is necessary that the physician should cooperate with the microbiologist and clinical pharmacist. It is particularly important in view of the resistance to antibiotics, which the WHO considers to be currently one of the greatest health hazards.

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