Original article

Drug Dosage Adjustment in Hospitalized Patients with Renal Failure

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Abstract

Introduction. Dose adjustment for certain drugs is required in patients with reduced renal function to avoid toxicity as many drugs are eliminated by the kidneys. The aim of this study was to assess whether appropriate dosage adjustments were made in hospitalized patients with renal failure.
Methods. A prospective study was carried out in the ward Service of Nephrology, University Hospital Center "Mother Teresa", Tirana. The patients admitted to hospital between October and December 2019 were included in the analysis. Data regarding serum creatinine level, age, gender, prescribed drugs and their dosage was collected from the patients' medical records. The estimated creatinine clearance was calculated using the Cockcroft-Gault equation. Guideline for Drug prescribing in renal failure provided by the British National Formulary was used as the standard for dose adjustment.
Results. There were 589 prescription entries for 74 patients with renal impairment. Dose adjustment was required in 56% (331/589) of prescription entries and 49.8% (165/331) prescription entries requiring dose adjustment were found to be inappropriate. Eleven (14.9%) patients had all of their drugs appropriately adjusted while 53 (71.6%) patients had some drugs appropriately adjusted, and 10 (13.5%) of patients had no drugs appropriately adjusted.
Conclusion. The findings indicate that dosing errors were common among hospitalized patients with renal failure. Improving the quality of drug prescription in patients with renal impairment could be of importance for improving the quality of care.

Keywords: dose adjustment, renal failure, prospective, creatinine clearance

Introduction

The progress in the field of medicine, both in terms of diagnostic and therapeutic goals, has led to a significant increase in the average age of the population, an increase in the number of patients affected by diabetes, obesity, cardiovascular diseases, which are subject to an increased incidence and prevalence of renal failure [1]. Drug dosing errors are today one of the major problems faced by patients with renal insufficiency. Most of the drugs and metabolites are excreted through the kidney. Therefore, a normal renal function is important to avoid potential toxicity in these patients. The impairment of kidney function has a significant influence on pharmacokinetic and pharmacodynamic parameters. Administration of specific doses of the drugs in patients with kidney deficiency is one of the most important steps in avoiding side effects of drugs as well as providing optimal efficacy [2,3]. Despite this important fact about regulating doses in patients with renal failure (RF), these adjustments in most cases are not taken into consideration. Consequently, if adequate dosing regimens are not used in patients with kidney failure, accumulation and immediate toxicity may occur [4].
The purpose of this study is to evaluate if appropriate dosage regimens are applied for the drugs administered to hospitalized patients with renal impairment at the Service of Nephrology and to identify and analyze factors that may influence the correct or not medication prescription in these patients.

Materials and methods

The present study for the assessment of the implementation of correct dosing regimens in patients with RF, included patients hospitalized during the period October-December 2019 at the Nephrology Unit, University Hospital Center "Mother Teresa", Tirana.
Clinical and demographic data were exported from the medical records of hospitalized patients during this period. The study protocol was approved by the head of the nephrology unit and by the Ethics Committee of Clinical Studies.
In total, 74 patients were hospitalized and diagnosed with renal failure (RF), out of which 11 were with acute renal failure (ARF) and 63 with chronic renal failure (CRF).

Data collection
To complete this study, a two-part questionnaire was drafted, the first part consists of patient's general data,

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and the second part includes clinical data obtained from the medical records. From all drugs administered to these patients, the second part of the questionnaire considered mainly those metabolized and excreted in the renal route, excluding drugs that are excreted and metabolized in other extrarenal pathways.

Statistical analyses

The data collected were analyzed using the Statistical Product Service Solutions (SPSS) statistical program and part of the data was analyzed with Excel. Results are reported as mean±SD.

The descriptive analysis focuses on the analysis of the distribution of the variables in the study population, including demographic factors, comorbidities and the reason for drug administration.

