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RENAL DOSAGE ADJUSTMENT IN DIABETIC PATIENTS IN A TERTIARY CARE TEACHING HOSPITAL

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ABSTRACT

Introduction: Diabetes mellitus is a group of metabolic disorders of fat, carbohydrate, and protein metabolism that results from defects in insulin secretion, insulin action (sensitivity), or both. It's hallmark clinical characteristics are symptomatic glucose intolerance resulting in hyperglycemia and alterations in lipid and protein metabolism. DM now ranks as the primary cause of End-Stage Kidney Disease (ESKD) requiring chronic renal replacement therapy. Decreased GFR and albuminuria are indicators of major health outcomes of this condition including End-Stage Renal Disease (ESRD) and death. Renal dysfunction may lead to accumulation of drugs and their metabolites. It may lead to toxicity of drugs. Therefore many drugs need adjustment can optimize therapeutic efficacy and minimize toxicity of drug. **Objective:** The primary objective of this study is to assess the renal dosage adjustment in diabetic patients. The secondary objective is to formulate dosage recommendation and to provide education and information regarding the disease and lifestyle modification. **Materials and Methods:** A prospective observational study was conducted on the renal dosage adjustment in diabetic patients in a tertiary care teaching hospital for a period of 6 months. Ethical clearance was obtained from the Institutional Ethical Committee. The study was conducted on 100 patients with Diabetes Mellitus. All inpatients diagnosed with diabetes irrespective of age and gender were included in the study. Patients who are not willing to participate in the study, patients with insufficient data in their records, Pregnant and pediatric patients, Comatose patients were excluded in the study. Prescribed dosage of drug was compared with dosage recommended by guidelines to assess appropriateness of dose in renal dysfunction. GFR was calculated by Cockcroft Gault equation. During ward rounds, cases were collected, and

collected data were assessed and analyzed using Micromedex. **Results:** Out of 100 patients, 67 were males, and 33 were females, and majority of patients belonged to the age group between 51to 60 years. Out of 652 drugs prescribed in renal impaired patients, 60 drugs required dosage adjustment. The dosage recommendation in renal impairment was formulated based on CrCl using Micromedex software. **Conclusion:** The study effectively reported that the severity of renal impairment was measured using Cockcroft Gault and drug dosage adjustment was done using Micromedex software. 60 drugs required dosage adjustment in patients with renal impairment. We conclude that, in patients with renal impairment, the medication should be individualized depending on the need and severity of renal impairment.

KEYWORDS: Renal Impairment, Diabetes Mellitus, Cockcroft Gault, Creatinine clearance, Dosage adjustment.

INTRODUCTION

Diabetic kidney disease (DKD) is a thoughtful complication that take place in 20% to 40% of all diabetics. In the Western world, diabetic kidney disease is the primary single cause of end-stage kidney disease (ESKD). Both type 1 and type 2 diabetes can lead to nephropathy, but in type 2 diabetes, a smaller proportion of patients progress to ESKD. Because of higher prevalence of type 2 diabetes, these patients represent more than half of diabeties on he-modialysis.[1] The incidence of DKD as a cause of ESKD is increasing each year. For clinical care and epidemiological studies, DKD is characterized by raised urine albumin excretion or reduced glomerular filtration rate (GFR) or both.[2]

There are guidelines to facilitate detection and appropriate management of patients with chronic kidney disease (CKD). The Kidney Disease:Improving Global Outcomes (KDIGO) 2012 clinical practice guideline for the evaluation and management of CKD has recently updated the original 2002 version with enhanced classification of CKD. This includes adding the cause and categories of albuminuria besides glomerular filtration rate (GFR) in the assessment, and refining GFR category 3 into 3a and 3b.[3]

Inappropriate dosing in patients with chronic kidney disease can cause toxicity or ineffective therapy. 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 comorbid conditions.[4] Chronic kidney disease can affect glomerular

bloodflow and filtration, tubular secretion and reabsorption and renal bioactivation and metabolism. Drug absorption, bioavailability, protein binding, distribution volume and non-renal clearance (metabolism) also can be altered in these patients. Physicians careful attention must be taken when considering drug therapies with active or toxic metabolites that can accumulate and contribute to exaggerated pharmacologic effects or adverse drug reactions in patients with chronic kidney disease.[5]

