ORIGINAL ARTICLE

CORRELATIONS BETWEEN THE STAGES OF KIDNEY DISEASE AND THE PHARMACOKINETIC PARAMETERS OF ORALLY ADMINISTERED CIPROFLOXACIN AT PATIENTS WITH CHRONIC KIDNEY DISEASE

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Abstract

Patients with chronic kidney disease (CKD) are a special population group, which often present associated infections, requiring antimicrobian therapy. The study concerned the surveillance of pharmacotherapy of ciprofloxacin administered in patients diagnosed with CKD and associated infections, to increase the efficiency of therapy and to avoid toxicity of the drug substance. The prospective, open pharmacokinetic study, was conducted over a 15 months interval and was carried out on 29 patients diagnosed with CKD for which the plasmatic and urinary concentration of ciprofloxacin was determined using a validated high-performance liquid chromatography method (HPLC), following the oral administration of the drug. The efficiency of ciprofloxacin therapy was assessed according to the clinical, para-clinical, pharmacokinetic and toxic criteria. The most significant proportion of side effects was recorded in patients with CKD stage 3 (n = 10). We have discovered correlations between ciprofloxacin individual half-life and estimated glomerular filtration rate (eGFR) ($p = 0.022$), as well as the percentage of the urinary cleared drug in 24 hours and the level of serum creatinine ($p = 0.024$). Furthermore, it was recorded that the values of lactate dehydrogenase (LDH) ($p = 0.033$) and total cholesterol ($p = 0.001$) were lower after ciprofloxacin therapy. In order to enhance the efficacy of ciprofloxacin in CKD patients, a dose decrease is required and not a shortening of the interval of administration, even at patients in the early stages of illness, to avoid side effects. Using the assessment of individual pharmacokinetic values of the studied patients, the study group can be extended, and a research based on populational pharmacokinetics could be initiated in the future.

Rezumat

Pacienţii cu boală cronică de rinichi (BCR) reprezintă o populaţie specială, care deseori prezintă infecţii asociate, la care se impune terapie antimicrobiană. Studiul are ca obiectiv monitorizarea farmacoterapiei ciprofloxacinei, administrată pacienţilor cu BCR, care asociază infecţii, în scopul creşterii eficienţei terapeutice şi evitarea toxicităţii substanţei medicamentoase. S-a efectuat un studiu farmacocinetic, deschis, prospectiv, pe o perioadă de 15 luni, incluzând 29 de pacienți diagnosticați cu BCR, cărora li s-a determinat concentrația plasmatică şi urinară a ciprofloxacinei, printr-o metodă validată de cromatografie în fază lichidă de înaltă performanţă (HPLC), după administrarea orală a medicamentului. Eficienţa terapiei cu ciprofloxacină a fost evaluată pe baza criteriului: clinic, paraclinic, farmacocinetic şi toxic. Ponderea cea mai mare a efectelor adverse a fost înregistrată la subgrupul de pacienți aflați în stadiul III de BCR (n = 10). Am descoperit corelații, între timpii de înjumătăţire ($T_{1/2}$) individuali şi estimarea ratei filtrării glomerulare (eRFG) ($p = 0,022$) precum şi între procentul de medicament eliminat urinar în 24 de ore şi nivelul creatininei serice ($p = 0,024$). De asemenea am observat că valorile activității lactat dehidrogenazei (LDH) ($p = 0,033$) şi cele ale colesterolului total ($p = 0,001$) au fost mai scăzute după terapia cu ciprofloxacină. La pacienţii cu BCR, pentru a creşte eficacitatea ciprofloxacinei, se impune o reducere a dozelor şi nu a intervalului de administrare, chiar şi la pacienţii aflaţi în stadii incipiente de boală, pentru evitarea efectelor adverse. Pornind de la evaluarea valorilor de farmacocinetică individuală la această populaţie specială studiată, se poate extinde gruoul de studiu şi proiecta în viitor o cercetare bazată pe un studiu de farmacocinetică populaţională.

