K. Shailaja et al /J. Pharm. Sci. & Res. Vol. 11(9), 2019, 3153-3159

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

A Prospective Study on Assessment of Therapeutic Management and Clinical Outcomes in Renal Impaired Patients

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Abstract

Aim: To assess the therapeutic management and clinical outcomes in renal impairment patients.

Methods: A prospective cross-sectional study was carried out in which all patients with creatinine clearance ≤59 ml/min were included. Data regarding serum creatinine level, age, sex and prescribed drugs and their dosage was collected from the patient medication records. The estimated creatinine clearance was calculated using the Cockcroft- Gault (CG) equation. Guideline for Drug prescribing in renal failure provided by the American College of Physicians was used as the standard for dose adjustment.

Results: A total of 112 patients were included in the final analysis as the renal impairment group. Males (72%) were more commonly affected and the highest age group was found to be 61-70 years consisting of 29 (26%) patients. Dose adjustment were required in 119 prescription entries. Out of which, 87 drugs were appropriately adjusted and 32 drugs were not appropriately adjusted. Inappropriate dose adjustment caused an increase in the serum creatinine levels in 81% patients. The highest percentage of the clinical outcome was shown in 49% patients on dialysis.

Conclusion: From the results it can be concluded that appropriate dose adjustment according to the guidelines and individualization of doses in renal impairment patient is required. The present study aptly signifies that it is important to strictly adhere the treatment guidelines and to consider pharmacokinetic variability of the patients for management of disease and effective therapeutic outcomes.

Key words: CKD, dose adjustment, pharmaceutical care, renal impairment

INTRODUCTION

Kidney is the major organ for maintaining homeostasis of fluid and electrolytes and, in particular, plays an important role in the disposition of many drugs. Chronic kidney disease (CKD) is divided into five stages [1]. It is important to know whether a patient is suffering from renal insufficiency (CKD stages 2 through 5) and, if so, at what stage, because nearly half of all drugs or their metabolites are excreted by the kidneys, and 30% of all adverse effects of medication have a renal cause or a renal effect [2]. Drug therapy adjustment according to renal function is therefore of major importance to improve drug therapy management (DTM). The glomerular filtration rate (GFR) is widely accepted as the preferred index of the kidney function. Inappropriate dosing in patients with kidney disease can cause toxicity or ineffective therapy [3]. In particular, older patients are at a higher risk of developing advanced disease and related adverse events caused by age related decline in renal function and the use of multiple medications to treat co-morbid conditions [4]. Drug accumulation and toxicity can develop rapidly if dosages are not adjusted in patients with impaired renal function. Drug dosing in renal insufficiency needs to be individualized whenever possible to optimize therapeutic outcomes and to minimize toxicity. The two major approaches are either to lengthen the interval between doses or to reduce the dose. Occasionally both interval and dose adjustments are needed. Therefore, the patients with renal dysfunction must be closely monitored for the drugs that require modifications of dosages or frequencies to prevent adverse effects [5]. The high prevalence of renal failure and the large number of drugs with renal elimination or potential nephrotoxicity suggest that physicians should consider renal function when prescribing [6,7,8].

Decreased kidney function affects every organ in the body and the pharmacokinetics parameters such as drug bioavailability, protein binding, biotransformation, volume of distribution, and renal excretion of many medications prescribed for renal impairment patients are significantly altered which requires dosage adjustment. To avoid toxicity by the drugs in these patients, dose adjustment based on the estimated serum creatinine is essential. These beliefs have been assimilated into drug-dosing guidelines for many decades and now it's available in the form of text books, journal articles, and electronic formats. More recently, serum creatinine measurement has been used to estimate glomerular filtration rate (eGFR) more consistently, and now it is reported routinely by most clinical laboratories. Combination of widely accepted drug-dosing guidelines for renal impairment and availability of serum creatinine levels before prescribing would facilitate appropriate drug dosing for patients with renal impairment. Long et al [9] reported renal-dosing guideline noncompliance rates ranging from 19% to as high as 67%. The reason behind this is availability of limited data on long term care. Several studies have mentioned that errors in drug dosing and risk of drug toxicity are more common among patients with renal impairment. So the present study was designed to assess the drug dose adjustment among hospitalized renal impairment patients, to assess the assess the effect of inappropriate dose adjustment and to assess the adherence

of standard dosing treatment guidelines while writing the prescription in renal impairment patients.

