Acta Poloniae Pharmaceutica – Drug Research, Vol. 68 No. 5 pp. 777–783, 2011 ISSN 0001-6837
Polish Pharmaceutical Society

GENERAL

THE PK/PD INDEX (C_{MAX}/MIC) FOR CIPROFLOXACIN IN PATIENTS WITH CYSTIC FIBROSIS

EDYTA SZAŁEK[1]*, AGNIESZKA KAMIŃSKA[1], JOANNA GOŹDZIK-SPYCHALSKA[2], EDMUND GRZEŚKOWIAK[1] and HALINA BATURA-GABRYEL[2]

[1]Department of Clinical Pharmacy and Biopharmacy, Karol Marcinkowski University of Medical Sciences, 61-861 Poznań, 14 Św. Marii Magdaleny St., Poland
[2]Department and Clinic of Pulmonology, Allergology and Lung Oncology, University of Medical Sciences, Poznań, 82/84 Szamarzewskiego St., Poland

Abstract: In order to evaluate the efficacy of an antibacterial therapy, three basic PK/PD indexes were defined: the ratio between the maximum drug concentration obtained after a single dose and minimum inhibitory concentration MIC (C_{max}/MIC), the ratio between the area under the curve of dependence between the drug concentration in blood and time within 24 hours to MIC (AUC_{24}/MIC), and the time when the concentration of the drug in blood is higher than MIC (T > MIC). The aim of the study was an analysis of the pharmacokinetics of ciprofloxacin and the PK/PD: C_{max}/MIC index in patients with cystic fibrosis. Six patients with cystic fibrosis, with the identified microbiological factor were subjected to the examination. The patients received ciprofloxacin in the dose of 400 mg/12 h (*i.v.*). Plasma drug concentration was measured by HPLC-UV method after the first dose (C_{max}^{1}) and at steady state (C^{ss}_{max}, C^{ss}_{min}). The following mean values of ciprofloxacin blood concentrations were obtained from the analyzed patients: C_{max}^{1} = 2.34 (± 1.15) μg/mL, C^{ss}_{max} = 2.49 (± 1.44) μg/mL, C^{ss}_{min} = 0.42 (± 0.22) μg/mL. The mean values of the C_{max}^{1}/MIC and C^{ss}_{max}/MIC indexes were 3.66 (± 2.34) and 3.38 (± 1.73), respectively. Low values of the C_{max}/MIC index for ciprofloxacin in the analyzed patients may indicate too low concentrations of the drug in the blood in relation to the MIC value of pathogens and the need to verify the assumed administration scheme.

Keywords: ciprofloxacin, pharmacokinetics, cystic fibrosis

The aim of the therapy monitored by drug concentration is to provide individual treatment, especially to patients with concomitant diseases, which may cause changes in the pharmacokinetics (PK) of received drugs. Currently increased interest in monitored therapy can be observed, especially in the cases of ineffective treatment despite the application of recommended dosage regimen. The continuing pathological process may influence the individual stages of drug transformation in the system (LADME: *liberation*, *absorption*, *distribution*, *metabolism*, *excretion*), which in consequence may alter its pharmacological effect completely. It is particularly visible in critically ill patients. They exhibit dynamic changes in the volume of compartments, especially the central one, which through intensive parenteral nutrition, the supply of hemodynamically active drugs (e.g., adrenaline, dopamine, dobutamine, milrinone or diuretics e.g., furosemide, torasemide), usually determine reduced drug concentrations (1, 2).

