MONITORING THE ANTIMICROBIAL THERAPY OF THE PATIENT WITH CHRONIC KIDNEY DISEASE USING THE PHARMACOKINETIC CRITERIA

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Abstract: *Therapeutic Drug Monitoring (TDM) in Chronic Kidney Disease (CKD) remains a permanent challenge for nephrologists especially when such pathology is associated with infectious phenomena which require a rapid and radical treatment, but at the same time a personalized one. We have conducted a prospective study which included 40 patients with CKD stages 3, 4, 5 treated with ciprofloxacin in different dosages, according to glomerular filtration rate, in order to eradicate certain microorganisms sensitive to this antibiotic. The research was conducted over a period of 42 months in the Department of Nephrology of Mureş Clinical County Hospital. In the studied group, during the therapy, a number of 55 side effects were recorded secondary to the administration of ciprofloxacin, more frequent in the case of those in end stage of CKD, even if the dosage was 50% smaller. That is why, it is mandatory that patients who are in end stage of CKD, stage 4 and 5, being more vulnerable, should benefit from a more complex evaluation such as pharmacokitnetic investigations in view of an optimum dosage adjustment of potentially nephrotoxic drugs. Therapeutic drug monitoring of the patient with CKD should include clinical assessment and laboratory, pharmacokinetic parameters for a correct dosage, in order to avoid over or under dosage of a potentially nephrotoxic treatment.*

INTRODUCTION

Chronic kidney disease is a public health issue, on one hand due to risk factors, which are accountable for its onset, and on the other hand due to the complications that may occur and result in the patients' death. We must not overlook the pharmacoeconomic aspect, especially the costs for the health systems worldwide, caused by the renal functions substitution therapies.(1) Considering such aspects, patients with CKD must be closely monitored, especially those diagnosed with various infectious phenomena (2) caused by bacterial species sensitive to common antimicrobials, such as fluroquinolones in the case of the present research.

Our research was generated by the assumption that although CKD cannot be healed, the renal function impairment may be slowed down, this way the therapy for the substitution of the renal function may be delayed, thus reducing the costs for the National Health Insurance House, but at the same time removing the discomfort inherent to renal function substitution treatments for the patient with such pathology.(3)

This aim cannot be achieved only by closely monitoring the therapy administered to patients with CKD, especially in the case of potentially nephrotoxic drugs (ciprofloxacin). The dosage of such drugs has to be adapted taking into account the glomerular filtration rate (GFR) in this special group of patients, with chronic renal failure.

Thus, according to the most competent authorities in the drug field: Food and Drug Administration (FDA) and the European Medicine Agency (EMEA), the "gold standard" is monitoring the pharmacotherapy according to the pharmacokinetic criteria.(4,5)

PURPOSE

The purpose of this study is to monitor antimicrobial therapy in patients in different stages of CKD according to current guidelines (6), based on pharmacokinetic measurable parameters, in view of administering optimum dosage, without side effects.

MATERIALS AND METHODS

The current study is a prospective, open study, conducted during 01.2011-07.2014, on a number of 40 patients admitted in the Nephrology Department of the Mureş Clinical County Hospital. The study has the approval of the Ethics Committee of the University of Medicine and Pharmacy Tîrgu-Mureş, and the patients have signed an informed agreement to be included in this study. The inclusion criteria for this study were met by all adult patients who were diagnosed with CKD according to current guidelines, and who presented urinary or respiratory infections with sensitive germs to ciprofloxacin therapy. Patients who were under renal function substitution therapy (hemodialysis, peritoneal dialysis, renal transplant) were not included in this study.

The patients were administered different dosages of ciprofloxacin according to the CKD stage, being thus divided into two groups: group 1 (16 patients) in stage 3 of CKD, with GFR > 30ml/min, received a dosage of 500mg of ciprofloxacin every 12 hours and group 2 (24 patients) in stage 4 and 5, with GFR < 30ml/min being in a more advanced stage of CKD received 500mg of ciprofloxacin in a single dose.

The urine samples (collected from patients at 24 hours) and blood samples (collected at 48, 72 hours, respectively from the first dose) were taken to determine steady state concentration and were analyzed with a validated high performance liquid chromatography method (HPLC) at the Drug Analysis Laboratory of the University of Medicine and Pharmacy Tîrgu-Mureş.(7)

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The results are presented as ±SD media. The statistical analysis was achieved with the help of Graph Pad Prismo 6 soft. Test T student was applied for unpaired data and Mann Whitney test for nonparametric data, p being considered statistically significant at a value of <0,05.