The search for significant statistical links was made through several tests where for values of p<0.05, correlation between the variables is statistically significant.
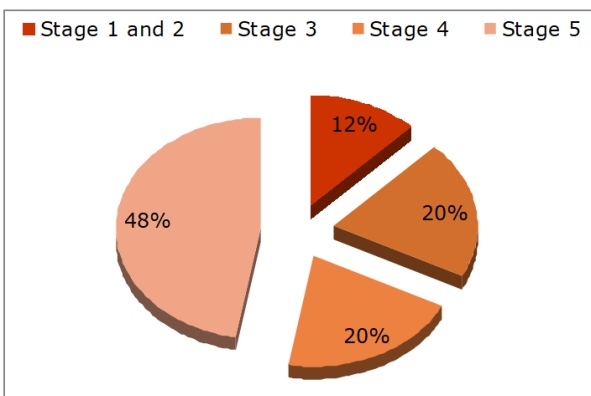
Results

From October 2019 to December 2019, 74 patients undergoing acute renal failure (ARF) and chronic renal failure (CRF), from stage I to pre-dialysis stage V, were included in the study. Patients in chronic dialysis and those hospitalized for other diagnoses were excluded from the study.

Data were received from the medical records of 74 patients. From these patients included in the study, 63 (86.5%) were diagnosed with CRF, while 11(13.5%) were diagnosed with ARF.

From the 74 patients diagnosed with renal failure (RF), 30 (40.6%) are female and 44 (59.4%) are male. The mean age of patients diagnosed with RF was 52.6 years, from the target age group 18-83 years.

Evidently, the CRF pre-dialytic stage V was predominant, with 48% of the cases, followed by CRF stage III and IV with 20% of cases each. While the cases in CRF stage I and II were present in 12 % of cases. These results are shown in Figure 1.

In the unit where the study was conducted, there were patients from all over Albania, although the presence of patients from the other municipalities was predominant compared to patients from Tirana. Other diseases such as arterial hypertension, diabetes mellitus type 2, secondary anemia, dyslipidemia, thrombosis, were present in 62/74 (83%) of patients with RF. 58/74 (78.3%) suffered HTA and dyslipidemia, 34/74 (45.9%) secondary anemia and 15/74 (20%) diabetes mellitus. Information about the stage of the disease was obtained from the patient medical records.

The total number of drugs administered in the patients included in the study was 589. The number of drugs used by the patients ranged from 3 to 18 drugs, showing a high presence of polypharmacy in this category of patients.

The average of the drugs used was 7 drugs per patient per day, with a distribution of the number of drugs per day as shown in Figure 2.
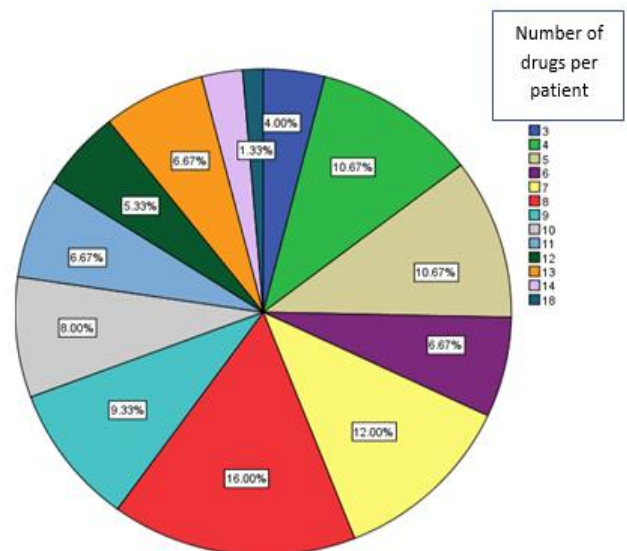
Fig. 2. Distribution of number of drugs /day in patients with RF

The prescribed therapy consisted in drugs for the treatment of renal symptoms or in drugs for the treatment of both renal and non-renal symptoms. The renal therapy consisted in drugs to correct conditions such as hy-