Keywords: chronic kidney disease (CKD), ciprofloxacin, HPLC

Introduction

The chronic kidney disease (CKD) is a recently introduced notion in nephrological clinical practice. The diagnosis of CKD can be set upon the following criteria, according to the study of National Kidney Foundation-Kidney Disease Outcome Quality

Initiative (NKF-KDOQI) of 2002: a) renal lesion of over three months, characterised by abnormal structures or functions of the kidney, with or without the diminishing of the glomerular filtration rate (GFR); b) GFR under 60 mL/min/1.73 m^2 for a duration of over three months, with or without renal lesion [18].

Therapeutic drug monitoring has been introduced in clinical practice in an attempt to individualise medical therapy, to minimise the side effects of drugs, especially since the alterations of the renal functions and not only, modify the relation between the doses and the plasma concentration level [1].

Infectious pathology is frequent in patients with CKD. The incidence of the most frequent infectious complications is significantly higher in patients with renal failure, compared to the general population, the majority of studies emphasising the high prevalence of urinary tract infections (UTI) and respiratory infections [12].

In the selection of the anti-infectious therapy, ciprofloxacin has been chosen as it has a broad antimicrobian spectrum, useful in different pathology types but especially in UTI pathology, after assessing the sensitive germs, adjusting its posology according to the CKD stage.

Whenever pharmacokinetic specific information is not available, the administered dosage must be reduced proportionally with renal impairment, by using two methods: the method of time interval and the method of dosage reduction. Drug clearance is reduced in CKD, thus the dose reduction implies the administration of the same dose at longer intervals. An alternative method is the administration of a smaller dose, maintaining the same time interval [2, 11].

In patients with CKD, a progressive reduction of GFR occurs. That is why the adaptation of ciprofloxacin dosage is mandatory, a drug frequently used at patients with renal pathology due to the tissular penetrability which is enhanced compared to other classes of antimicrobial drugs. Although recent studies recommend the necessity of adjusting dosage depending on the stage of the renal disease, the majority of such studies do not indicate a clear and precise adaptation. There are slight differences even among the medicine producers which are supervised by different regulatory authorities, concerning dosage adjustment in patients with CKD who therefore, recommend the undertaking of population pharmacokinetic studies [15, 16]. The most recent results show the necessity of re-assessing the pharmacokinetics of ciprofloxacin in the case of patients with CKD.

The present study aimed the assessment of the pharmaco-therapeutic safety profile in patients with chronic kidney failure to whom ciprofloxacin was administered orally in view of eradicating pathogen microorganisms. Also the study evaluated the onset of possible toxic phenomena depending on the stage of the kidney disease.

Materials and Methods

The present prospective study evaluated the safety of the treatment with ciprofloxacin, based on the following criteria: clinical, paraclinical (creatinine, urea, hepatic enzymes) and toxicological (the monitoring of side effects) assessing a number of 29 adult patients, diagnosed with CKD, between 01.2011 - 04.2012, in the Mures Clinical County Hospital having the agreement of the Ethics Committee of University of Medicine, Târgu-Mureş.

Admission criteria were CKD associated with bacterial infections or clinical situations that required the treatment with ciprofloxacin.

Exclusion criteria: renal replacement therapy, pregnancy/lactation, surgical interventions on the digestive tract which can alter the pharmacokinetics of ciprofloxacin (gastric, intestinal, biliary resection with the exception of appendectomy).

For eGFR we used the simplified form of the 4-variable MDRD (Modification of Diet in Renal Disease) Study Equation: eGFR = 186 x [Serum Creatinine]$^{-1.154}$ x [Age]$^{-0.203}$ x [0.742 if the subject is female] x [1.210 if the subject is black] [13].

