UNIVERSITY OF MEDICINE AND PHARMACY TÂRGU-MUREŞ
SCHOOL OF DOCTORAL STUDIES TÂRGU-MUREŞ

Monitoring of pharmacotherapy in patients with chronic kidney disease

PhD student: **Stoica Mihai Ciprian**
Scientific advisor: **Professor, PhD Dogaru Grigore**

INTRODUCTION Therapeutic drug monitoring (TDM) in patients with chronic kidney disease (CKD) represents a major challenge for clinicians. The complexity of clinical biological disorders that occur in different stages of CKD, alongside low renal clearance, may favor the onset of certain pathology secondary to the medication administered at this particular category of patients. All these aspects must be taken into consideration judiciously by the doctor in order to prevent the occurrence of unpleasant and serious medical events.

Drug therapy must be carefully monitored in patients with CKD, especially when drugs with a narrow therapeutic range are administered, since these are frequently used in nephrology wards. Immunosuppressive therapy is the most eloquent example of medication in this category, its administration in patients with kidney transplant being mandatory. Moreover, the clinical surveillance proved its efficacy in the case of prescribed antimicrobial drugs, due to their nephrotoxic potential in case of impaired clearance functions.

Even the authorities which closely supervise the field of medical therapy such as Food and Drug Administration (FDA) and European Medicine Agency (EMA) only recommend dosage adjustment, in case of many drugs (for example ciprofloxacin) suggesting as elective method the conduction of pharmacokinetic studies on patients.

OBJECTIVES In the first two prospective studies focusing on the monitoring of therapy with ciprofloxacin, the following main objectives were targeted:

- the evaluation of toxicity by clinical, biochemical and pharmacokinetic monitoring of patients introduced in the study and the identification of secondary reactions;
- the description of individual pharmacokinetics of ciprofloxacin and identification of the influence of co-variables (creatinine clearance, weight, the percentage of unmodified drug cleared urinary);
- bayesian adaptation of ciprofloxacin administration in patients with CKD because standard administration can be toxic or inefficient due to inter and intra- individual variability.

In the third, retrospective study we focused on:

- the comparative evaluation of two groups of patients with kidney transplant, divided according to the origin of the renal allograft, using the clinical, biochemical and pharmacokinetic criteria;
- identification of the most vulnerable category of patients and the description of possible factors which might modify the pharmacokinetics of tacrolimus.

MATERIAL AND METHOD The selection of patients of the two prospective studies was similar: diagnosed CKD, according to the K/DOQI and infections with germs which are sensitive to the therapy with ciprofloxacin. Oral therapy with ciprofloxacin was introduced after the informed consent of each patient was signed. Afterwards several blood samples were collected, in order to establish plasma peak and steady-state concentration, as well as a urine sample according to a program which was established beforehand. The chemical analysis of the biological products collected from the patients, was performed at The Analysis Drug Laboratory of The University of Medicine and Pharmacy, Targu Mures, using a method of liquid chromatography coupled to mass spectrometry (LC-MS), validated according to standard procedures for bioanalysis. The lot of patients included in the studies was recruited in the Department of Nephrology of The Clinical County Hospital, Targu Mures.

The third study was a retrospective research, which included a lot of 36 patients coming from a single Kidney Transplant Center, periodically monitored clinically and biochemically in the

Department of Nephrology of The Clinical County Hospital, Târgu Mures. The patients admitted in the study were only those who had tacrolimus in their therapeutic scheme and at least 3 months have passed after the kidney transplant, when steady-state concentration is achieved. The study analyses the efficiency and safety of the oral administration of tacrolimus, a drug with a low therapeutic index, used in immunosuppression, at patients with kidney transplant, based on the classic monitoring criteria described, the most important being the pharmacokinetic one (C_{trough} at steady-state of tacrolimus). Blood concentration samples of the studied drug was determined using a LC-MS method, in Synevo Laboratories, these data being taken from the ambulatory medical documents regarding the monitoring of medical therapy, from the Institute of Urology and Kidney Transplant, Cluj-Napoca.

The individual and collective pharmacokinetic data were gathered and represented graphically based on a mathematical model with the help of the specialized software – Kinetica Version 4.4.1 which uses an NPAG method (Non Parametric Adaptative Grid Approaches).

RESULTS In the first prospective study we have focused on the safety of oral administration of ciprofloxacin at patients with chronic renal impairment as well as on the determination of individual pharmacokinetics, using the study of 145 blood samples and 29 urine samples from the patients of the studied lot. Most adverse reactions were surprisingly registered at patients with the optimum renal clearance and the highest elimination rate constant, that is in the case of patients in 3rd stage of chronic kidney disease (10 patients). A comparative analysis of biochemical data pre and post therapy showed results which were statistically significant LDH (p=0.033), K (p=0.006), cholesterol (p=0.001), data which follow a similar pattern with the results of other clinical studies.

In the second prospective study, in which we have included 40 patients, we have focused on the comparative monitoring of clinical, biochemical parameters at the patients which have received ciprofloxacin orally. We aimed at evaluating the effects of the therapy with ciprofloxacin depending on the dose. Due to the number of patients included we have managed to produce a valid model of population pharmacokinetics which can improve the pharmacological approach at patients with CKD who receive the ciprofloxacin orally for different types of infections. To develop the population model 200 plasma concentration of ciprofloxacin were studied. The residual variability was higher in the case of using a multi-compartmental model thus the mono-compartmental model, first order kinetics, was more compatible with the data of the study. The equation rendered by the pharmacokinetic population model is $K_e=0.148058+Cr_{clearance}x0.00353253$.

In the third study, during surveillance, a number of 252 blood determinations of the concentration of tacrolimus at steady-state $C_{ssmin(trough)}$ were performed, with a mean of 7 determinations per patient. 58 of these were outside the therapeutic window, 44 samples pointed at underdosage and 14 determinations showed overdosage and toxic therapeutic level. The level of tacrolinemia varied in a wide interval, the smallest value being of 1.1 ng/ml and the highest value of 29.7 ng/ml.

CONCLUSIONS The studies which focus on pharmacokinetics are of major importance in order to comprehend the evolution of drugs in the human body and to increase precision in prescribing drugs, especially at patients with organ impairment.

The patient with CKD must benefit from a close monitoring due to the vulnerability caused by the disease, so that intervention is done on time and efficiently to avoid dire consequences. Any imbalance produced either by a pathogen agent or by a therapeutic agent with potentially nephrotoxic consequences on an impaired ground, will only contribute to further damaging of the renal function.

Therapeutic drug monitoring is an important evaluation method for the clinician, with clear applicability in clinical practice not just for the research field. This method is of paramount importance and should be used regularly, especially when patients are administered medication with low therapeutic index, when the efficient dose is very close to toxic dose but also when the patients have an impaired metabolic or elimination function, the medication being potentially nephrotoxic.

KEY WORDS: TDM, CKD, LC-MS, ciprofloxacin, tacrolimus.