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A PROSPECTIVE STUDY ON DRUG DOSING EVALUATION AND CONCURRENT FEEDBACK MECHANISM BY THE CLINICAL PHARMACIST TO IMPROVE DRUG SAFETY IN PATIENTS WITH RENAL IMPAIRMENT

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ABSTRACT

Title: A prospective study on drug dosing evaluation and concurrent feedback mechanism by the clinical pharmacist to improve drug safety in patients with renal impairment. **Plan**: To assess the incidence of inappropriate dosing of prescribed drugs, to improve the rate of achieving dosage adjustment of drugs and to optimize the drug therapy in patient with renal dysfunction. **Preface:** Inappropriate dosing in patients with renal dysfunction can cause renal drug accumulation and toxicity. **Method:** Creatinine clearance or estimated glomerular filtration rate of patients with serum creatinine greater than 1.5 mg% was calculated using Cockcroft-Gault equation and Modified Diet in Renal Disease equation respectively. Dose of all prescribed drugs especially potentially nephrotoxic drugs was evaluated using the published drug dosing guidelines and the new dose or dosing interval was recommended based on the patients individual degree or stage of renal impairment. **Outcome:** Thousand one hundred and twelve drugs in 100 patients were evaluated. Among the 1112 evaluated drugs, 115 drugs (10.34%) were renally eliminated and among those 48 (41.73%) required dose adjustments and rest of the 12(10.43%) drugs were either not recommended in kidney disease or contraindicated. Of these, dose of 37 (77.07%) were adjusted at the time of prescribing and 11 (22.91%) were not adjusted. **Conclusion:** Drug dosing evaluation and concurrent feedback mechanism by the pharmacist improved drug safety in patients with renal impairment.

KEYWORDS: Creatinine clearance, glomerular filtration rate, renal impairment, nephrotoxic drugs.

INTRODUCTION

The ability of an organ to perform a task is ultimately related to the structure of the organ. This is so evident in the case of the kidney. Increased mortality and morbidity are two well recognized complication of renal failure. Any degree of renal dysfunction is associated with an increased risk of death, particularly if the patient does not recover his or her baseline renal function at the time of hospital discharge. The kidneys are organs which plays important role in regulating volume and the amount of body fluid, elimination of many drugs and waste products of body metabolic processes. Kidneys are responsible for maintaining the homeostasis of body fluids by the regulation of water balance, electrolyte balance, acid – base balance and excretion of uremic toxins and also production of various hormones such as renin, erythropoietin and activation of Vit.D3. So if the kidney stops working all of these processes get interrupted.[1]

Kidney disease is a common and progressive illness that is becoming a global public health problem. The inability of the kidney to perform these functions adequately is termed as renal failure. Dysregulation of kidney function is classified as Acute Kidney Disease (AKD) and Chronic Kidney Disease(CKD). The type of renal failure is determined by the trend in the variation of serum creatinine values. ARF recently known as Acute Kidney Injury is the sudden reversible interruption of the kidney function characterized by oliguria (decreased urine production, quantified as less than 400 ml per day in adults), body water and body fluids disturbances and electrolyte management. CKD or Chronic Kidney Injury is a progressive irreversible deterioration of renal function that may occur even when the primary insult has been corrected or treated or become inactive.[2]

Chronic kidney disease (CKD)

Chronic kidney disease is defined as the kidney damage or glomerular filtration rate(GFR) <60 ml/min/1.73 m^2 for three months or more, irrespective of the cause. The lack of community-based screening programs has led to patients being detected with CKD at an advanced stage. The prevalence of CKD is estimated at nearly 25 million

people.[3] Long term follow up studies indicate that patients continue to recover renal function upto six months after hospital discharge, had a chance of development of some degree of CKD and need for renal replacement therapy (RRT). Even though the majority of patients will recover normal kidney function, approximately 25% will have CKD and 12.5% will remain dialysis dependent.[3]

STAGES OF RENAL IMPAIRMENT

The working group of National Kidney Foundation [NKF] And Kidney Dialysis Outcomes And Quality Initiative[K/DOQI] has developed a CKD classification system based on presence of structural kidney damage or functional changes in GFR present for a period of three months or more.[3] Thus CKD is categorized into stages 1to 5. The stages of renal function are listed in Table No:1.