MATERIALS AND METHODS:

The study was carried out for a period of 6 months from January to July 2018 at the Internal medicine department in a tertiary care, multispecialty hospital. Approval for conducting the study was obtained from the institution. The study was carried out on patients over eighteen years of age, receiving atleast one pharmacological agent, hospitalized for atleast one day and patients who had atleast one estimated creatinine clearance value of 59 ml/min or less. All patients admitted during the study period were enrolled. Among them, 122 patients who met the inclusion criteria were included for the study and 112 patients were followed till the final analysis. Patient chart review was used to collect individual patient data including age, sex, serum creatinine (this was later used to estimate CrCL), blood urea nitrogen, risk factors, co-morbid condition, reason for admission, complications and medications prescribed during hospitalization and medications that need dose adjustment using data abstraction format. The glomerular filtration rate was estimated based on creatinine clearance from serum creatinine (SCr) using the Cockcroft Gault equation as shown below for men and women respectively:

FOR MEN:

$$\text{CrCl (ml/min)} = \frac{[(140)\text{-age}] \times \text{weight (kg)}}{\text{SCr (mg/dl)} \times 72}$$

FOR WOMEN:

$$\text{CrCl (ml/min)} = \frac{[(140\text{-age}) \times \text{weight (kg)}] \times 0.85}{\text{SCr (mg/d))} \times 72}$$

SCr level ≥1.2 mg/dl was used as a cut-off point in the pre-selection. Appropriateness of drug therapy was determined by comparing practice with the guideline "Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and Children [10]. Patient were closely monitored to assess the clinical outcomes during their period of hospitalization.

Data were analysed by using social package for the social sciences. Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency and proportion for categorical variables. Data also represented using appropriate bar diagrams and pie diagrams. "Fischer Exact Test" was used to compare the effect of appropriateness of dose adjustment on serum creatinine. P valve <0.05 was considered as statistically significant.

RESULTS & DISCUSSION

The present study identified various risk factors that lead to the development and progression of renal disease. It discusses about the various complications and its therapeutic management. The dose adjustment done for the drugs were evaluated for its appropriateness by comparing with the standard guidelines and the effect of inappropriate dose adjustment on serum creatinine was studied. Males (73%) were most commonly affected than females (27%) shown in Figure 1. Iseki K et al., [11] supported that women seem to be somewhat protected from developing End Stage Renal Disease (ESRD). The cumulative incidence of ESRD remains low during the reproductive ages and begins to rise 10 years later in women than in men. Sex hormones such as estrogen, progesterone and testosterone modulates the renal function. Estrogen receptors are present in mesangial cells, endothelial and vascular smooth muscles of the kidney, estrogen exerts its action through its receptor, by the upregulation of the renal AT_1 receptor expression it exacerbates the renal injury and it modulate the sodium and chloride reabsorption therefore controls blood pressure which is the risk factor for renal impairment.

The mean age of the patients was found to be 62.2±15.5 years in which 4 (4%) were in the age group of 21 to 30 years, 7 (6%) between 31 to 40 years, 10 (95) between 41 to 50 years, 28 (25%) between 51 to 60 years, 29 (26%) between 61 to 70 years, 19 (17%) between 71 to 80 years and 15 (13%) above 80 years shown in Table1.

Highest age group of patients with renal impairment was found to be 61 to 70 years (26%) and 51 to 60 years (25%). Several studies showed that the highest incidence of chronic kidney disease occurred among those aged above 60 years. In recent years there is an increasing prevalence of comorbidities and risk factor such as hypertension, diabetes and obesity that predisposing to high progression of renal impairment in these population [12].

Among life style changes, smoking and alcoholism are known risk factors for the development of renal impairment. In the present study 21% were alcoholic and 29% were smokers. Smoking found to be the risk factor for many diseases recently, percentage of renal impairment in smoking patients found to be increasing.