In the population of the Caucasian race cystic fibrosis (CF) is the most common incurable disease caused by mutation of a single gene located on the long arm of chromosome 7 coding CFTR *(Cystic Fibrosis Transmembrane Conductance Regulator)* protein. One of its functions is connected with the role of the chloride channel dependent on cAMP. Its dysfunction leads to the disorder of transport of Cl^- ions through cell membranes and increased absorption of Na^+ and water. These changes lead to the formation of thick and sticky secretion cumulating in the discharge ducts, which determines the abnormal function of the glands of external secretion. CF is a systemic disease, which leads to patients' shorter lives (3). According to the WHO, the classification of the disease comprises: 1. CF with symptoms of the respiratory system, 2. CF with symptoms of the

* Corresponding author: e-mail: czechow73@wp.pl; phone: +48618529057

alimentary tract, 3. CF with symptoms of other organs and 4. indefinite CF (4). The preliminary diagnosis of CF is done by means of a sweat test, which shows high values of chlorides in the sweat (Cl^- > 60 mmol/L, in infants > 40 mmol/L). Besides the implementation of an appropriate diet, the treatment of CF and its complications comprises the supplementation of vitamins A, D, E, K, pancreatic enzymes, the application of mucolytic drugs, bronchodilators and anti-inflammatory drugs as well as a periodical or long-term antibiotic therapy, depending on the indications (3). CF involves frequent administration of chemotherapeutics due to the patient's susceptibility to infections. CF may cause changes in the pharmacokinetics of drugs, e.g., by increased distribution volume and clearance of the drug (5–7). The increased activity of CYP1A2 and CYP2C8 in patients with CF may additionally affect faster elimination of drugs metabolized with those isoenzymes (8). Ciprofloxacin is a second generation fluoroquinolone with a wide antibacterial spectrum. It shows, e.g., efficacy and synergic effect with other drugs (e.g., tobramycin) against multiresistant strains of *Pseudomonas aeruginosa*, which are frequently isolated in patients with CF (9–11). Many authors suggest that the efficacy of fluoroquinolones in bacterial infections is determined by the possibility to obtain appropriate values of pharmacokinetic and pharmacodynamic indexes (PK/PD): $AUC_{(0\text{-}24)}$/MIC (the area under the concentration-time curve over 24 h in steady-state divided by the MIC) and C_{max}/MIC (the peak level divided by the MIC). MIC is the minimum inhibitory concentration for the organism/antibiotic combination (mg/L). The recommended values of the abovementioned indexes for total drug are: $AUC_{(0\text{-}24)}$/MIC ≥ 125, or C_{max}/MIC > 10 (1, 12, 13). The aim of this study was to analyze the pharmacokinetics of ciprofloxacin and PK/PD indexes: C_{max}/MIC after the first dose and at steady state and $AUC_{(0\text{-}24)}$/MIC at steady state in patients with cystic fibrosis.

MATERIALS AND METHODS

All the described procedures were reviewed and approved by the Institutional Review Board at Poznań University of Medical Sciences. The research was done at the Department and Clinic of Pulmonology, Allergology and Lung Oncology, University of Medical Sciences, Poznań, and the Department of Clinical Pharmacy and Biopharmacy, University of Medical Sciences, Poznań. Six patients (5 men and 1 woman), who were hospitalized to treat the exacerbation in the course of basic disease, were subjected to the measurement of ciprofloxacin concentration in the blood plasma. Table 1 presents the characteristics of the analyzed group. The CF patients were treated with ciprofloxacin (*Ciprinex®,* Polpharma SA; solution for infusion) in the intravenous dose of 400 mg (200 mL of solution; 2 mg/mL), which was infused for a 30-min period, twice a day (bid). The patients with identified microbiological factor were qualified for the research. Creatinine clearance for each patient was calculated using Cockroft-Gault formula (14).

In order to measure the concentration after the first dose of ciprofloxacin (C_{max}^1), blood (2 mL) was collected from the cubital vein 0.5 h after finishing the first intravenous infusion of the drug. To determine the drug concentrations at steady state: the maximum concentration C^{ss}_{max} and the minimum concentration C^{ss}_{min}, blood samples were taken 0.5 h after finishing the intravenous infusion of the fifth dose of ciprofloxacin and a short moment before the administration of the sixth dose of ciprofloxacin, respectively. The steady state is achieved after about $7t_{0.5}$. The biological half-life of ciprofloxacin equals about 3.4 h in patients with normal renal function (15) and about 3.7 h in critically ill patients (16), therefore concentrations $C^{SS}_{min\ meas}$ and $C^{SS}_{max\ meas}$, measured after the fifth dose correspond to the steady state. The measurement of ciprofloxacin concentration in the blood was carried out by means of the HPLC method with UV detection, which was an adapted version of the method developed by May et al. (17). The parameters of chromatographic separation: column XTerra®RP 18 3.5 µm 4.6 × 150 mm (Waters), mobile phase: acetic acid (5%) – methanol – acetonitrile (90 : 5 : 5, v/v/v), flow rate of the mobile phase 1 mL/min, UV detector wavelength 280 nm.