The guidelines provided by the National Kidney Foundation (NKF) for the evaluation, classification and stratification of CKD in the Kidney Disease Outcomes Quality Initiative (K/DOQI) define the following as diagnostic criteria for CKD: a eGFR value below 60 ml/min/1.73 m2 in a time period equal or superior to three months or the presence of renal lesion with or without reduced GFR in a time period equal or superior to three months.[6] The CKD staging system developed by the Kidney Disease Outcomes Quality Initiative (KDOQI) of the National Kidney Foundation (NKF) uses estimated glomerular filtration rates (eGFRs) to facilitate early identification and stage-specific diabetes treatment and dosing adjustment.[4] Under this system, KDOQI recommended avoiding glyburide treatment in stages 3–5 of CKD and initiating treatment with other agents, using appropriate dose adjustments, and urges special care with metformin. The Kidney Disease: Improving Global Outcomes (KDIGO) updated CKD staging in 2012, accounting for the presence of albuminuria, and sub dividing stage 3 into 3a (eGFR 45–59) and 3b (eGFR 30–44).[2]

The current Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines advocate creatinine-based equations for estimating GFR to identify patients with potential kidney disease and to classify them into different stages on the basis of these results. These stages also include individuals with normal or near-normal GFR. Such stratification requires an accurate and precise measurement of GFR that is inexpensive, reliable and widely available. The most commonly used formula was introduced by Cockcroft and Gault (CG) in 1976 on the basis of observations in predominantly hospitalized male patients. The original purpose of this formula was to calculate creatinine clearance, but it also estimates GFR with acceptable performance.[7]

The clearance of many drugs and their metabolites depends on adequate renal function. Renal clearance is especially important for some drugs where the gap between efficacy and toxicity is narrow. Doses of these drugs need careful adjustment if they are prescribed for patients with impaired renal function. Some drugs also have the potential to cause renal toxicity. This

is particularly likely to occur in patients who already have some degree of renal impairment, although other factors can increase the risk.[8]

Cockcroft-Gault equation for calculating creatinine clearance

Creatinine Clearance ml/min = (140 – age) x weight (kg) x 0.85 (for women)/72 x serum creatinine (mmol/L).[9]

Drug dosage adjustment for patients with acute or chronic kidney disease is an accepted standard of practice. The challenge is how to accurately estimate a patient's kidney function in both acute and chronic kidney disease and determine the influence of renal replacement therapies on drug disposition. Kidney Disease: Improving Global Outcomes (KDIGO) held a conference to investigate these issues and propose recommendations for practitioners, researchers and those involved in the drug development and regulatory areas. The conference attendees discussed the major challenges facing drug dosage adjustment for patients with kidney disease.[10]

In patients with kidney dysfunction, the renal excretion of parent drug and/or its metabolites will be impaired, leading to their excessive accumulation in the body. In addition, the plasma protein binding of drugs may be significantly reduced, which in turn could influence the pharmacokinetic processes of distribution and elimination. The activity of several drug-metabolizing enzymes and drug transporters has been shown to be impaired in chronic renal failure. In patients with end-stage renal disease, dialysis techniques such as hemodialysis and continuous ambulatory peritoneal dialysis may remove drugs from the body, necessitating dosage adjustment. Inappropriate dosing in patients with renal dysfunction can cause toxicity or ineffective therapy. Therefore the normal dosage regimen of a drug may have to be adjusted in a patient with renal dysfunction.[11]

Dosage adjustment is based on the remaining kidney function, most often estimated on the basis of the patient's glomerular filtration rate (GFR) estimated by the Cockcroft–Gault formula. Net renal excretion of drug is a combination of three processes: glomerular filtration, tubular secretion and tubular reabsorption.[20] The two principal organs responsible for the elimination of drugs and their metabolites from the body are the liver and the kidney. In many cases, drugs are rather lipid soluble and therefore cannot efficiently be removed from the blood circulation by renal excretory mechanisms but must first undergo biotransformation to more polar metabolites. The number of drugs that are completely or

almost completely eliminated from the body by renal excretion in unchanged form is rather limited.[11]