As cigarette contains many chemicals that are highly toxic to humans creates negative affects endothelial function, oxidative stress, activation of growth factors such as angiotensin-II and endothelin-1, impaired lipoprotein metabolism and insulin resistance. Nicotine has vasoconstrictive properties, which induces transient rise in blood pressure and decrease of glomerular filtration rate and renal blood flow after exposure which affects the kidney function, so decreased frequency of smoking can also decrease the risk of kidney disease [13]. Apart from smoking and alcohol intake, level of abdominal fat also plays an essential role in chronic kidney disease. In obese patients, compensatory mechanism of hyper filtration that leads to intensified metabolic demands of the increased body weight which leads to increase in intraglomerular pressure that can damage the kidney structure and raise the risk of developing CKD [14]. Other risk factors like hypertension 63% and diabetes 79% also identified which was shown in Figure 2.

Table 2. shows stages of renal impairment in the study population, the percentage of grade 5 classification was found to be 40%, followed by grade 4(31%), grade 3b (21%), grade 3a (5%) and grade 2 (4%). Cockcroft Gault equation was used to calculate eGFR in adults. Similar

studies were carried out by Botev R et al., [15] reported that GFR is now an integral part of the daily clinical practice and is used routinely for evaluation and monitoring of renal function. It is very important for the clinician to know about the formulas to calculate the stages of kidney function which is an integral part in the treatment of renal impairment.

Figure 3. shows complications in the study population, hypertension (63%), diabetes (79%), anemia (83%), volume overload (12%) and electrolyte imbalance (94%). Kidney is the major organ which regulates the blood pressure in the human body. If the kidney function decreases typically blood pressure rises and sustained elevations in blood pressure again hasten the progression of kidney disease. Similar study was conducted by Judd E et al., [16] reported that hypertension is one of the earliest sign of kidney dysfunctions and appropriate management is necessary to prevent the further complications. Tight glycemic control is essential to delay or to prevent the onset of diabetic nephropathy. So it is highly obligatory to monitor the glucose levels regularly at frequent intervals in a particular age groups. Hahr. J A et al [17] in his study also mentioned about diabetes the risk factor of renal impairment. To delay the onset of diabetic complications it is necessary to control the glycemic levels, and it can be a challenging task for the physician in selection of safer drugs. In addition, individualization of doses is also required for glycemic control.

Anemia is an another hallmark of progressive CKD, it is mainly due to absolute and relative decrease in erythropoietin production by the kidneys. Out of 112 patients, 106 patients were with anemia and were treated by multivitamin 14%, iron supplements 32%, erythropoietin 28% and folic acid supplements 26% shown in figure 4. The study conducted by Bonomini et al., [18] showed that normocytic normochromic anemia is the common complication in CKD and is associated with many adverse clinical consequences. In Tanaka S et al., [19] study, iron deficiency anemia is more common cause of hypo responsiveness to erythropoiesis stimulating agents (ESA). He also reported that with iron supplementation, ESA dose can be decreased, resulting in lower treatment costs and possibly lower risk for cardiovascular diseases.

Volume overload is a vital factor associated with end organ damage, prolonged hospital stay, morbidity and mortality. Perhaps it is one of the most risk factor for mortality in patients suffering from chronic kidney disease and end stage renal disease. In dialysis patients, volume overload is the most common cause of hypertension and may contribute to poor cardiovascular outcomes, hydration status and increased mortality. Controlling volume overload is the important and essential factor to manage blood pressure without the use of anti-hypertensive drugs in patients undergoing hemodialysis also it could help to maintain overall health of these patients [20]. In this study 12% were experienced volume overload of whom, 6 patients were managed by administration of furosemide, 2 patients with combination of furosemide and metolazone and 5 patients with dialysis shown in figure 5. The study by Del Granado RC et al., [21] reported that fluid overload in critically ill patients leads to several complications like pulmonary edema and cardiac failure. Loop diuretics 5% are frequently used as an initial therapy.

As kidney plays a central role in regulation of electrolytes, in CKD and ESRD electrolyte imbalance occurs and leads to hyperkalemia, metabolic acidosis and hyperphosphatemia which in turn leads to serious complications like muscle wasting, demineralization, vascular calcification and mortality. Renal replacement therapy and dialysis is most commonly used treatment modalities. The present study identified 25% hypokalemia, 28% hyperkalemia, 9% patients had hyponatremia, 9% hyperuricemia. 7% hyperphosphatemia, and 18% hypocalcemia