Kinetic analysis

The first order elimination rate constant (K_e) and volume of distribution (V_d) were calculated for each patient by means of equations based on a one-compartment open model using a modified two-point Sawchuk-Zaske method (18). K_e was determined by:

$$K_e = \frac{\ln(C_{max} / C_{min}}{\Delta t}$$

where C_{max} and C_{min} are the measured peak and trough concentrations (milligrams per liter) and Δt (hours) is the time interval between the measured peak and trough levels. V_d was calculated as:

$$V_d = \frac{D(1 - e^{-K.T})}{K_e T(C^{SS}_{max} - C^{SS}_{min} \cdot e^{-K.T})}$$

where D is the intravenous dose, T is the infusion time [h]. The other equations used in the calcula-

tions are: the biological half-life time $t_{0,5} = \ln 2/K_e$, mean concentration at steady state $C^{SS}_{mean} = \frac{D}{V_d \cdot K_e \cdot \tau}$, ciprofloxacin clearance $Cl_{cipro} = K_e \cdot V_d$, area under the curve C = f(t) in one dosage range $AUC_s = C^{SS}_{mean} \cdot \tau$, mean residence time $MRT = 1/K_e$, the percentage of concentration fluctuations at steady state $PTF = \frac{100\% \cdot (C_{max} - C_{min})}{C^{SS}_{mean}}$. The extrapolated maximum concentration was estimated by equation:

$$C^{SS}_{max\ extrap} = C^{SS}_{max\ meas} \cdot e^{Ke \cdot t_{max\ mean}}$$

PK/PD model

MICs were determined by means of the Etest® (bioMérieux, France). For ciprofloxacin, the measurement of peak serum concentrations and quotient of the concentration by the MIC of the infecting organism resulted in C_{max}/MIC ratios. AUC/MIC ratios for total drug can be estimated mathematically on the basis of the equation (19):

$$AUC/MIC = \frac{D}{V_d \cdot MIC} \cdot \frac{t_{0.5}}{0.693} \cdot \frac{24}{\tau}$$

It is recommended to use the prefix *f* in the equation for AUC/MIC if the free fraction of the drug is used in calculations, e.g., *f* AUC (20).

Considering $AUC_t = C^{SS}_{mean} \cdot \tau$, AUC/MIC index can be calculated as:

$$AUC_{0\text{-}24} / MIC = 24 \cdot C^{SS}_{mean} / MIC$$

RESULTS

The results are given as the mean ± SD. A statistical comparison ($C_{max}{}^1$/MIC *vs*. $C^{ss}{}_{max}$/MIC) was made with Wilcoxon test, with $p < 0.05$ regarded as significant. Table 2 shows the measured and extrapolated values of ciprofloxacin concentrations in the plasma (C) after the first dose of ciprofloxacin ($C_{max}{}^1$) and minimum ($C^{ss}{}_{min}$) and maximum ($C^{ss}{}_{max}$) concentrations at steady state in the analyzed patients. The mean values of the C_{max}/MIC index for measured concentrations of ciprofloxacin after the first dose ($C^1_{max\ meas}/MIC$) and at steady state ($C^{SS}_{max\ meas}/MIC$)

Table 1. The characteristics of patients included in the research (n = 6).

Parameter	Value (S ± SD)
Males/females	5/1
Age [years]	25.8 ± 2.2
Body mass [kg]	44.3 ± 2.2
CL_{CR} [mL/min]	66.1 ± 16.3
CRP [mg/L] at the beginning of therapy	37.6 ± 11.9
CRP [mg/L] at the end of therapy	9.2 ± 11.8

S = arithmetic mean; SD = standard deviation; CL_{CR} = creatinine clearance estimated by the Cockroft-Gault formula (14).