In India it accounts 1 out of 10,000 are affected from chronic kidney disease and one lakh new diagnosis are with end stage renal disease annually. Many medications and their metabolites are eliminated through the kidney. Thus, adequate renal function is important to avoid toxicity. Renal impairment may cause medicines to accumulate or cause toxicity, especially if the medicine has a narrow therapeutic index. Before, dose adjustment in renal disease calculation of glomerular filtration rate is needed this reflects the stages of renal disease.[17] The glomerular filtration rate is the best parameter for assessing renal function. The measurement of GFR can be accomplished using many exogenous substances. Urinary clearance of inulin, which is the gold standard, is rarely performed except for research purposes because of the limited availability of the substance and the labor intensity of the procedure and the assay. Clinically, creatinine clearance is widely used to assess renal function.[19] The determination of GFR utilizing an endogenous substance has therefore been based on the urinary clearance of creatinine (CrCl) derived from a 24 hour urine collection. Blood urea nitrogen (BUN) and serum urea are secondary indicators of renal function. As serum urea and BUN may be affected by the patient hydration status and other factors, these parameters are less sensitive indicators of renal function than serum creatinine.[12]

Renal impairment may cause medicines or their metabolites to accumulate. This may result in toxicity, especially if the medicine has a narrow therapeutic index (eg. digoxin, lithium). Potential adverse effects can be prevented by reducing the dose, extending the dose interval, or by prescribing an alternative medicine that is less likely to accumulate.[18] Up to 15% of drug-induced acute renal failure is caused by hypersensitivity reactions that cause renal tubular and interstitial inflammation. Whereas the total daily dose of a medication is based on the overall systemic clearance of the drug, changes to the dosing interval should be made on the basis of relative half-life differences.[13] The metabolism and elimination of certain drugs are altered in situations of renal failure. In such cases, dose adjustment or modification of the dosing frequency is needed.[12]

Nephrotoxicity can be reduced by taking drug-specific precautions. The proper dosing of medications for patients with renal impairment can maximize therapeutic efficacy and minimize toxicity.[14] Proper dosing can also have an economic impact on the health system. Dosage adjustment can result in avoidance of costs associated with drug-related toxicity and

in cost savings in terms of drug costs. There are also a number of commonly used medicines that can impair renal function or cause nephrotoxicity. These include ACEIs, ARBs and NSAIDs. Acute interstitial nephritis is a very rare adverse effect of proton pump inhibitors (PPIs); but the high volume of PPI prescribing means that PPIs are a leading cause of acute interstitial nephritis.[12]

Chronic kidney disease affects renal drug elimination and other pharmacokinetic processes involved in drug disposition (e.g., absorption, drug distribution, non-renal clearance [metabolism]). Drug dosing errors are common in patients with renal impairment and can cause adverse effects and poor outcomes. Dosages of drugs cleared renally should be adjusted according to creatinine clearance or glomerular filtration rate and should be calculated using online or electronic calculators.[3] Recommended methods for maintenance dosing adjustments are dose reductions, lengthening the dosing interval, or both. Physicians should be familiar with commonly used medications that require dosage adjustments. Resources are available to assist in dosing decisions for patients with chronic kidney disease. Loading doses usually do not need to be adjusted in patients with chronic kidney disease. Published guidelines suggest methods for maintenance dosing adjustments: dose reduction, lengthening the dosing interval or both.[15]

Dose reduction involves reducing each dose while maintaining the normal dosing interval. This approach maintains more constant drug concentrations, but it is associated with a higher risk of toxicities if the dosing interval is inadequate to allow for drug elimination.(16) Normal doses are maintained with the extended interval method, but the dosing interval is lengthened to allow time for drug elimination before re-dosing. Lengthening the dosing interval has been associated with a lower risk of toxicities but a higher risk of sub therapeutic drug concentrations, especially toward the end of the dosing interval.[5]

METHODOLOGY

Study Site: A tertiary care teaching hospital SSIMS & RC

Study Duration: The study was conducted for a period of 6 months

Study Design: A prospective observational study

Proposed Sample Size: 100

Achieved Sample Size: 100

Study Criteria: The study was carried out by considering the following inclusion and exclusion criteria.

INCLUSION CRITERIA

- All inpatients diagnosed with diabetes irrespective of age and gender.

Exclusion Criteria

- Patients who are not willing to participate in the study and patients with insufficient data in their records.
- Pregnant and paediatric patients.
- Comatose patients.

Source of Data

The data about patients was collected from the case sheets of all inpatients with diabetes in SSIMS & RC.

Ethical Consideraton

The ethical clearance for the study was obtained from Institutional Ethical Committee, Davangere.