Fig 1. Distribution according to the stages of chronic renal failure
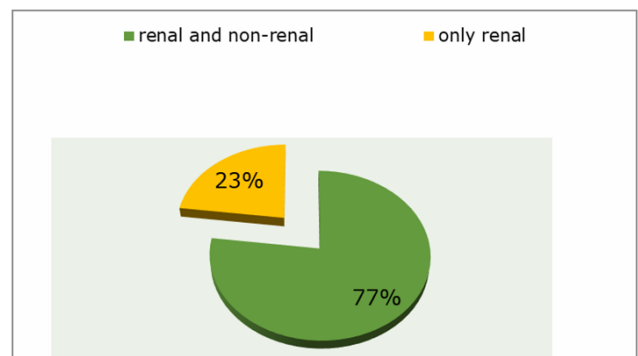
Fig. 3. Distribution of prescription according to the pathology

perphosphatemia, acidosis, hyperkalemia, RF caused by uremia. Nevertheless, renal and non-renal therapy consisted in the treatment of above mentioned health conditions as well as other accompanying diseases. Prevalence of renal and non-renal therapy was 77%, followed by renal therapy only with 23% (Figure 3).

Using the guidelines and the British National Formulary (BNF) [5], each of these drugs was examined and carefully dosed according to renal failure stage. The study excluded drugs that were metabolized and excreted in a large scale by hepatic pathways. These drugs included folic acid 5 mg, iron fumarate 350 mg and erythropoietin administered to control anemia, sodium bicarbonate to correct acidosis, sevelamer carbonate to correct the increase in phosphate levels, keto-acids to correct the deficiency of amino acids and high levels of creatinine in the blood.

On the other hand, more attention was given to large-scale kidney-excreted drugs. For each drug used, its dose was accordingly adapted for each patient.

Out of the 589 medications taken into consideration, 258 drugs (43.8%) did not need dose adjustment, while in 331 (56.2%) it was necessary to adjust the dose before administration to these patients.

Out of these, about 331 drugs that needed a regulated dosage system, only for 166 (50.15%) drugs the doses were appropriately adjusted based on the creatinine clearance values of the patient and for 165 (49.85%) drugs the doses were not appropriately adjusted. The scheme in Figure 4 describes this fact.
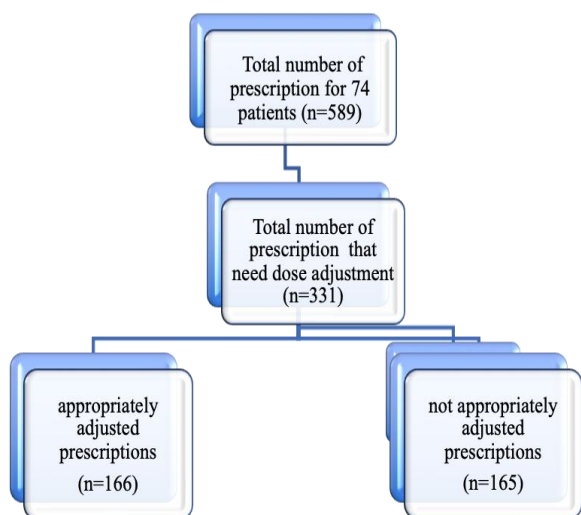

Fig. 4. Appropriateness of prescription in patients (n = 74)

In only 11 out of 74 patients (14.9%) all drugs doses were appropriately adjusted. While at 10 (13.5%) none of the medicines resulted to be adjusted. In most patients, 53/74 (71.6%), only a part of the prescribed drugs had an appropriate dosing regimen.

Based on a detailed assessment of the drugs used in the patients under study, the most prescribed drug was ranitidine. It is mainly excreted in the renal pathway

and dose adjustment in patients with damaged renal function is very important. But only in 11/53 (21%) cases an appropriate dosing system was performed while in 42/53 (79%) dosing resulted improper. Nebivolol was administered to 33/74 patients and the dose was appropriately adjusted in only 8/33 (24%) of patients, moxonidine was administered to 17/74 patients where only in 7/17 (41%) cases a suitable dosing system is implemented. Ciprofloxacin administered to 20/74 (27%) patients is the only drug whose dose was appropriately adjusted in all cases (Table 1). We can also say that in patients with RF, hospitalized in the Nephrology Service, there is a tendency to use drugs, whenever possible, that do not need dose adjustment (extrarenal excretion) such as ceftriaxone, cefuroxime etc.