Table 2. The measured (*meas*) and extrapolated (*extrap*) values of ciprofloxacin concentrations in the plasma (C) after the first dose of ciprofloxacin (C^1_{max}) and minimum (C^{ss}_{min}) and maximum concentrations (C^{ss}_{max}) at steady state in the analyzed patients with cystic fibrosis.

Patient	1	2	3	4	5	6	S	SD	Median	CV %
$C^1_{max\ meas}$ [mg/L]	2.03	3.18	1.71	4.14	2.09	0.87	2.34	1.15	2.06	49.1
$C^{ss}_{max\ meas}$ [mg/L]	0.43	0.77	0.27	0.57	0.18	0.27	0.42	0.22	0.35	52.4
$C^{ss}_{max\ meas}$ [mg/L]	1.62	2.56	1.37	5.32	1.96	2.09	2.49	1.44	2.03	57.8
$C^1_{max\ extrap}$ [mg/L]	2.15	3.36	1.84	4.58	2.33	0.95	2.70	1.61	2.24	59.6
$C^{ss}_{max\ extrap}$ [mg/L]	1.72	2.70	1.47	5.89	2.18	2.29	2.71	1.62	2.24	59.7
C^{ss}_{mean} [mg/L]	0.92	1.52	0.71	2.30	0.81	0.94	1.20	0.61	0.93	50.8

Table 3. The values of parameters $AUC_{0\text{-}24}$/MIC and C_{max}/MIC for ciprofloxacin after the first dose (C_{lmax}/MIC) and at steady state (C^{ss}_{max}/MIC) in the analyzed patients with cystic fibrosis.

Parameter	Patient						S	SD	Median	CV %
	1	2	3	4	5	6				
$C^{1}_{max\ meas}$ / *MIC*	8.12	2.77	3.29	2.71	4.18 4.18	0.40	3.66	2.34	3.29	63.9
$C^{1}_{max\ calc}$ / *MIC*	8.60	2.92	3.54	2.99	4.66 4.66	0.44	3.97	2.49	3.54	62.7
$C^{ss}_{max\ meas}$ / *MIC*	6.49	2.23	2.64	3.47	3.93 3.93	0.96	3.38	1.73	3.47	51.2
$C^{ss}_{max\ calc}$ / *MIC*	6.88	2.35	2.83	3.85	4.36 4.36	1.05	3.67	1.85	3.85	50.4
$AUC_{0\text{-}24}$ / *MIC*	88.32	31.72	32.77	36.08	38.88 38.88	10.40	39.58	23.62	36.08	59.7

Table 4. The pharmacokinetic parameters of ciprofloxacin in the analyzed patients with cystic fibrosis.

Pharmacokinetic parameters	S ± SD	Median	CV %
K_e [h^{-1}]	0.16 ± 0.04	0.16	25.0
V_d [L]	211.9 ± 90.0	195.2	42.5
V_d/kg [L/kg]	4.8 ± 2.0	4.5	41.7
$t_{0.5}$ [h]	4.5 ± 1.3	4.2	28,9
Cl_{cipro} [mL/min]	32.7 ± 12.2	35.5	37.3
AUC_{τ} [mg·h/L]	14.4 ± 7.3	11.2	50.7
MRT [h]	6.5 ± 1.9	6.1	28.8
PTF [%]	188.2 ± 50.0	191.9	26.6

Table 5. Minimum inhibitory concentrations (90th percentile) of cultured pathogens in analyzed patients.