Materials Used

- Patient case sheet
- Data collection form
- Informed consent form
- Patient Information Leaflet
- NKF Kidney Disease Outcome Quality Initiative (K/DOQI) Guideline

Resources Used

- Micromedex

Study Procedure

- **Phase I**: The first step in the study was to design a data collection form. The patient data collection form will be used to collect all the details like name, age, sex, patient complaints, past medical and medication histories, social and family history, co-morbidities, diagnosis, date of admission, date of discharge and drugs prescribed.
- **Phase II**: The second step in the study will be prescription analysis.
- **Phase III:** The collected data was analyzed for the following parameters

1. Demographic details

2. Severity of renal impairment according to the CrCl using Cockcroft & Gault formula.
3. Dosage adjustment
4. Dosage recommendation in renal impairment patients

Method of Collection of Data

1. A prospective observational study will be conducted in the inpatients with renal impairment in SSIMS & RC, DVG.
2. The data required for the study will be collected from the patient case sheets.
3. Inpatients in medicine and emergency wards meeting the inclusion criteria will be enrolled in the study.
4. The demographic details, number of drugs prescribed, dose and frequency both during admission and discharge will be recorded in a properly designed data collection form.

RESULTS

Number of Drugs Requiring Dosage Adjustment In Patients With Renal Impairment

The number of drugs requring dosage adjustment in patients with renal impairmet was 60 (9.2%).

Table 1: Number of drugs requiring dosage adjustment in patients with renal impairment (n=652).

Total Number of Drugs Prescribed In Renal Impaired Patients	Number of Drugs Requiring Dosage Adjustment	Percentage (%)
652	60	9.2

Number of Drugs with Dose Adjusted and Number of Drugs To Be Dose Adjusted In Patients With Renal Impairment

Out of 60 drugs requiring dosage adjustment, the number of drugs with dose adjusted was 18 (30%) and the number of drugs to be dose adjusted was 42 (70%).

Table 2: Number of drugs with dose adjusted and number of drugs to be dose adjusted in patients with renal impairment (n=60).

Number of drugs requiring dosage adjustment	Number of drugs with dose adjusted	Percentage (%)	Number of drugs to be dose adjusted	Percentage (%)
60	18	30	42	70

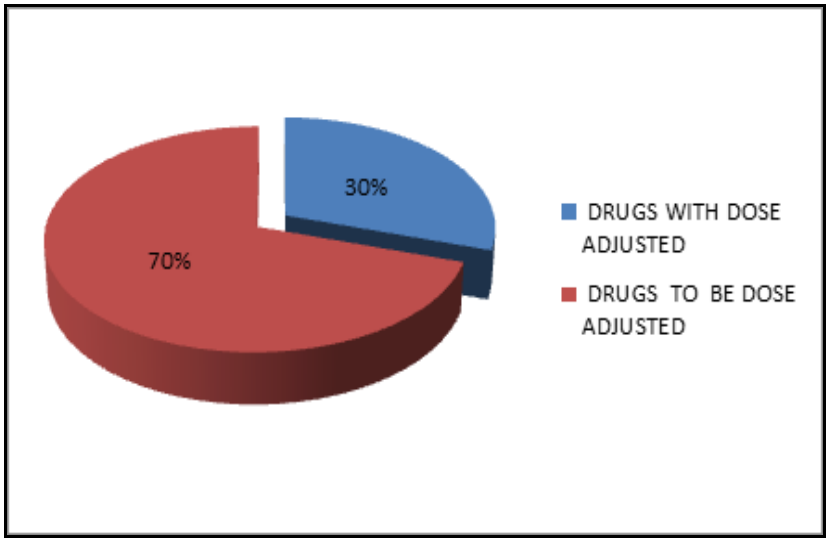

Figure 9.1: Number of drugs with dose adjusted and number of drugs to be dose adjusted in patients with renal impairment.

DOSAGE ADJUSTMENT IN PATIENTS WITH RENAL IMPAIRMENT

The list of drugs and the number of patients requring dosage adjustment in patient with renal impairment based on CrCl are mentioned below;

Table 3: Dosage adjustment in patients with renal impairment.