Table 1. The most prescribed drugs

Drugs administered	Number of patients treated with drug	Number of patients treated with the adjusted drug dose
Ranitidine	53	11
Nebivolol	33	8
Moxonidine	17	7
Ciprofloxacin	20	20
Nitrofurantoin	25	17

According to the RF stage, we noticed that in CRF stage III, out of 73/331 administered drugs, about 5/73 (61.6%) were dosed appropriately and in 28/73 (38.4%) of drugs, the dosages are not adjusted properly. In the CRF stage IV, out of 65/331 administered drugs, about 37/65 (56.9%) were dosed appropriately and in 28/65 (43.1%) of drugs, medication doses have not been appropriately adjusted. While in patients in CRF pre-dialysis stage V, there were administered about 162/331 of medicines, where 59/162 (36.4%) of the medication was subject to anappropriate dose adjustment and in 103/162 (63.6%) of the administered medicines, the medication doses were not appropriately adjusted.

Creatinine data was obtained from patient medical records and was calculated using the ClCr values using
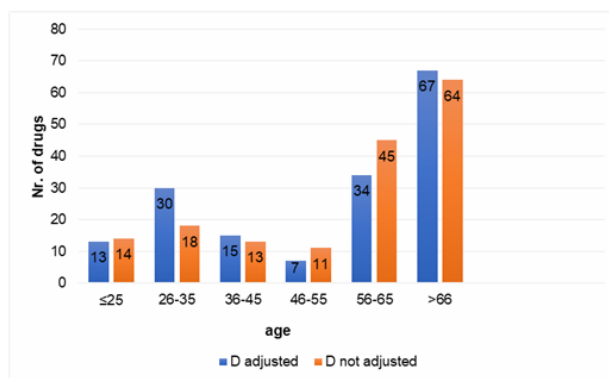

Fig. 5. Distributions of drugs according to age

Cockcroft/Gault formula for each patient. The mean creatinine clearance value (ClCr) was 27.9 ml/min. This confirms once again the severity of the condition in hospitalized patients in this Service and the predominance of the patients in pre-dialysis stage V. It was noticed that the lowest value of ClCr (under 30 ml/min) is present among 50 to 70 years old patients. The largest number of drugs was prescribed in age groups >66 years, and in most cases (67 drugs) the dose was adjusted appropriately, while in 64 drugs the dose did not appear to be adjusted, as shown in Figure 5. According to the stage of the disease, we evidenced the highest number of drugs used in the CRF pre-dialysis stage V, but also the highest number of unproper dose recommendation (59 out of 162 drugs unproperly dosed). On the other hand, in CRF stage III and IV predominate drugs whose dose was adjusted in comparison to those that were not adjusted (Figure 6).
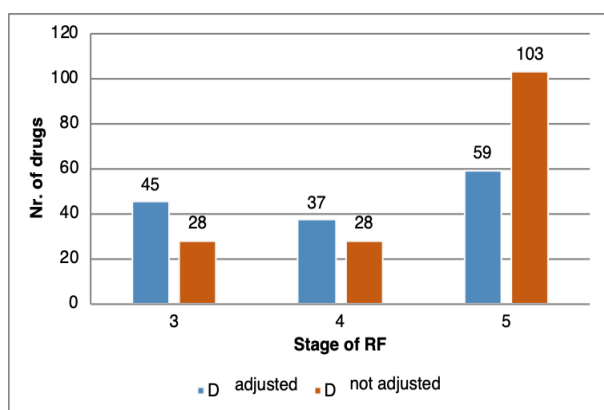

Fig. 6. Distributions of drugs according to renal failure stage

Overall, 18.1% of patients have a prescription for any relatively contraindicated drug like acarbose, chlorpropamide, nitrofurantoin or any non-steroid anti-inflammatory drug (NSAID), aminoglycosides, prescribed from family doctor. Ibuprofen and naproxen are the most commonly used NSAID, while from aminoglycosides gentamycin is the most frequent used drug. The last drug classes are the causes of ARF. From patients complicated with ARF only two of them required dialysis.