RESULTS

In the studied group, the female gender patients were predominant, 55% (n=22), mean age being 65±10 years. From the point of view of CKD etiology, the pathologies which were the underlying cause for over 80% of patients were the Tubulo-interstitial nephritis 32% (n=13), diabetes 30% (n=12) and arterial hypertension 20% (n=9). Regarding the stages, most patients selected for the study were in stage 4 of CKD, 42% (n=17). Respiratory tract infections were more often recorded comparatively with the infections of the urinary tract, while of the isolated microorganisms sensitive to ciprofloxacin, in over 50% of cases these were infections with *Staphylococcus Aureus MSSA* (*Methicillin-sensitive staphylococcus aureus*) 35% (n=14) and *Escherichia Coli* 22% (n=9) (table no. 1).

Analyzing the clinical parameters of the two groups of studied patients, we have found higher values of the mean of patients from group 1 (GFR > 30ml/min), in case of alanin aminotransferase (ALT), p=0.03, post therapy. Also, there were higher values of the mean of patients from group 2 (GFR < 30ml/min), serum creatinine, p=0.0001 as well as alterations of the hemoleucogram in the same group, especially of: red blood cells (RBC), p=0.005, Hematocrit, p=0.003, Haemoglobin, p=0.001 (table no. 2).

Analyzing the pharmacokinetic parameters we can state that the daily dosage, adjusted to weight, was significantly higher in patients from group 1 (GFR > 30ml/min), p=0.0001, which led to a higher percentage of unaltered drug cleared urinary, as well as to a higher concentration at 48 hours at steady-state, p=0.002. From a toxicological perspective as shown below, the most significant side effects were recorded in patients from group 2 (GFR < 30ml/min) (table no. 3).

Table no. 1. Demographic and clinical characteristics of the studied population

Males, %	**45**
Females, %	**55**
Age at beginning of study (mean±SD)	**65.01±10.65**
Weight, kg (mean±SD)	**81.07±16.00**
Height, m (mean±SD)	**1.63±0.08**
SBP, mmHg (mean±SD)	**128.60±13.27**
DBP, mmHg (mean±SD)	**77.55±6.59**
CKD etiology	%
Diabetes	**30**
Chronic Tubulo-interstitial Nephritis	**32**
High Blood Pressure	**22**
Glomerular Nephropathy	**13**
Polycystic Kidney Disease	**3**
CKD stage before treatment	%
Stage 3	**40**
Stage 4	**42**
Stage 5	**18**
Type of Infection	%
Urinary Tract Infections	**45**
Respiratory Infections	**55**
Etiologic Microorganism	%
Staphylococcus Aureus MSSA	**35**
Escherichia Coli	**22**
Klebsiella Pneumoniae	**15**
Other	**28**

SD: Standard deviation; SBP: Systolic blood pressure; DBP: Diastolic blood pressure;CKD: Chronic kidney disease; MSSA: Methicillin-sensitive staphylococcus aureus.

Table no. 2. Clinical parameters and comparisons between the groups of patients

Parameter	Group 1 GFR>30 ml/min (n=16)		P	Group 2 GFR<30 ml/min (n=24)		P
	Group 1 mean±SD before treatment	Group 2 mean±SD before treatment		Group 1 mean±SD at end of treatment	Group 2 mean±SD at end of treatment	
ALT (UI/L)	18.81±11.61	14.08±6.07	NS[a]	20.3±12.4	12.70±5.96	0.03[b]
AST (UI/L)	19±5.83	17.75±6	NS[b]	20.43±7.3	16.16±5.28	NS[a]
GGT (UI/L)	41.25±36.10	28.87±19.21	NS[a]	41.5±40.5	28.37±16.8	NS[a]
LDH (UI/L)	333.6±72.3	373.5±111.7	NS[b]	316.5±85.8	335.6±111	NS[b]
Cholesterol (mg/dL)	205.6±51.6	191.2±50.2	NS[b]	179.4±46.3	172.9±44.5	NS[b]
HDL (mg/dL)	45.81±12.67	44.57±15.76	NS[a]	41.25±11.4	42.57±14.7	NS[b]
LDL (mg/dL)	131.4±47.4	108.3±46	NS[b]	109.4±39.4	104.2±46.3	NS[b]
Serum Creatinine (mg/dL)	1.49±0.25	3.10±0.90	0.0001[b]	1.60±0.39	3.19±0.88	0.0001[b]
Urea (mg/dL)	68.18±12.54	110.1±40.9	0.0001[b]	83.45±37.4	113.41±33	NS[a]
Potassium (mmol/L)	4.95±0.71	5±0.60	NS[b]	4.46±0.54	4.51±0.80	NS[b]
Glucose (mg/dL)	99.37±23.74	111.9±37.5	NS[a]	93.12±15.4	102.5±32.9	NS[a]
WBC (10^3/µL)	7.87±2.35	7.15±2.27	NS[a]	8.35±2.67	8.41±3.59	NS[a]
RBC (10^6/µL)	4.51±0.88	3.7±0.78	0.002[a]	4.4±0.79	3.68±0.64	0.005[b]
Haemoglobin (g/dL)	13.71±1.85	11.06±2.11	0.002[a]	12.86±1.51	10.99±1.78	0.001[b]
Hematocrit (%)	40.2±6.44	33.82±6.23	0.005[a]	39.33±5.81	33.52±5.24	0.003[b]
Platelets (10^3/µL)	248.25±58	225.9±54.2	NS[a]	249.2±43.6	229.9±74.1	NS[b]

ALT: Alanin aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma-glutamyl transpeptidase, LDH: Lactate dehydrogenase, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, WBC: White blood cells, RBC: Red blood cells, [a]Mann-Whitney test, [b]Student's t-test, NS: not significant.