DRUGS	NUMBER OF PATIENTS	PRESCRIBED DOSE AND FREQUENCY	INFERENCE	RECOMMENDED DOSE
INJ.TAZOBACTAM+PIPERACILLIN	5	4.5mg BID	Overdose	For CrCl<20ml/min, 2.25gm every 8 hours
INJ.TAZOBACTAM+PIPERACILLIN	1	2.25mg QID	Overdose	For CrCl<20ml/min, 2.25gm every 8 hours
TAB.GLIPIZIDE	1	5mg BID	Overdose	Initially 2.5MG OD
TAB.ETHAMBUTOL	2	400mg OD	Under dose	20-25mg/kg 3 times a week
INJ.VANCOMYCIN	1	1gm OD	Overdose	15mg/kg initially in renal impairment
INJ.VANCOMYCIN	1	500mg TID	Overdose	15mg/kg initially in renal impairment
TAB.AMOXICILLIN+CLAVULANATE	1	625mg BID	Overdose	For CrCl<10ml/min, usual dose(625mg/12hrs) every 24hrs.
INJ.CEFUROXIME	2	1.5mg BID	Overdose	For CrCl 10-20ml/min, 750mg every 12hrs

TAB.CEFIXIME	1	200mg BID	Overdose	For CrCl ≤20ml, 200mg orally ODF
TAB.FLUCONAZOLE	1	150mg OD	Overdose	For CrCl<50ml/min, 50% of usual dose(200mg)
TAB.RANITIDINE	1	150mg BID	Overdose	For CrCl<30ml/min 75mg orally BID
TAB.RISPERIDONE	1	2mg OD	Overdose	For CrCl<30ml/min, initial dose is 0.5mg BID
TAB.OFLOXACIN	1	400mg BID	Overdose	For CrCl<20ml/min One half of usual dose (800mg/day) every 24 hours
TAB.OFLOXACIN	1	200mg BID	Under dose	For CrCl 20-50ml/min, 300mg orally BID
INJ.MEROPENEM	2	1gm TID	Overdose	For CrCl<10ml/min, one half of the recommended dose (3gm/day); increase dosing interval to every 24 hours
INJ.MEROPENEM	2	500mg BID	Overdose	For CrCl<10ml/min, one half of the recommended dose (3gm/day); increase dosing interval to every 24 hours
TAB. LEVOFLOXACIN	2	250mg OD	Overdose	For CrCl 10-19ml/min, 250mg every 48 hours
TAB. LEVOFLOXACIN	1	500mg BID	Overdose	For CrCl 10-19ml/min, 250mg every 48 hours
TAB. LEVOCETRIZINE	1	5mg OD	Overdose	For CrCL 10-30ml/min, 2.5mg twice weekly
TAB.GLIMEPIRIDE	1	4mg OD	Overdose	For renal impairment, 1mg OD
TAB.GLIMEPIRIDE	1	1mg BID	Overdose	Initiate at 1mg OD
TAB.GLIMEPIRIDE	1	4mg ½-0-1/2	Overdose	Initiate at 1mg OD
TAB.GLIMEPIRIDE	2	2mg OD	Overdose	Initiate at 1mg OD
TAB.BISOPROLOL	1	1.25mg OD	Under dose	2.5mg/day initially
TAB. ACETAMINOPHEN	1	650mg TID	Under dose	Increase dose interval to every 6 hours
INJ. ACETAMINOPHEN	1	1gm/100ml BID	Under dose	For CrCl, 10-50ml/min, Increase dose interval to every 6 hours
TAB. ROSUVASTATIN	1	20mg OD	Overdose	For CrCl<30ml/min 5-10mg OD
TAB. PREGABALIN	1	100mg BID	Overdose	For CrCl 15-30ml/min, 25-150mg/day
TAB. CEFPODOXIME	1	200mg BID	Overdose	For CrCl <30ml/min, increase dosing interval every 24 hours

TAB.CLONIDINE	1	0.1mg TID	Overdose	Lower initial dose is beneficial
TAB. SPIRONOLACTONE	1	25mg OD	Contraindicated	In Anuria
TAB.METFORMIN	3	500mg BID	Contraindicated	For CrCl <30ml/min
TAB.NITROFURANTOIN	1	100mg BID	Contraindicated	For CrCl <60ml/min
TAB.TORSEMIDE	2	100mg OD	Contraindicated	In Anuria
TAB.TORSEMIDE	4	20mg OD	Contraindicated	In Anuria
TAB.GABAPENTIN	1	100mg 0-0-1/2	Contraindicated	For CrCl <30ml/min
TAB.PERINDOPRIL	1	8mg BID	Contraindicated	For CrCl <30ml/min
TAB.ASPIRIN	1	325mg OD	Contraindicated	For CrCl <10ml/min
TAB.ASPIRIN	1	75mg OD	Contraindicated	For CrCl <10ml/min
TAB.PREGABALIN	3	75mg OD	Contraindicated	For CrCl <30ml/min
TAB.PREGABALIN	1	100mg BID	Contraindicated	For CrCl <30ml/min
CAP.PREGABALIN	1	75mg OD	Contraindicated	For CrCl <30ml/min