Figure 6. Electrolyte imbalance in CKD is found to be life threatening, so treatment plays a pivotal role, among 25% patients with hypokalemia (9%) were treated with potassium chloride supplementation, out of 28% with hyperkalemia (18%) of them treated with calcium polystyrene sulphonate. Tolvaptan was used to treat 6% hyponatremia out of 9%, Febuxostat was to treat 4% of patients with hyperuricemia among 11%. Sevelamer is the most commonly used drug to treat 4% hyperphosphatemia out of 7%. Among 18% patients having hypocalcemia only 9% patients were treated with calcium supplementation. Similar studies conducted by various authors revealed that treatment for hypokalemia includes administration of potassium supplements but in rare cases potassium sparing diuretics will be beneficial, and for hyperkalemia, potassium binder is effective

Gopinath S et al., [22] reported that Vaptans have been the best option for the treatment of hypovolemic hyponatremia and patients with syndrome of inappropriate antidiuretic hormone. Vaptans is vasopressin antagonist, they act by increase in plasma sodium concentrations via their augmentation of free-water clearance. Eleftheriadis T et al., [23] reported that 90% cases of hyperuricemia are due to an impaired renal excretion. Hruska AK et al., [24] revealed that hyperphosphatemia in CKD represents a signal that heterotrophic sites of mineralization are being used to compensate for the failure of reservoir function of the skeleton in positive phosphate balance. Patel L et al., [25] reported that patients with CKD stage 3-5 using Sevelamer have lowered all-cause mortality.

Kolamunnage TS et al., [26] reported that hypocalcemia is found in over half of the patients admitted to intensive care unit. Arora P., [27] reported that calcitriol can alleviate hypocalcemia in CKD by increasing intestinal calcium absorption and helps to prevent the secretion of calcium in the kidneys.

As most of the drugs are eliminated by the kidneys, dose adjustment is required in patients with reduced kidney function to avoid the toxicity. The present study was designed in such a way to assess the effect of inappropriate dose adjustment on serum creatinine levels and clinical outcomes in renal impairment patients.

A total of 1538 drugs were studied with an average of 13 drugs per patient, of which 119 drugs required dose adjustment whereas 87 (73%) drugs were appropriately

adjusted and 32 (27%) drugs were not appropriately adjusted. The percentage in our study was found to be higher when compared with another study by Getachew et al., [28] (49%) and Salomon et al., [29] (34%). This is quite encouraging and it is because of the increased awareness of dose adjustment and the well-experienced physicians in our hospital. In developed countries automated system was introduced for reporting the renal function which helps the physician and alert them about the necessities of dose adjustment.

Out of 112 renal impaired patients, 67 (60%) patients required dose adjustment for atleast one prescribed drug while 45 (40%) patients did not need dose adjustment at all shown in Figure 7. This may be because they did not require dose adjustment for any of their drugs or nephrotoxic medication was avoided. The study results were similar to the previous study conducted by Getachew et al., [27] 74% patients required atleast one drug that required dose adjustment. Inappropriate dose adjustment was seen in Cotrimoxazole 90%, Meropenem 71%, Piptaz 70%, Imipenem 67%, Ranitidine 57% and Bisoprolol 57%.

Most of the drugs that required dose adjustment were antibiotics 47% of which Meropenem 18% was frequently used and ranked the highest among antibiotics being recommended for dose adjustment followed by Cotrimoxazole and Piptaz 8%. Apart from antibiotics, ranitidine 18%, metformin 8% and bisoprolol 6% were also the highest among the drugs recommended for dose adjustment shown in figure 8. The results were compared with the previous study results and found that antibiotics required dose adjustment in highest percentage [30,31].

Many physicians prefer to use broad spectrum antibiotics specifically in primary care as there is no immediate access to the laboratory data and it is very limited, which may lead to further deterioration of renal function in patients already with renal impairment. Antibiotic resistance is more common and can be predicted if it is appropriately used in patients, so physician should keep in mind and very careful before prescribing.

Figure 9: shows the dose adjustment of prescription entries by stage of renal impairment, in stage- 3, dose adjustment was done appropriately for 23 drugs whereas for 3 drugs it was inappropriate. In stage-4, 49 drugs were appropriately adjusted their dose and 15 drugs were inappropriate. In stage-5, for 15 drugs the dose was adjusted appropriate and for 14 drugs it is inappropriate. Inappropriate dosing in patients with chronic kidney disease can cause toxicity or treatment failure. The reason behind this may be due to undiagnosed renal function before prescription and lack of knowledge about all the drugs that require dose adjustment especially in kidney failure patients. So it is obligatory to carry out the renal function test even for patients with known renal impairment before writing prescription and health care professionals who involved in providing better health care to the patients should update their knowledge by attending regular seminars and conferences.