The patients with eGFR < 60 mL/min (stage 3) received 1000 mg of ciprofloxacin per day in two separate doses at a regular interval and those with eGFR < 30mL/min (stages 4 and 5), were administered 500 mg once daily. After administering an initial dose, 3 blood samples were collected from all patients at set time intervals following plasma peak levels, to determine individual $T_{1/2}$. Afterwards, 2 blood samples were collected (after 48 hours) to assess the plasma concentration of ciprofloxacin at steady-state, one immediately prior to the administration of the next dose $C_{ssmin(trough)}$, another one at 30 minutes post dose. The blood samples of 5 mL were collected by venepuncture, the blood being afterwards stored in K3 EDTA vacutainer collection tubes. Each sample was centrifuged at 3500 rmp for 10 minutes. The plasma collected was introduced in special polypropylene tubes to be analysed. From the 24 hours urine also a sample of 2 mL was obtained in order to establish the percentage of the unprocessed drug cleared renally. The plasma and urine samples were then stored and frozen untill their use. Using the blood samples collected from patients, individual pharmacokinetics was determined, having as support the plasma concentration level at steady-state and correlating it with the CKD stage.

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The determination of plasma concentration level of ciprofloxacin, orally administered, has been performed by using a validated HPLC method, by successive sampling at set time intervals to determine individual $T_{1/2}$ and plasma concentration level at steady-state as shown before [6, 7, 17].

Due to high risks of inhibiting the cytochrome P_{540} (CYP) 1A2 by ciprofloxacin, the following drugs administration was stopped during the study: xanthinic derivates (teophylline, caffeine, pentoxifylline) and other drugs which can alter the pharmaco-kinetics of the drug by modifying the oral absorbtion of ciprofloxacin: antiacids containing ions of calcium, magnesium, aluminium, bismuth, sucralfate and iron supplements were also prohibited [9].

In case of simultaneous treatment, several factors were taken into account, such as the fact that ciprofloxacin mildly inhibits the cythocrome CYP 3A4 (isomorph involved in the metabolization of approximately 50% of the drugs used in therapy). Some reports evidenced the increase of anticoagulation and oral antidiabetics effects. Nevertheless, the interaction of CYP 3A4 dependence was not well documented and the weak binding of plasma proteins excludes the interaction through movement [5, 14].

The results are presented as mean ± SD. Student's t-test has been used to compare the mean of laboratory tests pre and post ciprofloxacin therapy and Pearson correlation between the resulting pharmacokinetic parameters. The statistical analysis has been performed with the help of the statistic programme Graph Pad Prism 6, and p was considered statistically significant at the value $p < 0.05$.

Results and Discussion

The studied population comprised 29 patients; the average age was 65 years (± 11.05), the gender proportion was approximately equal, the female gender slightly higher of 52%.

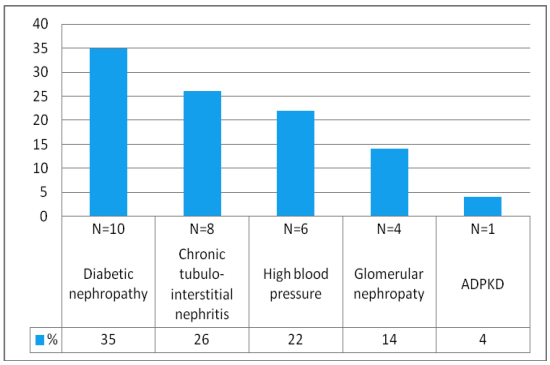

Figure 1.
CKD aetiology

Considering the CKD, most patients who met the eligibility criteria were in stage 3 - 45 %, in stage 4 - 34 % and in stage 5 - 21 %. According to CKD etiology, the most frequent condition was diabetic nephropathy - 35% (Figure 1).

Considering the type of infections which required the treatment with ciprofloxacin, there was a slight prevalence of respiratory infections - 59% in the detriment of the urinary tract infections - 41% (Figure 2). From an aetiological perspective the most frequent germs involved were *Staphylococcus aureus* (methicillin sensitive *Staphylococcus aureus – MSSA)* 38%, *Escherichia Coli* 21% and *Klebsiella Pneumoniae* 17% (Figure 3).