Dosage Recommendation In Renal Impaired Patients

The dosage recommendations for drugs requiring dosage adjustment based on CrCl are listed below;

Table 4: Dosage recommendation in renal impaired patients.

Drugs	Category	Dosage Adjustment Based On Creatinine Clearance
TAB. OFLOXACIN	FLUORO-QUINOLONE	• For CrCl 20 to 50 ml/min, usual dose every 24 hours • For CrCl <20ml/min, one half of usual dose every 24 hours
INJ. MEROPENEM	CARBAPENEM	• For CrCl >50ml/min, no dosage adjustment required. • For CrCl 26 to 50ml/min, increase dosing interval to every 12 hours. • For CrCl 10 to 25 ml/min, one half of the recommended dose depending on type of infection, increase dosing interval to every 12 hours. • For CrCl <10ml/min, one half of the recommended dose depending on type of infection, increase dosing interval to every 24 hours • Hemodialysis- An additional dose following hemodialysis session is recommended • Hemofilteration/ hemodiafilteration, critically ill-1gm IV every 12 hours

TAB.AMOXICILLIN+ CLAVULANATE	PENICILLIN+BETA LACTAMASE INHIBITOR	• For CrCl 10 to 30ml/min, usual dose every 12 hours • For CrCl <10ml/min, usual dose every 24hrs. • Extended release tablet and 875mg tablet should not be used in hemodialysis patients or patients with CrCl <30ml/min • Hemodialysis- Usual dose every 24 hours, additional dose both during and after hemodialysis session
TAB.LEVOCETRIZINE	ANTIHISTAMINE	• For CrCl 50 to 80ml/min, 2.5mg daily • For CrCl 30 to 50ml/min, 2.5 mg every other day • For CrCl 10 to 30ml/min, 2.5mg twice weekly (once every 3-4 days) • For CrCl <10ml/min, use is contraindicated • Use is contraindicated in 6 months to 11 years • Geriatric- Use caution with dose selection and start at low end of dosage range • Hemodialysis- Use is contraindicated

AB.PREGABALIN	ANTICONVULSANT	• For CrCl ≥ 60ml/min, no adjustment required • For CrCl 30 to 60ml/min, reduce usual dosage by 50% • For CrCl <30ml/min, use not recommended, patient should receive immediate release formulation • For CrCl ≥60ml/min, no adjustment required • For CrCl 30 to 60 ml/min, 75 to 300mg/day in 2 to 3 divided doses • For CrCl 15-30ml/min, 25 to150mg/day given once daily or in 2 divided doses • For CrCl <15ml/min, 25 to 75mg once daily • Hemodialysis- Use not recommended, patient should receive immediate release formulation
INJ.CEFUROXIME	CEPHALOSPORINS	• For CrCl >20ml/min, usual dose • For CrCl 10 to 20ml/min,750mg every 12hrs • For CrCl <10ml/min, 750mg every 24 hours • In pediatric patients above 3 months of age, adjust dose consistent with adult recommendations • Hemodialysis- A supplemental dose should be given after hemodialysis

AB.PIPERCILLIN+TAZO BACTAM	PENICILLIN+BETA LACTAMASE INHIBITOR	• For CrCl >40ml/min, no dose adjustment is necessary (all indications except nosocomial pneumonia) • For CrCl 20 to 40ml/min, 2.25gm every 6 hours (all indications except nosocomial pneumonia) • For CrCl <20ml/min,2.25gm every 8 hours (all indications except nosocomial pneumonia) • For CrCl >40ml/min, no dose adjustment necessary (nosocomial pneumonia) • For CrCl 20 to 40ml/min, 3.375gm every 6 hours (nosocomial pneumonia) • For CrCl <20ml/min, 2.25gm every 6 hours (nosocomial pneumonia) • Hemodialysis- 2.25gm every 12 hours plus 0.75gm after each dialysis session (all indications except nosocomial pneumonia) • Hemodialysis- 2.25gm every 8 hours plus 0.75gm after each dialysis session. • Continuous ambulatory peritoneal dialysis (all indications except nosocomial pneumonia) 2.25gm every 12 hours • Continuous ambulatory peritoneal dialysis (nosocomial pneumonia)- 2.25gm every 8 hours