Among 87 drugs which were appropriately prescribed, 52 (60%) drugs found to decrease or maintained serum creatinine and 35 (40%) drugs found to increase serum creatinine levels. Among 32 drugs which were inappropriately prescribed, 26 (81%) drugs caused an increase in serum creatinine levels while 6 (19%) drugs found to decrease or maintained serum creatinine levels. Our study showed that appropriate dose adjustment was maintained and decreased creatinine levels by 60% whereas inappropriate dose adjustment increased the serum creatinine levels by 81% in most patients which was shown in Table 3.

Fischer Exact test was used to compare the effect of appropriate use of drugs on creatinine levels, a significant difference ($P<0.0001$) was observed between appropriate and inappropriate dose adjustment of drugs. The relative risk was found to be 3.225 (%CI 1.664 to 6.916). Thus our study revealed an associated risk of renal toxicity in patients receiving inappropriate dose adjustment.

Clinical outcomes of the patients were measured in terms of 23% length of hospital stay, 15% required intensive care, 11% readmitted, 49% underwent dialysis and 19% had renal transplant shown in table 4. Need for dialysis and intensive care and transplantation indicates the poor prognosis of the patients. The study clearly signifies that though the patient is treated with drugs, there is no much difference in the clinical outcomes. So we have to consider patient related outcomes, before treating the patients, assessment of pharmacokinetic parameters individually is essential for better therapeutic outcomes.

Table 1: Age wise distribution of patients (total no of patients =112)

Age (in yrs.)	No. of Patients
21-30	4 (4%)
31-40	7 (6%)
41-50	10 (9%)
51-60	28 (25%)
61-70	29 (26%)
71-80	19 (17%)
>80	15 (13%)

Table 2: Stage wise categorization of patients (total no of patients =112)

Stages	Percentage
Stage 2	4 (4%)
Stage 3a	6 (5%)
Stage 3b	23 (21%)
Stage 4	35 (31%)
Stage 5	44 (39%)

Figure 1. Shows the gender distribution in study population, male population is more prone for renal impairment compared to female.

Figure 2. shows various risk factors associated with renal impairment, 21% alcoholic, 29% smokers, 7% Obesity, 63% Hypertension and 79% Diabetes Mellitus. The highest percentage of risk associated with renal impairment is found to be Hypertension and Diabetes Mellitus.

Table 3: Effect of dose adjustment on serum creatinine levels (N=119 Number of drugs that requires dose adjustment)

Dose adjustment	Maintained/ Decreased serum creatinine	Increased serum creatinine
Appropriate (n=87)	52 (60%)	35 (40%)
Inappropriate (n=32)	6 (19%)	26 (81%)
Fischer Exact Test	P value <0.0001	Statistically significant

Table 4. Clinical outcomes in renal impaired patients (total no of patients =112)

Outcomes	Percentage
Length of hospital stay	26(23%)
Intensive care	17(15%)
Readmission	12(11%)
Dialysis	55(49%)
Transplant	21(19%)

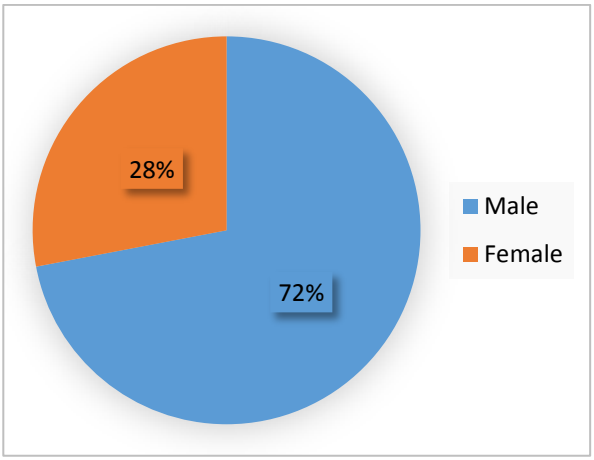

Figure 1: Gender distribution of patients (total no of patients =112)