Patient	Pathogens	Biological material	MIC_{90} (mg/L)
1	*Pseudomonas aeruginosa*	BAL	0.25
2	*Pseudomonas aeruginosa*	BAL	1.15
3	*Streptococcus viridans*	BAL	0.52
4	*Staphylococcus aureus*	sputum	1.53
5	*Staphylococcus aureus*	BAL	0.5
	Pseudomonas aeruginosa	BAL	0.5
6	*Klebsiella oxytoca*	blood	2.17

were 3.66 (± 2.34) and 3.38 (± 1.73), respectively (Table 3). The mean values of the C_{max}/MIC index for extrapolated concentrations of ciprofloxacin after the first dose ($C^{1}_{max\ extrap}$/*MIC*) and at steady state ($C^{SS}_{max\ extrap}$/*MIC*) were 3.97 (± 2.49) and 3.67 (± 1.85), respectively (Table 3). In patient No. 5 two bacterial strains were cultured – *Staphylococcus aureus* and *Pseudomonas aeruginosa*, therefore two values of C_{max}/MIC index are considered. On the basis of the ciprofloxacin concentrations the pharmacokinetic parameters were calculated (Table 4). Table 5 presents minimum inhibitory concentrations (90th percentile) of cultured pathogens in the analyzed patients.

DISCUSSION

Changes in the pharmacokinetics of drugs in patients with cystic fibrosis comprise, above all, delayed absorption of orally administered drugs, increased distribution volume, reduced concentrations and intensified process of drug excretion (21). They are the effect of numerous pathophysiological changes which take place in the course of the disease. The most important of them include hypersecretion of gastric acid and duodenal secretions which are of small volume, viscous and low in bicarbonate, increased intestinal permeability to some sugars and probe substances, hypergammaglobulinemia and sometimes hypoalbuminemia, significant elevation of free fatty palmitoleic acid level and decreased low-density and high-density serum lipoproteins, an average increase by 30 to 45% in plasma volume in patients with cystic fibrosis who have moderately severe pulmonary disease, right ventricle hypertrophy and dilatation, abnormal bile acid metabolism and enterohepatic recirculation, and enlarged kidneys and glomerulomegaly with increased glomerular filtration rate, tubular clearance and urine flow rate in some patients with cystic fibrosis (21).

Reduced concentration of some drugs in the dosage range may be the consequence of increased distribution volume (V_d), whose causes include increased lean body mass (LBM) per kilogram of body mass. It is the consequence of malnutrition and lower content of fatty tissue, which occur more frequently in this group of patients (7). Increased V_d can be observed mainly for highly hydrophilic drugs. In comparison with control groups (healthy volunteers) CF patients do not exhibit changes in the binding degree between most drugs and proteins (7, 8). Only for theophylline a considerable reduction in the degree of binding to blood proteins was proved (21). Therefore, during the therapy of asthma concomitant with cystic fibrosis it is necessary to observe the patient for the occurrence of possible adverse reactions. The increased clearance of drugs in CF patients is the consequence of such factors as: intensified metabolic processes, both in the first and second phase. Higher activity of CYP1A2 and CYP2C8, glucuronyltransferase, acetyltransferase (NAT1) and sulfotransferase can be observed. However, the induction of CYP3A4 and CYP2C9 was not proved (8). The intensification of metabolic processes was proved, e.g., in the study of pharmacokinetics of second generation fluoroquinolone, fleroxacin in patients with cystic fibrosis (22). The increased renal and extrarenal excretion of drugs in CF patients may contribute to reduced concentrations of the drugs. The optimization of antibiotic therapy in this group of patients comprises, e.g., increasing the dose of β-lactams by 20–30% and monitoring the concentration of aminoglycosides (8). The increased renal clearance may result from the limited resorption process (22), whereas the increased secretion of drugs with bile or bronchial secretion increases their extrarenal clearance (21). Additionally, the altered pharmacokinetics of antibiotics may result from patients' age. Rapid drug clearance can be observed in pediatric patients (23, 24).