Table No. 1: STAGES OF RENAL FUNCTION

STAGES	DESCRIPTION	GFR
1	Signs of mild kidney disease but with normal or better GFR	Greater than 90%
2	Mild kidney disease with reduced GFR	60-89%
3	Moderate chronic renal insuffiency	30-59%
4	Severe chronic renal insuffiency	15-29%
5	End – stage renal failure (include only patients on dialysis)	Less than 15%

Guidelines by the [NKF-K/DOQI] and KDIGO provide information to assist healthcare providers in clinical decision and the design of appropriate therapy to manage complications.

Individualized drug therapy

The presence of a marked reduction in kidney function, whether it in AKD or CKD in any patient, necessitates that the clinician individualize drug therapy to maximize therapeutic outcomes. Individualization of a drug dosage regimen for a patient with reduced kidney function is based on the pharmacodynamics /pharmacokinetic characteristics of the drug and the patients degree of residual renal function.[4]

If a drug is predominantly renally eliminated unchanged, a dosage regimen adjusted may be calculated on the basis of the ratio of the patients residual renal function relative to an age and gender, normal value for estimated creatinine clearance or GFR. However for medications that are extensively metabolized or for which dramatic changes in protein binding and/or distribution volume have been noted, a more complex adjustment strategy may need to be employed.

In this study a particular framework for drug dosage adjustment for renal patients have been discussed. Inspite of numerous published journals regarding drug dosing for patients with reduced kidney function, there is insufficient evidence to guide decisions on many commonly used drugs.[5]

ASSESSMENT OF KIDNEY FUNCTION

Glomerular Filtration Rate (GFR)

The standard measure of kidney function is the Glomerular Filtration Rate. Estimates of glomerular filtration rate (GFR) are used to estimate renal function, in diagnosing renal disease and are also used to estimate renal drug clearance. GFR is the product of the number of nephrons and a single nephron GFR. So the GFR is affected by chronic kidney disease, in which reduces the number of nephrons. The normal level of GFR varies according to age, gender and body size. The normal mean GFR is approximately 120 to 130 ml/min/1.73m.[2]

The determination of GFR using an endogenous substance based on urinary clearance of creatinine (CLcr) derived from a 24 hour urine collection has many limitations of its own. Therefore GFR is predominantly estimated in clinical practice from the measurement of endogenous substances such as serum creatinine (Scr) and then compared with patient factors to estimate the GFR using estimating equations. Estimating equations are on average, more accurate than measured creatinine clearance.[5]

Cockroft-Gault Equation

Historically, the most frequent clinically used equation to estimate GFR has been the Cockroft-Gault(CG) equation. A drug renal clearance is proportional to creatinine clearance (Clcr), which may be measured directly or estimated from the serum creatinine level (Scr).

$$\textbf{In men: Clcr} = \frac{\textbf{(140 – age) x weight (kg)}}{\textbf{72 x Scr (mg/dl)}} \ \textbf{(mL/min)}$$

For women, the estimate by the above equation should be multiplied by 0.85 to reflect their smaller muscle mass. It should also be noted that this equation is not valid for patients with severe renal insufficiency (Clcr < 5 mg/dl) or when renal function is changing rapidly.[1,4] The Cockroft-Gault Equation is reported in units not adjusted for body surface area, which is appropriate for drug dosage adjustment. But some limitations such as in CG equation, the use of lean body mass when estimating GFR in obese patients has not properly proposed or validated.

Modification of Diet in Renal Disease (MDRD)
The MDRD GFR equation estimates glomerular filtration rate based on creatinine and patient characteristics.
GFR= 186.3× (Scr) $^{-1.154}$× (Age) $^{-0.203}$×0.742 (Female).