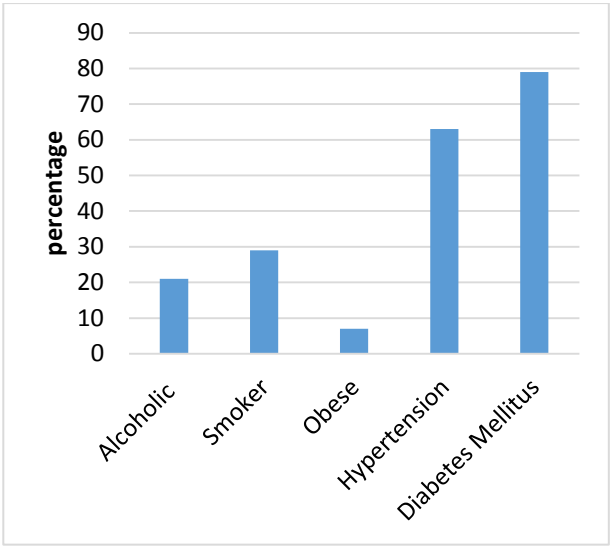

Figure 2. Risk factors associated with renal impairment (total no of patients =112)

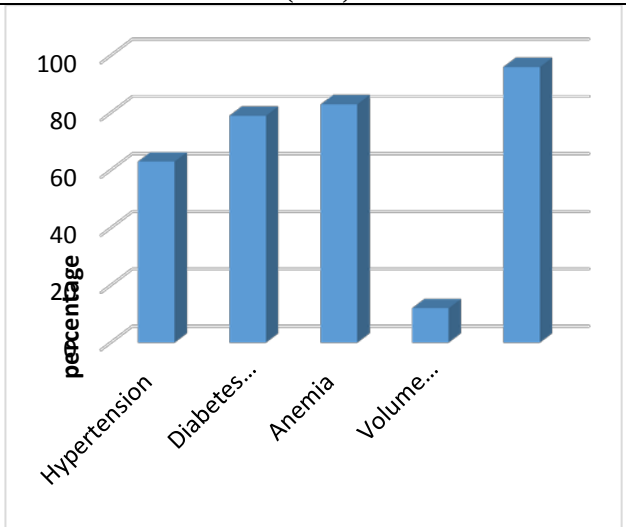

Figure 3. Complications associated with renal impairment (total no of patients =112)

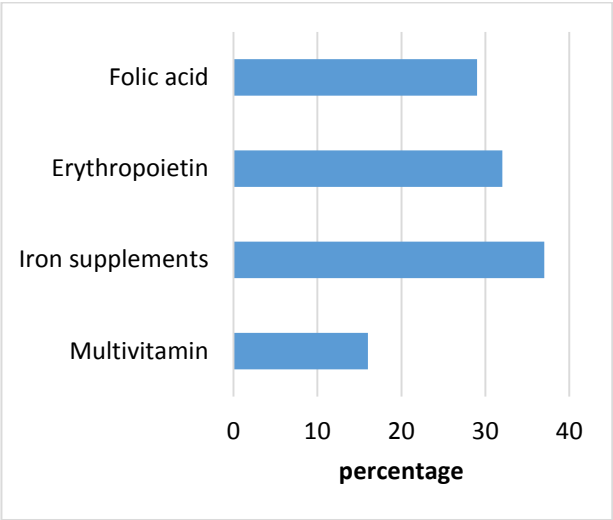

Figure 4. Management of anemia (n= 93)

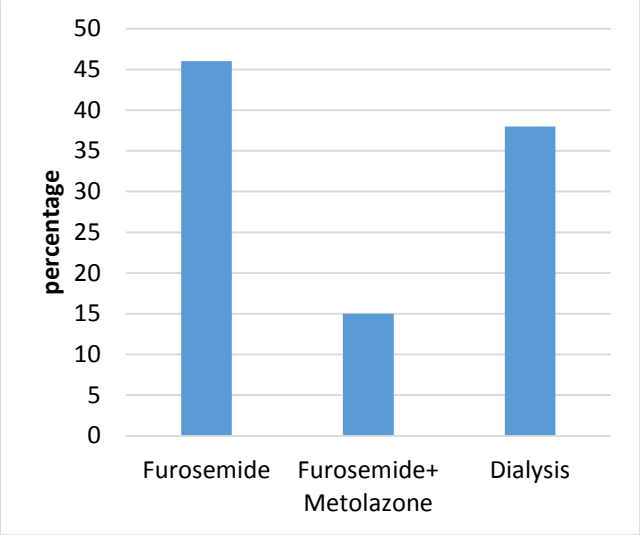

Figure 5. Management of volume overload (n=13)