INJ.VANCOMYCIN	GLYCOPEPTIDE	• Renal Impairment- 15mg/kg initially and then optimize dose and interval based on serum drug concentrations • Hemodialysis- 1. less than 70kg, 1000mg LD and then 500mg MD infused over last 30 minutes of dialysis 2. 70-10kg, 1250mg LD and then 750mg MD infused over last 60 minutes of dialysis. 3. 100kg, 1500mg LD and then 1000mg MD infused over last 90 minutes of dialysis. • Anephric patient- Initially 15mg/kg of body weight, dosage required to maintain stable concentration is 1.9mg/kg/24 hours • Anuric patient- 1gm every 7 to 1 days
TAB. FLUCONAZOLE	ANTIFUNGAL	• For CrCl >50ml/min, no adjustment. • For CrCl ≤50ml/min, administer 50% of the usual dosage • Hemodialysis- Give initial LD of 50-400mg, follwed by the usual dosage after each hemodialysis session and 50% of usual dose on non-dialysis days if CrCl is ≤50ml/min
TAB. ETHAMBUTOL	ANTI TUBERCULAR	• For CrCl <30ml/min, 20-25mg/kg orally 3 times per week. • Hemodialysis- 20 to 25mg/kg orally 3 times per week after dialysis

TAB. RISPERIDONE	ANTIPSYCHOTICS	• Initial 0.5mg orally BID for one week, then dose may be increased to 1mg BID or 2mg OD in the second week. • For CrCl <30ml/min Initial 0.5mg orally BID, increase dose in increments of not more than 0.5mg BID, with increase to dosages above 1.5mg BID occuring at intervals of at least 1 week.
TAB. ROSUVASTATIN	HMG-CoA REDUCTASE INHIBITORS	• For CrCl <30ml/min/1.73m2, initially 5mg orally OD, maximum 10mg OD
TAB. GLIMEPIRIDE	SULFONYLUREAS	• Renal Impairment- Initiate at 1mg/day • Dialysis- Initiate at 1mg/day
TAB. GLIPIZIDE	SULFONYLUREAS	• Renal impairment- Conservative dosing recommended to avoid hypoglycemia • Renal impairment, extended-release; initial 2.5mg orally OD
TAB.RANITIDINE	HISTAMINE 2 RECEPTOR BLOCKERS	• For CrCl <50ml/min, 150mg orally or 10ml of a 15mg/ml oral solution every 24 hours • For CrCl <30ml/min, 75mg orally BID • For CrCl 1.7gm/dl, 150mg orally OD for 7 days was safely used • For CrCl <50ml/min, 50mg IV every 18 to 24 hours • For CrCl ≤20ml/min, administer one-half the daily IV dose • Hemodialysis- Adjust schedule to administer ranitidine at the end of dialysis • Peritoneal dialysis- Doses of 150mg OD are sufficient • Hemofilteration- Dose supplementation is not required

IXIME	CEPHALOSPORINS	• For CrCl ≥60ml/min, adjustment not necessary • For CrCl 21 to 59ml/min oral suspension, adjust dose to 6.5ml daily of 200mg/5ml concentration or 2.6ml daily of 500mg/5ml concentration. • For CrCl ≤20ml/min, oral suspension, adjust dose to 8.6ml daily of 100mg/5ml concentration or 4.4ml daily of 200mg/5ml concentration or 1.8ml daily of 500mg/5ml concentration. Tablets or chewable tablets 200mg OD • Continuous peritoneal dialysis- Tablets or chewable tablets, 200mg OD • Hemodialysis- Oral suspension, adjust dose to 6.5ml daily of 200mg/5ml concentration or 2.6ml daily of 500mg/5ml concentration • Hemodialysis- Tablets and chewable tablets are not appropriate
TAB.BISOPROLOL	BETA ADRENERGIC RECEPTOR BLOCKER	• For CrCl <40ml/min, initial 2.5mg orally OD • Hemodialysis- Dose replacement is not necessary.
TAB.LEVOFLOXACIN	FLUOROQUINOLONES	• For CrCl ≥50ml/min, no dose adjustment is necessary • For CrCl 20 to 49ml/min, 750mg every 48 hours • For CrCl 10 to19ml/min or hemodialysis, 750mg initially, then 500mg every 48 hours • For CrCl<30ml/min (in patients being treated for TB)- 750 to 1000mg orally /IV 3 times/week • Hemodialysis in patients being treated for TB- 750 to 1000mg orally/IV 3 times/week.