The clinicians have ready access to at least one GFR estimate for all of their patients. Therefore clinicians should use the method that provides the most accurate assessment of GFR.[3, 4]

Drug dosage modification in patients with renal insufficiency
Most dosage adjustment guidelines suggest the approximate understanding of following three goals.
a) Increase of dosage intervals without changing the dose
b) Reduction of the dose without changing the frequency and
c) Combination of both; Increase of dosage intervals and dosage modification.

The following parameter may help to guide individual therapy.

Loading Dose
The loading dose is the same for patients with normal renal function and those with chronic renal insufficiency as it depends only on the volume of distribution (Vd) and not on the drug clearance except in those with expanded extracellular fluid volume who would require a larger loading dose.

Maintenance Dose
The maintenance dose is the fraction of the normal dose in renal insufficiency and can be calculated as follows:
a) Dose in renal failure = Dose in normal renal function x (t½ normal/ t½renal failure), Where t½ is the half-life for elimination and inversely proportion to clearance.

Or
b) The Dose is constant and the dosing interval increased Dose interval in renal failure = normal dose interval/(t½ normal/ t½ renal failure).[5]

Dosing Adjustments
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.[4] 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. Normal doses are maintained with the extended interval method, but the dosing interval is lengthened to allow time for drug elimination before redosing. Lengthening of the dosing interval has been associated with a lower risk of toxicities but a higher risk of subtherapeutic drug concentrations, especially towards the end of the dosing interval.[6]

MATERIALS AND METHODS

STUDY DURATION
Six months from October 2014 to March 2015.

STUDY SITE
The study is planned to be conducted at a 350 bedded hospital in the Department of Nephrology.

STUDY DESIGN
Prospective-observational study.

Inclusion criteria
Patients with Renal Impairment with or without other co-morbidities.

Exclusion criteria
• Pregnant women and children.
• Patients not willing to participate in the study.
• Patient who are physically and mentally not stable.

DATA COLLECTION
A total of about 154 patients were admitted in the Nephrology department during the study period in the mentioned teaching hospital among those about 100 patients who met the criteria were actually considered for the study. The protocol of the study was approved by the institutional ethical committee and review board then only we start collecting the cases for the study. Before data collection, patients are informed about the study objectives and the written consent from patients or their care givers will be obtained. Patient data will be collected in the specially designed data entry format which includes patient's demographic details. Past medical histories including medications, clinical lab data and present therapy. After determining the degrees of renal insufficiency the patients were grouped according to their stages of renal impairment as recommended by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) and Food & Drug Administration (FDA).

DATA ANALYSIS
The obtained cases are thoroughly analysed to evaluate the prescription patterns of renally excreted drugs and the risks associated with its use. Dosage adjustment of drugs has done according to creatinine clearance or glomerular filtration rate using Micromedex Software, British National Formulary. Recommended methods for dosing adjustments are dose reductions, lengthening the dosing interval, suggesting alternatives using the published drug dosing guidelines for the patients individual degree of renal impairment.

Creatinine clearance was calculated by Cockroft -Gault equation,

$$\text{CrCL} = \frac{(140\text{-age}) \times \text{Weight in Kg}}{\text{Serum Creatinine} \times 72}$$

Instead of creatinine clearance, GFR was calculated by using Modification of Diet in Renal Disease (MDRD) formula whenever patients weight was not available.

GFR = 186.3 x (Serum creatinine)$^{-1.154}$ x (Age)$^{-0.203}$ x 0.742 (Female)

For obese patients, the dosing weight was calculated before calculating creatinine clearance by Cockroft-Gault equation.