Table no. 3. Pharmacokinetic characteristics of the groups

No of Patients	Groups GFR (ml/minute)	Daily Dose (mg)	Adjusting Daily Dose (mg/kgc) (mean±SD)	$C_{min48(trough)}$ (ng/ml) (mean±SD)	$C_{min72(trough)}$ (ng/ml) (mean±SD)	GFR MDRD ecuation (mean±SD)	Procent of the dose urinary cleared in 24h (mean±SD)	Diuresis (ml/24h) (mean±SD)	Side effects (N)					
									Elevated Creatinine level	Bone marrow depression	Elevated liver enzymes	Diarrhoea	Nausea/vomiting	Rash
16	>30	500 bid	12.52±2.04	1.4±0.57	1.4±0.66	41.68±8.2	17±8.5	2012±846	10	3	1	3	2	0
24	<30	500 qd	6.48±1.38	0.99±1.0	1.34±1.3	19±5.97	13±8.2	1170±718	16	9	2	5	1	3
			0.0001[b]	0.002[a]	NS[a]	0.0001[b]	NS[a]	NS[b]						

GFR-MDRD Study Equation: Glomerular Filtration Rate-Modification of Diet in Renal Disease, [a]Mann-Whitney test, [b]Student's t-test, NS: not significant.

DISCUSSIONS

The infectious processes occurring in vulnerable patients, such as those with CKD, must be rapidly eradicated through a prompt anti infectious therapy in order to slow down the process of renal function impairment requiring an optimal monitoring of therapy in this category of patients.

As seen from the results presented in table no. 2, group 1 (GFR > 30ml/min) of patients, who were administered a higher dosage of ciprofloxacin (1000mg/24 hours), had a higher value of the mean of post therapy alanin aminotransferase, p=0.03. This can be explained most likely by the hepatotoxic effect of ciprofloxacin (8), as well as the attempt to metabolise and clear the drug by the billiary tract in patients where the regular clearance system is impaired. Still, compared to group 2 (GFR < 30ml/min), there was no record of an increased number of side effects with an elevated level of hepatic enzymes reaching pathological values.

In addition, changes of serum creatinine values post therapy were recorded in both groups, the cause being, on one hand an evolution of CKD, but being such a short interval between collections of samples, most likely it was caused by a nephrotoxic effect of ciprofloxacin (table no. 2).(9)

Analysing the studied parameters, alterations of the red blood cells from the bone marrow are noticeable, with alterations of hemoglobin, hematocrit and red blood cells in both groups post therapy. The normochromic, normocytic anemia which occurs in patients with renal impairment secondary to erithropoietin deficiency can be an underlying cause but another cause can be the suppressive effect of ciprofloxacin on the bone marrow (table no. 2).(10)

Studying the pharmacokinetic data from table no. 3, we may say that from the point of view of pharmacovigilance, 50% more side effects persisted in patients from group 2 despite an adjusted therapy.

The limitations of the study are determined by the small number of enrolled patients due to their reduced compliance on one hand, and on the other hand due to their recruitment from one Department of the Mureş Clinical County Hospital. In the future, we aim at reaching a target of 70-100 patients as well as conducting a study of population pharmacokinetics, on this special population with CKD.

CONCLUSIONS

Monitoring the pharmacotherapy is vital in a special population such as patients with CKD in order to avoid under dosage – thus, inefficiency of therapy administration or overdosage – resulting in the onset of toxic phenomena. By monitoring we imply establishing an optimum therapy, avoidance of potential drug interaction, efficient dosage adjustment, clinic and paraclinic assessment to discover possible side effects, considering that in the case of these patients one of the clearance pathways is impaired.

In case of patients in stage 3 of CKD, benefitting from antimicrobial therapy with ciprofloxacin, dosage reduction is recommended, due to side effects occurring in this group of patients. Those patients who are in an advanced renal failure stage, such as those of stages 4 and 5 of CKD, must be more closely monitored than those in the initial stages especially in the case of the administration of potentially nephrotoxic drugs, such as ciprofloxacin which is frequently administered in hospitalized patients. This category of patients with GFR<30ml/min, in the absence of pharmacokinetic parameters, requires dosage adjustment by using a combined method which involves the increase of the time interval between administrations as well as dosage reduction.

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