The aim of antibiotic therapy is eradication of microorganisms at the place of infection. It can be achieved through obtaining an appropriate effective concentration of the antibiotic with simultaneous avoidance of toxic effects. The effective concentration remains above the minimum inhibitory concentration (MIC) or minimum bactericidal concentration (MBC). The parameters which give a possibility to evaluate the effectiveness of an antibacterial treatment with ciprofloxacin is AUC/MIC and C_{max}/MIC. In comparison with the AUC/MIC an undoubted advantage of the C_{max}/MIC index is the possibility to collect only one blood sample from a patient (13). Montgomery et al. (9) prove that the usually applied dosage of ciprofloxacin, i.e., 400 mg/12 h or 400 mg/8 h does not guarantee the desirable values of AUC/MIC and C_{max}/MIC in most CF patients. Similar conclusions result from the study by Odoul et al. (25), whose aim was an analysis of the pharmacokinetics of orally administered ciprofloxacin in pediatric patients with cystic fibrosis. The individual values of the C_{max}/MIC parameter are also low in this limited number of analyzed patients with CF (Table 3). The dosage of 400 mg/12 h did not give the possibility to achieve desirable values of C_{max}/MIC (> 10) and AUC/MIC (> 125) (12, 13). The mean values of ($C^{I}_{max\ meas}/MIC$, ($C^{SS}_{max\ extrap}/MIC$) $AUC_{0\text{-}24}/MIC$ and indexes in the analyzed patients were 3.97, 3.67, and 39.58, respectively. When the values of measured maximum concentrations are taken into consideration, the values of ($C^{I}_{max\ meas}/MIC$, $C^{SS}_{max\ meas}/MIC$) indexes are slightly lower (Table 3). The high values of the variability coefficient (CV > 30%) for the values of measured concentrations (Table 2) and pharmacokinetic parameters (Table 4) of ciprofloxacin in the analyzed patients point to big inter-subject variability, which is typical of hospitalized patients. No statistically significant differences between C^{1}_{max}/MIC and C^{ss}_{max}/MIC ($p = 0.553$) were found, which also calls for the need to verify the established dosing regi-

men. The results of numerous studies say that the pharmacokinetics of ciprofloxacin is well described by the two-compartment model (9, 26, 27). However, due to the limited possibilities of collection of many blood samples from patients subjected to the trial (at least for ethical reasons) the authors adopted the one-compartment model applying the Sawchuk-Zaske method, limiting the sampling to this part of the curve whose phase of distribution was in practice finished. The estimation of C_{max} half an hour after finishing the intravenous infusion is also a great simplification. Assuming the biological half-life of $t_{0.5}$ = 3.4 h, with the corresponding k_e = 0.2 h^{-1} it is possible to calculate that within half an hour the concentration drops by about 10%. Correction of such lowering of the C^{ss}_{max} does not change the main conclusion of the study, but it affects the values of the calculated PK parameters. Table 4 shows the PK parameters based on the extrapolation of the C_{max} value. Nevertheless, in order to develop a routine procedure for therapeutic drug monitoring (TDM) in hospitals, sometimes it is advisable to adopt certain simplifications in estimation of PK parameters (e.g., the measurement of C_{max} half an hour after finishing the intravenous infusion). The mean values of the calculated parameters correspond to the data from the literature (16, 28, 29), except V_d/kg. Among the analyzed patients as many as 5 out of 6 exhibited higher distribution volume (> 2–3 L/kg), and in two patients the values exceeded 6 L/kg.

In conclusion, the intravenous dosage of ciprofloxacin 400 mg twice a day may be an ineffective regimen for CF patients. The application of higher doses of ciprofloxacin (1200 mg daily) should be considered to ensure bacterial killing and avoid antibiotic resistance. This can be achieved either by increasing the doses (to 600 mg bid) or by reducing the dosing intervals from 12 to 8 hours (400 mg three times a day). In order to achieve higher C_{max}/MIC value the former option seems to be more appropriate. Because of pathophysiological changes in patients with CF, 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 requires the possibility to monitor the drug concentration in the biological material and to mark the actual MIC value. It is particularly important in view of the resistance to antibiotics, which the WHO considers to be currently one of the greatest health hazards.