TAB.ACETAMINOPHEN	ANALGESIC	• For CrCl<10ml/min, increase dosing interval to every 8 hours for adults and children • For CrCl ≤30ml/min, a longer dosing interval and a reduced total daily dose may be warranted • For CrCl 10 to 50ml/min, adult increase dosing interval to every 6 hours, pediatric, give usual weight or age-based dose • For CrCl>50ml/min, adult, increase dosing interval to every 4 hours, pediatric, give usual weight or age- based dose • Dialysis- Supplemental doses not required following hemodialysis or peritoneal dialysis
TAB. CEFPODOXIME	CEPHALOSPORINS	• For CrCl<30ml/min, Increase dosing interval to every 24 hours • Hemodialysis- change dose frequency to 3 times a week after hemodialysis.
TAB.CLONIDINE	ALPHA AGONIST HYPOTENSIVE AGENTS	• Renal impairment- Lower initial dose may be beneficial • Geriatric- Consider lower initial doses • Hemodialysis- No dosage supplementation required • Peritoneal dialysis- Initial doses of 0.1mg daily may be appropriate.

Contraindicated Drugs In Patients With Renal Impairment Based ON CrCl

The contraindicated drugs in renal impairment based on CrCl are listed below;

Table 5: Contraindicated drugs in patients with renal impairment based on CrCl.

Drugs	Category	Indication	Inference
TAB.SPIRONOLACTONE	POTASSIUM SPARING DIURETIC	For CrCl <30ml/min	Contraindicated
TAB.METFORMIN	BIGUANIDE	For CrCl<30ml/min	Contraindicated
TAB.NITROFURANTOIN	ANTI BACTERIAL	For CrCl <60ml/min	Contraindicated
TAB.ASPIRIN	NSAID	For CrCl <10ml/min	Contraindicated
TAB.GABAPENTIN	ANTICONVULSANT	For CrCl <30ml/min	Contraindicated
TAB.TORSEMIDE	LOOP DIURETIC	In Anuria	Contraindicated
TAB.PERINDOPRIL	ACE INHIBITOR	For CrCl <30ml/min	Contraindicated
TAB.PREGABALIN	ANTICONVULSANT	For CrCl <30ml/min	Contraindicated

DISCUSSION

Inappropriate dosing in patients with chronic kidney disease can cause toxicity or ineffective therapy. 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 comorbid conditions.[9] Chronic kidney disease can affect glomerular bloodflow and filtration, tubular secretion and reabsorption and renal bioactivation and metabolism. Drug absorption, bioavailability, protein binding, distribution volume and non-renal clearance (metabolism) also can be altered in these patients. Physicians careful attention must be taken when considering drug therapies with active or toxic metabolites that can accumulate and contribute to exaggerated pharmacologic effects or adverse drug reactions in patients with chronic kidney disease.[31]

Details of the patients included in the study

The overall data of 100 patients with diabetes in a tertiary care teaching hospital were collected. The present study monitored the renal dosage adjustment in diabetic patients.

Drugs requiring dosage adjustment in renal impaired patients

In our study, out of 652 drugs prescribed in renal impaired patients, only 60 drugs required dosage adjustment ie, 9.2%. Similarly, in the study conducted by Rathod Mrudangsinh M et al. out of 983 drugs, 175 drugs required dosage adjustment, i.e., 17.80%.[28]

CONCLUSION

The present study was carried out in order to assess the renal dosage adjustment in diabetic patients. The severity of renal impairment was measured using Cockcroft-Gault formula and the drug dosage adjustments were done using Micromedex software. Our study concluded that, the medications prescribed should be monitored for the dosage based on CrCl depending on the need, severity of renal impairment and alternatives available.

We formulated the dosage recommendations in renal impairment based on CrCl using Micromedex software. We successfully designed a patient information leaflet on diabetes mellitus for providing patient education and to improve their quality of living.

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CONFLICT OF INTEREST

There is no conflict of interest between the authors.

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