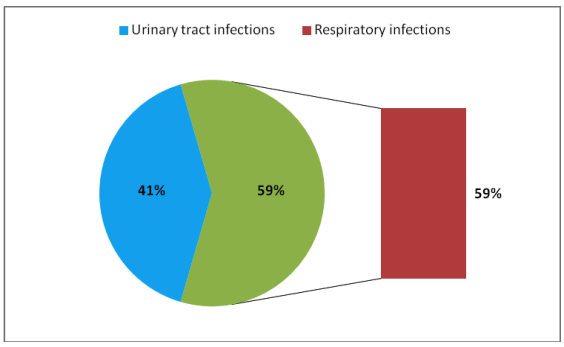

Figure 2.
Type of infection

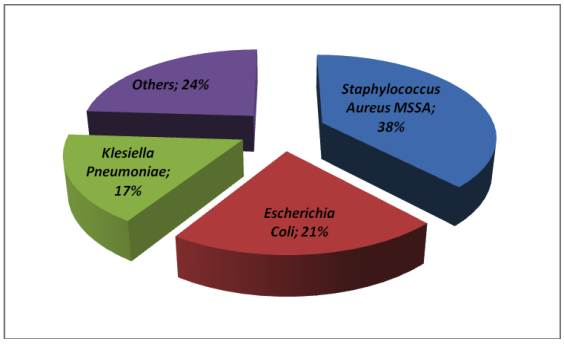

Figure 3.
Etiologic microorganisms

The increase of the value of serum creatinine at the end of therapy has been considered a side effect, being the most common, present at 59% (n = 17) of patients, without significant impairment of the renal function (Table I). Digestive side effects were present in the case of 28% (n = 8) of patients, namely: vomiting, diarrhoea, gastralgia. Also cutaneous eruptions were noticed at 10% (n = 3) of the monitored patients and an increase of hepatic enzymes at 10% (n = 3) of the patients (Table II). Considering the pattern of data in current research regarding hepatic function impairment, it may be considered that in the studied group, a slight increase of the hepatic enzymes was recorded in three cases only, post medication, which we have thus labelled as side effects, the mean values of hepatic enzymes decreased generally after

ciprofloxacin therapy. LDH (p = 0.033) and total cholesterol (p = 0.001) decreased post therapy in the studied lot (Table I).

Table I

Laboratory results of the studied population

Measurements	Mean ± SD	Median (Min-Max)	Mean ± SD	Median (Min-Max)	p - value
	Before Treatment	Before Treatment	At the end of treatment	At the end of treatment	
Serum creatinine, mg/dL	2.46 ± 1.12	1.9 (1.1-5.2)	2.56 ± 1.16	2.3(0.8-4.6)	0.298*
eGFR – MDRD	28.65 ± 13.56	28 (8-60)	27.96 ± 15.02	27(10-71)	0.547*
WBC, mm^3	7.64 ± 2.37	7.54 (3.2-12.6)	8.24 ± 2.56	8.51 (1.9-14.3)	0.207*
Hb, g/dL	12.21 ±2.19	12.5 (6.0-15.6)	11.86 ± 1.88	12.2 (6.7-14.9)	0.105*
Platelet, mm^3	233.76 ±56.94	235 (140-428)	221.52 ±57.25	228 (97-310)	0.194*
AST, IU/L	18.31 ± 6.18	17 (10-39)	18.41 ± 7.00	16 (10-35)	0.935*
ALT, IU/L	17.13 ± 9.40	15 (4-53)	16.96 ± 10.82	13 (6-50)	0.906*
GGT, IU.L	39.48 ± 30.38	30 (13-156)	38.86 ± 32.55	28 (16-168)	0.739*
LDH, IU/L	350.34 ± 103.70	325 (220-652)	326.41 ± 111.99	286 (215-643)	0.033*
Total Cholesterol, mg/dL	196.83 ± 54.09	203 (87-301)	174.48 ± 44.45	179 (78-246)	0.001*
HDL Cholesterol, mg/dL	45.70 ± 13.86	46 (25-80)	42.69 ± 12.71	41 (25-77)	0.096*
LDL Cholesterol, mg/dL	116.98 ± 50.66	115 (30-223)	106.39 ± 42.59	99 (27-198)	0.124*