REFERENCES

1. Scaglione F, Paraboni L. J.: Antimicrob. Agents 32, 294 (2008).
2. Roberts JA, Lipman J.: Crit. Care Med. 37, 840 (2009).
3. Castellani C., Southern K.W., Brownlee K., Dankert Roelse J., Duff A., Farrell M., Mehta A. et al.: J. Cyst. Fibros. 8, 153 (2009).
4. http://www.cfww.org/docs/who/2002/who_report_classification_of_cf_and_related_disord.pdf (1 July 2010).
5. Lindsay C.A., Bosso J.A.: Clin. Pharmacokinet. 24, 496 (1993).
6. Touw D.J., Vinks A.A., Mouton J.W., Horrevorts A.M.: Clin. Pharmacokinet. 35, 437 (1998).
7. Touw D.J.: Pharm. World Sci. 20, 149 (1998).
8. Rey E., Tréluyer J.M., Pons G.: Clin. Pharmacokinet. 35, 313 (1998).
9. Montgomery M.J., Beringer P.M., Aminimanizani A., Louie S.G., Shapiro B.J., Jelliffe R., Gill M.A.: Antimicrob. Agents Chemother. 45, 3468 (2001).
10. Cantón R., Cobos N., de Gracia J., Baquero F., Honorato J., Gartner S., Alvarez A. et al.: Clin. Microbiol. Infect. 11, 690 (2005).
11. Bilton D., Henig N., Morrissey B., Gotfried M.: Chest 130, 1503 (2006).
12. Scaglione F., Paraboni L.: Expert Rev. Anti. Infect. Ther. 4, 479 (2006).
13. Scaglione F.: Int. J. Antimicrob. Agents 19, 349 (2002).
14. Cockcroft D.W., Gault M.H.: Nephron 16, 31 (1976).
15. Hassan Y., Alfadly S.O., Azmin M.N., Peh K.K., Tan T.F., Noorizan A.A., Ismail O.: Singapore Med. J. 48, 819 (2007).
16. Conil J.M., Georges B., de Lussy A., Khachman D., Seguin T., Ruiz S., Cougot P. et al.: Int. J. Antimicrob. Agents 32, 505 (2008).
17. Maya M.T., Goncalves N.J., Silva N.B., Morais J.A.: J. Chromatogr. B 755, 305 (2001).
18. Sawchuk R.J., Zaske D.E.: J. Pharmacokinet. Biopharm. 4, 183 (1976).
19. Mohr J.F., Wanger A., Rex J.H.: Diagn. Microbiol. Infect. Dis. 48, 125 (2004).
20. Mouton J.W., Dudley M.N., Cars O., Derendorf H., Drusano G.L.: J. Antimicrob. Chemother. 55, 601 (2005).
21. Prandota J.: Drugs. 35, 542 (1988).
22. Mimeault J., Vallée F., Seelmann R., Sörgel F., Ruel M., LeBel M.: Clin. Pharmacol. Ther. 47, 618 (1990).

23. Payen S., Serreau R., Munck A., Aujard Y., Aigrain Y., Bressolle F., Jacqz-Aigrain E.: Antimicrob. Agents Chemother. 47, 3170 (2003).
24. Santos R.P., Prestidge C.B., Brown M.E., Urbancyzk B., Murphey D.K., Salvatore C.M., Jafri H.S.et al.: Pediatr Pulmonol. 44, 148 (2009).
25. Odoul F., Le Guellec C., Giraut C., de Gialluly C., Marchand S., Paintaud G., Saux M.C. et al.: Therapie 56, 519 (2001).
26. Forrest A., Ballow C.H., Nix D.E., Birmingham M.C., Schentag J.J.: Antimicrob. Agents Chemother. 37, 1065 (1993).
27. Preston S.L., Drusano G.L., Berman A.L., Fowler C.L., Chow A.T., Dornseif B., Reichl V. et al.: JAMA 279**,** 125 (1998).
28. Sánchez Navarro M.D., Sayalero Marinero M.L., Sánchez Navarro A.: J. Antimicrob. Chemother. 50, 67 (2002).
29. van Zanten A.R., Polderman K.H., van Geijlswijk I.M., van der Meer G.Y., Schouten M.A., Girbes A.R.: J. Crit. Care 23, 422 (2008).

Received: 20. 09. 2010