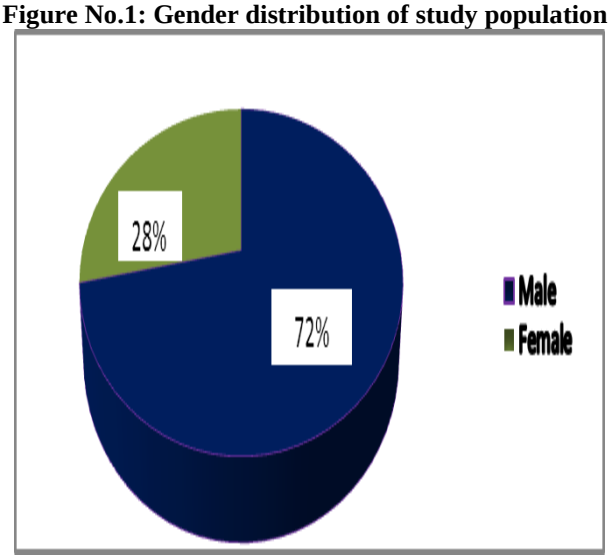
IBW for male patients = [Height (cm) -80] x 0.7
IBW for female patients = [Height (cm) -70] x 0.6
Dosing weight = (ABW-IBW) x 0.4 + IBW

RESULTS AND DISCUSSION

The study was conducted across 100 patients admitted in the nephrology department. A total of 1112 drugs in 100 patients were evaluated in the present study with a mean of 11.22 (range: 3-18) drugs per patient.

GENDER DISTRIBUTION

Figure No.1: Gender distribution of study population



AGE DISTRIBUTION

The age of the study population ranged between 25 to 91 years with a mean age of 64.44 years. The details were given in the Table No:2. It was also understood that most of the patients (59%) were in the late adulthood (61-80yrs). 9% of the patients were in geriatrics range.

Table No. 2: Age distribution.

S.No	AGE (Years)	PERCENTAGE (n=100)
1	20-40	7
2	41-60	25
3	61-80	59
4	81-100	9

DIAGNOSIS

The diagnosis of overall population were found out and listed in Fig No: 2.

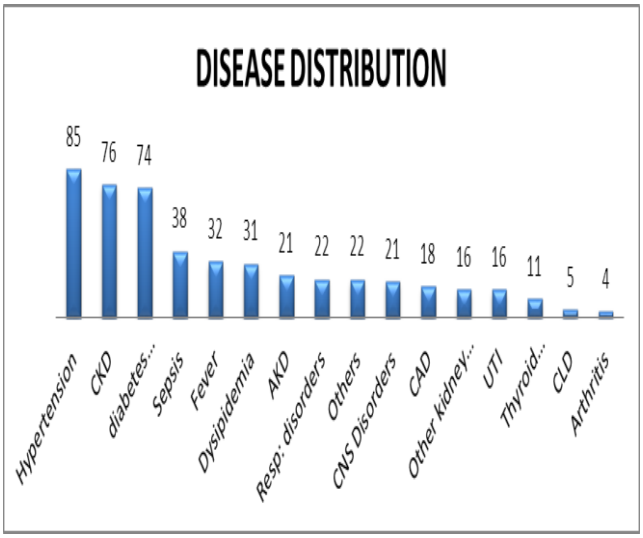


Figure No.2: Disease distribution (n =100)

The major diagnosis were renal failure or other kind of kidney abnormalities(97.0%), Hypertension (85.0%) and Diabetes Mellitus (74%). About 84% of patients had multiple comorbidities.

DRUGS PRESCRIBED

Total of 1112 different drugs were prescribed to the study population. The major drug category prescribed was anihypertensives (16.45%), antibiotics (12.67.07%) and GI drugs (10.25%) drugs. The details of drugs were listed and given in figure 3.

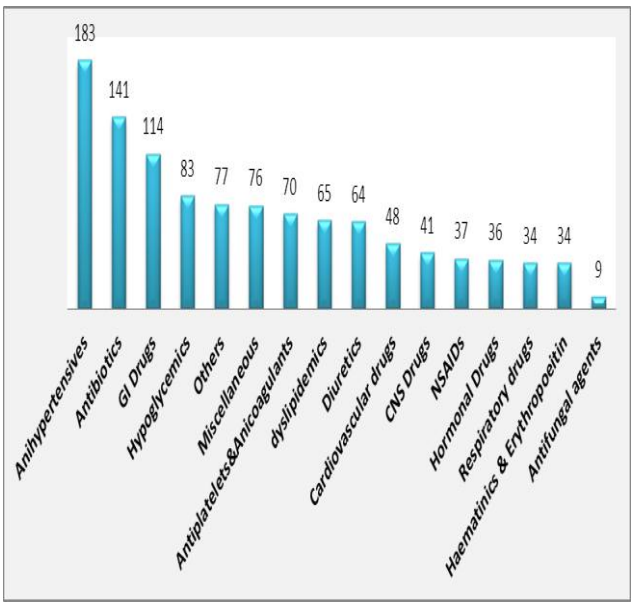


Figure No.3: Drugs prescribed.