This fact need to be evaluated and to reinforce further continuous professional education for family doctor.

Discussion

This study can be considered representative of the Albanian population as it includes patients from all over Albania in the University Hospital in Tirana. The prevalence of RF was higher in males compared to females, namely 40.6% of patients were females and 59.4% males. This datades not accord with other similar studies indicating that women's prevalence is higher [5-13]. Meanwhile, 6.1% of British population, from the age 16 suffer from RF, from this percentage, namely 1 in 5 males and 1 in 4 females [8]. Also, the largest percentage is represented by the elderly population, over 65 years

of age, with predominance of CRF stage III-IV [8,9]. Renal insufficiency is becoming a global problem, and this is due to the growth of diseases such as hypertension, type 2 diabetes mellitus and obesity considered to be its main causes [14,15].

Several studies focused on renal disease conclude that in the last 20 years, the number of people with RF is growing dramatically. Our study has performed an assessment of dosing regimens in patients diagnosed with RF. In this way, it identified the percentage of administered medications at the right dose in RF patients. Our study points to the fact that dose adjustments were necessary in 56.2% of the prescribed drugs, based on the value of ClCr. While 43.8% of the administered drugs in these patients were not considered as dose-necessary adjustment. This may be the influence of prescribed drugs that do not need dose adjustment (excretion in the extrarenal pathway), nephrotoxic drugs are avoided, and/or prescription of drugs with a wide therapeutic index (safe drugs) [16]. In our study, only 11 out of 74 patients (14.9%), were correctly adjusted for drug doses. While in 10/74 (13.5%) patients none of the medicines was adequately regulated. In most patients, 53/74 (71.6%), only a part of the prescribed drugs had an appropriate dosing regimen.

In a study conducted in Spain by Paula Arrabal-Duran *et al*. 13 in 2014, it turned out that it was necessary to apply a regulated dosage system to the 221 prescribed drugs. In 65.6% of cases it was recommended a dose reduction, while in the 26.7% the dosing interval was prolonged and at 7.2% the use of the drug was avoided. Antimicrobials comprised the category of drugs that had the highest dose modification [17] and the dose of the drug that was mostly modified was levofloxacin. On the other hand, even in the study conducted in our country, it turned out that the levofloxacin analogue drug, ciprofloxacin was the drug more precisely dosed in all administered cases. In a study conducted by Baum S *et al*. [17], Institute of Clinical Pharmacology, Germany, in 2010 showed that in 55/85 patients, on average one of the prescribed drugs was not regulated by protocol. Out of the 220, which was the total number of drugs prescribed, 46.0% of the medication was needed to adjust the dose. Henok Getachew *et al*. [18] showed in their study that only a limited number of patients had a correct dosing system. Thus in 15/54 (28%) patients the dose of drugs was adequately adjusted, in 22/54 (41%) patients only in some drugs the dose was adjusted, while in 17/54 (31%) did not result in the application of an appropriate dosing regimen [18]. Markota NP *et al*. [19] in their study showed that 161 out of 712 patients altogether had 874 drugs out of which 171 (19.6%) of the prescriptions were found to need dose adjustment. From where in 81/171 (47.4) cases dose adjustment was done in accordance with protocols and in 90/171 (52.6%) this was not realized [19]. In another study in the Netherlands by Van Dijk EA *et al*.

[20] involving 647 patients under study, 237 (36.6%) of them needed dose adjustment. The total number of prescribed drugs was 1718 out of which 411 of them (23.9%) was necessary to adjust the dose. The drugs were correctly dosed at 242/411 (58.9%) of the prescriptions and in 169/411 (41.1%) doses were not adjusted.

Above mentioned studies and other similar ones in the literature indicate that much work is still needed to achieve appropriate dose regimens in most RF patients.