*Student's t-test; WBC: White blood cells; Hb: Haemoglobin; AST: Aspartate Transaminase; ALT: Alanine Transaminase; GGT: Gamma-glutamyl trasferase; LDH: Lactate dehydrogenase; HDL: High-density lipoprotein; LDL: Low-density lipoprotein

Table II

Pharmacokinetic parameters of ciprofloxacin

Stage of CKD/No	3/13	4/10	5/6
$C_{ssmin(trough)}$ (μg/mL) (Mean ± SD)	1.35 ± 0.38	1.36 ± 0.91	1.76 ± 1.80
$T_{1/2}$ (h)(Mean ± SD)	5.24 ± 1.52	8.56 ± 4.94	9.05 ± 2.78
Procent of the dose urinary cleared in 24 h (Mean ± SD)	17.83 ± 9.33	16.75 ± 7.05	11.72 ± 5.75
Side effects, Subgroup%/total	77%/10	70%/7	67%/4

Applying the Pearson correlation factor in the studied group, between the different pharmacokinetic parameters, we discovered statistically significant correlations between ciprofloxacin individual half-life and the eGFR calculated with the help of MDRD Study Equation (Figure 4) and the percent of the drug cleared urinary in 24 hours and the level of serum creatinine (Figure 5). Both correlations are moderate, negative, with a r = -0.42 / r = -0.41 and p = 0.022 / p = 0.024.

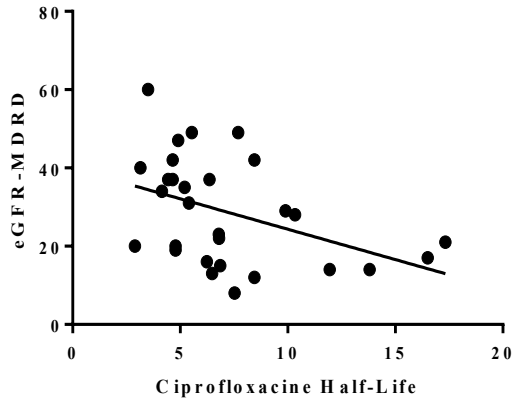

Figure 4.

Correlations between ciprofloxacin individual half-life *vs*. eGFR-MDRD

On the basis of pharmacokinetic parameters there is a progressive increase of average $C_{ssmin(trough)}$ at 48 hours, directly proportional with the CKD level, irrespective of posology, which differs according to the creatinine clearance, for stage 3 of CKD on one hand and stages 4/5 on the other (Table II).

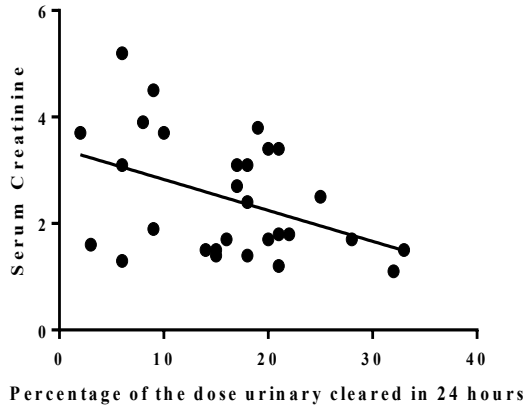

Figure 5.