STAGES OF RENAL FUNCTION

The different stages of renal function of the subjects with frequency are shown in figure No.4.

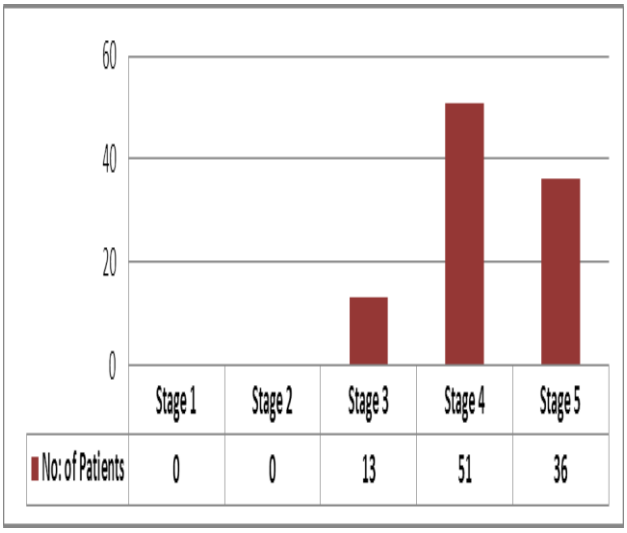


Figure No.4: Stages of renal function.

It was found that 115 drugs (10.34%) among the total prescribed drugs(1112) were renally eliminated. On an average each patient with renal dysfunction received about 4-6 renally eliminated drugs.

Their mean serum creatinine level was 4.14 mg% (range: 1.7 to 15.5 mg/dl) and mean creatinine clearance was 21.85mg/ml (range 5.26 to 64.49 ml/min).

Among the 1112 evaluated drugs, 115 drugs (10.34%) were renally eliminated. Dose adjustments was considered mandatory if atleast 70% of bioavailable, active form of drug is eliminated by the kidney in unchanged form or potential nephrotoxicity is previously documented in the literature, in this study 60 drugs were belongs to the aforesaid category. Among those 48 (41.73%) required dose adjustments, 12(10.43%) drugs were either not recommended in kidney disease or contraindicated and rest of the 55(47.82%) drugs does not require dose adjustment. Out of these 48 drugs, dose of 37 (77.07%) were adjusted at the time of prescribing and 11 (22.91%) were not adjusted. Inspite of dosage adjustment made for 48 patients no particular dosage adjustments was recommended for those patients who undergone dialysis.

Table No.3: Errors in prescribing renally eliminated drugs and their adjusted dose (n=60)