Calculation of the ClCr not only enables an assessment of the patient's condition but creates a positive impact, as it allows medical personnel to prescribe more safe medicines for patients. The median of the medicines prescribed for the patient in our study resulted in 7 medications per patient and in 83.7% of patients it resulted in 5 drugs. The reason for the administration of the drugs was renal and non-renal or only renal, with 77% of the renal and non-renal followed by 23% of renal failure.

This situation is related to the fact that patients with RF have other accompanying diseases such as HTA, secondary anemia, dyslipidemia, diabetes, which aggravate the patient's condition as a whole.

As a consequence, the number of drugs used by the patient increases and the reason for their use is not only renal [6] In many cases, drugs prescribed in the nephrology unit do not need dosing regimen modifications, in particular antibiotics such as ceftriaxone, cefuroxime. Also, there were prescribed drugs metabolized and excreted in a large percentage by hepatic pathways and less by renal pathways. The drug administered at a high frequency was ranitidine, and mainly the dose was kept unchanged despite creatinine clearance and RF Stage values. In an analogue study conducted by Henok Getache *et al*. regarding dosage regimens it was found that cimetidine, the ranitidine analogue, was administered at a high frequency and the dose of which was also not adjusted according to ClCr. It was also noted that V-RF stage predominated, with 47% involving mainly dialysis patients, kidney transplant patients, and patients with severe V-stage [18]. This may be for a variety of factors such as late diagnosis of the disease, use of nephrotoxic medications for long periods of time, late referral to nephrologists, use of medicines for the treatment of accompanying diseases, and the genetic factor plays a role as well. Over the years these diseases reduce renal function by precluding renal failure. Also, in our study it was found that 78.6% of patients hospitalized in the nephrology unit at the stated period had HTA accompanying disease and 20% diabetes. Promoting health and early screening of these diseases can reduce the incidence of RF [14].

The latest data conclude the importance of cooperation between healthcare providers for a successful metabolic therapy in patients with renal failure. The steady increase in the list of drugs makes it difficult for the medical staff to stay informed. In this way, clinical pharmacists who have the proper knowledge about pharmacokinetics, pharmacodynamics and drug action mechanisms can be helpful [21-23].

Our study presents some limitations. The number of patients analyzed and the period of study was limited. In this study is used the Cockcroft / Gault formula for the Calculation of ClCr. It should be noted that the Calculation of ClCr value, which is used as an indicator of how the dosage regimens need to be adjusted, is achieved using the average weight in both females (60 kg) and males (70 kg). Consequently, the values of ClCr may have deficiencies, which are then reflected in the dosage regimens and automatically in the number of medications adjusted under this regime. Also, doctors who prescribe drugs may have used different guidelines from ours. When the clearance values are below 10mL, the doses of the drugs are difficult to adapt, since there is a risk of undergoing ineffective therapeutic concentration. But on the other hand, there is a risk of not reducing the dose depending on the creatinine clearance values, the drug accumulates in the body and causes toxic effects.

This study did not take into account patient compliance that could increase drug complications. Previous studies have evidenced a considerable level of inappropriate drug use by Albanian patients [24,25], which should be further explored and taken into consideration while interpreting the data.

The distribution drug system in the hospitals is often the reason for the prescription of certain drugs. The choice is therefore made upon the availability of the drugs in the hospital. This may be also the cause for the prescription of ranitidine and not of other similar drugs.

Conclusion

The results of this study show that drug therapy in renal failure in Albania is analogous to other countries. Prescription of drugs in this category of patients was only partially performed according to the rules and protocols of the field. Among the major causes that complicate the regulation of dosage regimes is the presence of a large number of medications, which is due to the age of patients developing the disease and the presence of other diseases. One way to improve dosage regimens would be to reduce the number of medications to the possible minimum and to prescribe extrarenal excretion drugs. Collaboration between the medical doctor and the pharmacist is essential to achieve safe, effective medication therapy with as few side effects as possible for the patient.

Conflict of interest statement. None declared.

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