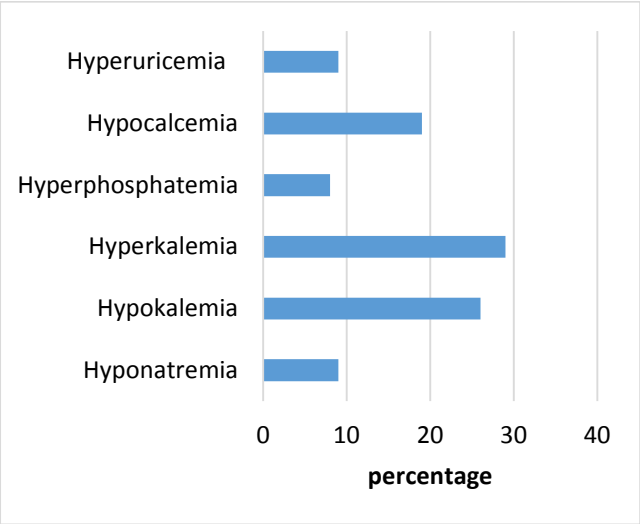

Figure 6. Types of electrolyte imbalance (n=107)

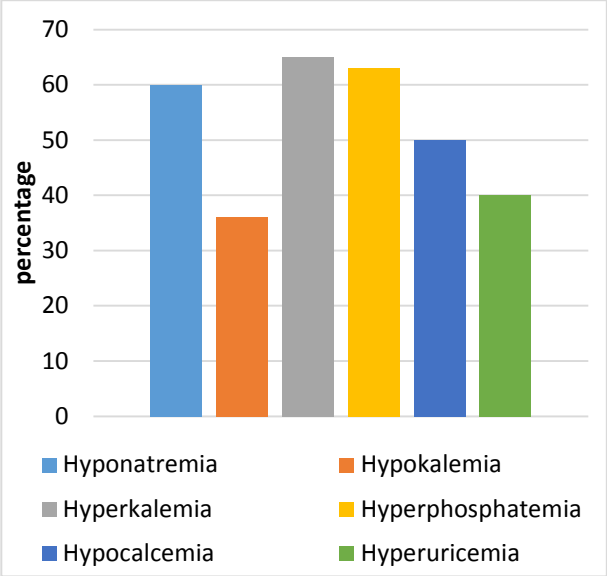

Figure 7. Management of electrolyte imbalance (n=107)