Sl No:	Drug prescribed	Stage of renal function	Creatinine (mg/dl)	Crcl ml/min	GFR ml/min/1.73m^2	Errors	Prescribed dose	Dose adjustment/ Intervention
1	Levofloxacin	5	_	10-19	_	Over dose and Wrong frequency	750 mg BD	500 mg Q48H
2	Levofloxacin	4	_	20-49	_	Wrong frequency	750 mg BD	750 mg Q48H
3	Prulifloxacin	3	_		_	Over dose	600 mg OD	450 mg OD
4	Ofloxacin	4	_	20-50	_	Wrong frequency	300 mg BD	300 mg OD
5	Ofloxacin	5	_	<20	_	Over dose and wrong frequency	300 mg BD	200 mg OD
6	Ciprofloxacin	3	_	<10	_	Over dose	500 mg BD	250 mg BD
7	Ciprofloxacin	4	_	<10	_	Over dose	500 mg BD	250 mg BD
8	Ciprofloxacin	5	_	<10	_	Over dose	500 mg BD	250 mg BD
9	Ceftazidime	4	_	16-30	_	Wrong frequency	1 gm. BD	1 gm OD
10	Ceftazidime	5	_	6-15	_	Over dose and wrong frequency	1 gm BD	0.5 gm OD
11	Cefazolin	4	_	11-34	_	Over dose	1 gm BD	500 mg BD
12	Cefazolin	5	_	≤10	_	Wrong frequency	1 gm BD	1gm Q18H to Q24H
13	Cefixime	3	_	21-60	_	Over dose	200 mg BD	260 mg OD
14	Cefixime	4	_	<20	_	Over dose	200 mg BD	200 mg OD
15	Cefpodoxime	4	_	<30	_	Wrong frequency	200 mg BD	200 mg OD
16	Cefuroxime	4	_	10-20	_	Wrong frequency	750 mg Q8H	750 mg Q12H
17	Cefuroxime	5	_	<10	_	Wrong frequency	750 mg Q12H	750 mg Q24H
18	Ampicillin	5	_	<10	_	Wrong frequency	500 mg Q6H	500 mg Q12H-Q16H
19	Amoxicillin/ Clavulanate	4	_	10-30	_	Over dose	875/125 mg Q12H	500/125 mg Q12H
20	Cefoperazone	4	_		_	Over dose	1.5 gm BD	1 gm BD
21	Piperacillin / Tazobactam	3	_	20-40	_	Over dose	4.5 gm Q6H	2.25g IV Q6H
22	Piperacillin/ Tazobactam	5	_	<20	_	Over dose and wrong frequency	4.5 g Q6H	2.25g IV Q8H
23	Imipenem/ Cilastin	3	_	20-30	_	Over dose and wrong frequency	500 mg Q8H	250mg Q12H
24	Imipenem / Cilastin	5	_	20-30	_	Over dose and wrong frequency	500 mg Q8H	250mg Q12H
25	Meropenem	4	_	<10	_	Over dose and wrong frequency	1 g Q8H	0.5 g Q24H
26	Meropenem	5	_	<10	_	Over dose and wrong frequency	1 g Q12H	0.5 g Q24H
27	Colistin	3	_	10-29	_	Over dose and wrong frequency	2.5 mg /kg OD IV Q12H	1.5 mg/kg OD IV Q36H
28	Colistin	4	_	10-29	_	Over dose and wrong frequency	2.5 mg /kg OD IV Q12H	1.5 mg/kg OD IV Q36H
29	Amikacin	3	_	25-60	_	Wrong frequency	250 mg Q12H	250 mg Q24H
30	Teicoplanin	4	_	<30	_	Over dose	400 mg BD	200 mg BD
31	Clarithromyc-in	4	_	<30	_	Over dose	500 mg BD	250 mg BD
32	Ertapenem	4	_	<30	_	Overdose	500 mg BD	500 mg OD
33	Chlorthalido-ne	5	_	<10	_	_	12.5 mg OD	Contraindicated
34	Hydrochlorth-iazide	5	_	<10	_	_	12.5 mg OD	Contraindicated
35	Spironolacto-ne	4	_	<30	_	_	50 mg OD	Avoid use
36	Ramipril	4	_	≤40	_	Over dose	5 mg BD	5 mg OD