Correlations between percentage of drug urinary cleared in 24 hours *vs*. serum creatinine

Also, on the basis of the data from the studied patients, $T_{1/2}$ increases progressively being directly proportional with the CKD stage due to the reduction of the clearance of the drug substance

secondary to renal function impairment (Table II), requiring a reduction of doses [10]. Applying the Pearson correlation coefficient in the studied group we have discovered that 42% of causes which lead to the increase the ciprofloxacin half-life, are caused by CKD and the rest by other factors [Figure 5]. Ciprofloxacin is mainly cleared renally; however, the drug is hepatically metabolised and partially eliminated through the biliar system in the intestines. These alternative ways seem to compensate the reduced renal excretion at patients with renal failure. Still, in preliminary studies of patients with stable hepatic cyrosis, no significant change in the pharmacokinetics of ciprofloxacin was noticed, an aspect emphasised in our study by the statistically significant decrease of hepatic enzymes, especially LDH in pre and post therapy determinations, as well as by the reduced rate of toxic events by the increase of hepatic enzymes [4]. Applying the correlation coefficient between the percentage of drug renally excreted in 24 hours and the serum level of creatinine, we have noticed that 41% of effects which lead to the decrease of the drug substance urinary cleared are related to CKD and the rest to other factors, most probably factors such as hepatic metabolization and biliary and intestinal excretion (Figure 5).

The quantity of drug substance eliminated renally in 24 hours decreases indirectly proportional with $T_{1/2}$, modifying the diuresis as well. This finding emphasises the risk of the onset of toxic side effects which outnumber in cumulated proportion the patients in stages 4 and 5, those in stage 3. Following these findings, the possibility of decreasing the doses at patients in the early stages of CKD can be assessed, as well as a closer monitoring of ciprofloxacin therapy of such patients (Table II).

There are also several studies which show that ciprofloxacin could induce bone marrow depression, shown by the decrease of the concentration of haemoglobin, decrease of white blood cells and the increase or decrease of platelets. Certainly in the case of patients with CKD, secondary anaemia is present due to the inadequate secretion of erythropoietin, but this work hypothesis is worth to be investigated in patients treated with this antimicrobial, but which are not part of this special population with renal failure [3]. Moreover, there are recent studies which highlight the hypolipidemic effect of ciprofloxacin, an aspect confirmed by the results of our study as well, an aspect worth to be researched in the future in patients with CKD [8].

Conclusions

Based on the preliminary results of the current research we can state that in order to increase the efficacy of therapy in patients with CKD it is mandatory to reduce the dose of ciprofloxacin so that an optimum blood level of ciprofloxacin will be achieved in order to enhance the therapeutic effect, avoiding in the same time the risk of secondary effect. The method of modifying the time interval between administrations is less efficient in patients with impairment of the renal function. Hepatic clearance is insignificant, only partially compensating renal impairment.

Side effects are present in the highest proportion at the group of patients in stage 3 of CKD, the most reasonable explanation being that these patients have been administered a double dose, compared to those in stage 4 and 5 of CKD. Taking all this into account, we consider that in order to meet the therapeutic objective and to avoid toxicity, in case of patients with early CKD and associated bacterial infections sensitive to ciprofloxacin, it is a reconsideration of dose that is required and not of the therapeutic interval (Table II).

On the other hand, we may conclude that by decreasing the percentage of drug substance urinary cleared in patients in stages 4 and 5, the positive aspect achieved is an optimum and efficient plasma concentration level maintained longer, which is beneficial for the respiratory infections. The negative element is the progressive reduction of the quantity of drug renally cleared, a negative aspect because of the reduced action at the level of the urinary tract. Thus, paradoxically we have, at least theoretically, a higher efficiency from the point of view of the pharmacokinetics of ciprofloxacin in patients who associate CKD to an extra-renal infection, contrary to the case of patients with UTI.

Considering the results of this work a populational pharmacokinetic study could be carried out, on the special population with CKD, being in complete agreement with guidelines.

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