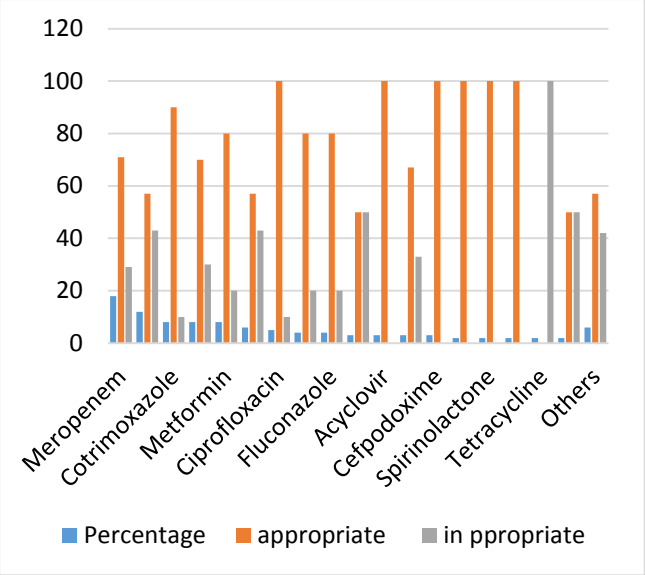

Figure:8 Categorization of Dose adjustments by type of medications

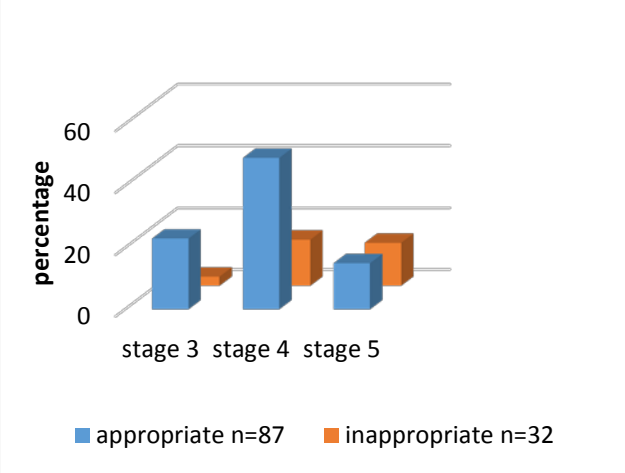

Figure:9 Dose adjustment of prescription entries by stage of renal impairment (no of drugs =119)

Figure 3. Illustrates that renal impairment patients with 94% Electrolyte imbalance, 83% Anemia, 79% Diabetes Mellitus showing the higher percentage followed by Hypertension 37% and Volume overload 12%.

Figure 4. Illustrates iron supplements showed a higher percentage 37%, followed by erythropoietin 32%, folic acid supplementations 29% and multivitamins 16%.

Figure 5. Illustrates that Furosemide 46% was found to be mostly used drugs among diuretics and also it is used as initial therapy in the treatment of volume overload.

Figure 6. Revealed that hypokalemia 28% showed a highest percentage among the electrolyte imbalance followed by hyperkalemia 25%, hypocalcemia 17%, hyperuricemia and hyponatremia 9% and hyperphosphatemia 7%.

Figure 7. Illustrates that patient with hyperkalemia managed with Potassium binder in 17% patients showed a higher percentage, followed by hypokalemia with potassium chloride 9%, hypocalcemia with calcium

supplements 9%, hyponatremia with Tolvaptan 5%, hyperphosphatemia with Sevelamer 4% and hyperuricemia with febuxostat 4%.

The current study shows that most of the drugs that dose adjustments were antibiotics (47%). Meropenem (17.6%) were frequently given and ranked highest among antibiotics being recommended for dose adjustments followed by Cotrimoxazole and Piptaz (8.4%). Besides antibiotics, Ranitidine (12%) and metformin (8%) and bisoprolol (6%) were also highest among the drugs recommended for renal dose adjustment.

Appropriate dose adjustment was done mostly in stage 4 patients and inappropriate dose adjustment was observed mostly in stage 5 patient.

CONCLUSION:

The results concluded that individualization of doses was not calculated appropriately according to the guidelines in renal impairment patient. The present study aptly signifies that it is important to strictly adhere the treatment guidelines and to consider pharmacokinetic variability of the patients for management of disease and effective therapeutic outcomes. Inappropriate dosing of drugs leads to increase in serum creatinine levels resulting in potential nephrotoxicity. Appropriate dosing of drugs is necessary in renal impairment patients to prevent such toxicities by the drugs since most of the drugs are eliminated by the kidney. Dose adjustment for patients with multiple complications is a challenging task which involves the pharmacokinetic parameters and proper utilization of treatment guidelines for effective clinical outcomes. The study also illustrates the prescribing trends of physicians in managing the co-morbidities and complications of the patients. It provides an outline about the management strategies and will be influential in healthcare decision making. Development of renal dosing guidelines in hospitals for renal impairment patients can improve the prescribing pattern and active participation of health care professionals in Continuing Educational Programs will be useful to avoid the unwanted toxicities by the drugs and helps to provide safe, effective and therapeutic outcomes.

ACKNOWLEDGEMENTS:

This research was supported by Fortis Malar Hospital, Chennai. We thank Dr. Ananath Mohan Raj, Medical Superintendent, Dr. C.M. Thigarajan, Dr. D. Divakar, Dr. Srinivas Prasad, Dr. Prince and Mr. Shankar, clinical pharmacist, for their valuable suggestions and co-operation throughout the study period. We would like to thank Dr. Grace Rathnam, C.L. Baid Metha College of Pharmacy, for her benevolent and ever helping arms in providing us all the facilities in carrying out our research.

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