37	Perindopril	4	_	<30	_	_	4 mg BD	Not recommended
38	Bisoprolol	5	_	<40	_	Over dose	5 mg OD	2.5 mg OD
39	Atenolol	5	_	<50	_	Over dose	50 mg OD	25 mg OD
40	Nebivolol	4	_	>250 µmol/l	_	_	5 mg OD	Avoid use
41	Gliclazade	4	_	_	_	_	4 mg OD	Not recommended
42	Metformin	4	1.5 mg/dl	_	_	_	500 mg TID	Contraindicated
43	Vildagliptin	4	_	_	_	Over dose	100 mg OD	50 mg OD
44	Olmesartan		_	<20	_	Over dose	40 mg OD	20 mg OD
45	Rosuvastatin	5	_	<30	_	_	5 mg OD	Contraindicated
46	Fondaparinux	4	_	30-50	_	Over dose	7.5 mg OD	5 mg sc OD
47	Enoxaparin	5	_	<30	_	Wrong frequency	40mgSC BD	40 mg OD
48	Cilostazol	5	_	_	_	_	100 mg BD	Avoid use
49	Terbutaline	4	_	<50	_	Over dose	5 mg tid	2.5 mg tid
50	Ranitidine	4	_	<50	_	Wrong frequency	150 mg BD	150 mg Q24H
51	Loratidine	4	_	<30	_	Wrong frequency	10 mg BD	10 mg OD
52	Silodosin	5	_	30-50	_	Over dose	8 mg OD	4 mg OD
53	Methyldopa	5	_	_	<10	Over dose and wrong frequency	250 mg BD	200 mg OD
54	Allopurinol	3	_	3-10	_	Over dose	300 mg OD	150 mg OD
55	Memantine	4	_	5-29	_	Over dose	10 mg BD	5 mg BD
56	Fluconazole	3	_	≤50	_	Over dose	200 mg BD	100 mg BD
57	Gabapentin	4	_	<30	_	_	600 mg OD	Contraindicated
58	Erythropoeit-in	3	_	_	_	Over dose	4000 units/ml	3000 units/ml
59	Etoricoxib	4	_	_	<30	_	90 mg OD	Contraindicated
60	Ropinirole	5	_	_	<30	_	1 mg QID	Avoid use

TYPES OF ERRORS IDENTIFIED

The American society of health system pharmacist (ASHP) definition of medication errors includes prescribing, dispensing, medication administration and patient compliance errors. Major types of errors identified were overdose, 29(29%); and wrong frequency of administration, 18 (18%); and over dose with wrong frequency of administration, 18 (18%). About 13% of the drugs were to be avoided strictly in renal impairment as per the available evidence mentioned in the Table No 4. Further, 70% of the patients needed dosage adjustment for at least one drug prescribed.

Table No. 4.: TYPES OF ERRORS IDENTIFIED

S.NO	TYPE OF ERROR	NO:OF PATIENTS	PERCENTAGE(%)
1	Over dose	25	25%
2	Wrong frequency	12	12%
3	Over dose and wrong frequency	11	11%
4	Contraindicated/Not recommended	12	12%

It has been shown that only a small percentage of medication errors actually result in harm to the patient.

DRUG INTERACTIONS

The prescribtion analysis revealed that 183 drug-drug interactions has been found between the prescribed drugs. Of these 86 (46.99%) were major interactions and 97 (53%) were moderate interactions. Clonidine with Metoprolol and Pantoprazole with Clopidogrel was the most frequently identified interacting drug combinations. Interactions which can directly influence kidney function were also observed in 2 cases. These included Sodium bicarbonate with Levofloxacin and Cefoperazone with Furosemide. Figure No.5 shows the type of drug interactions and Table No.5 shows the list of major drug interactions.

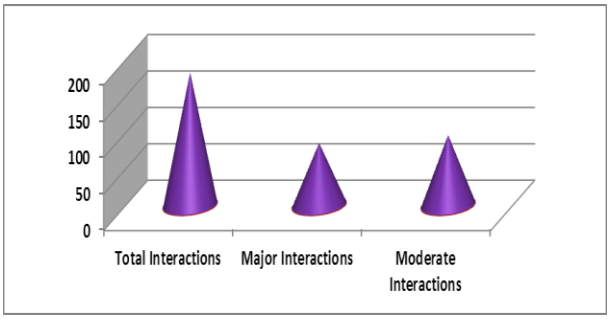


Fig No. 5: Drug interactions (n= 183).

Table No.5: Major drug interactions.

INTERACTING DRUGS	INTERACTION	SEVERITY
Pantoprazole+Clopidogrel	Decrease the effect of Clopidogrel	Major
Clonidine+Metoprolol	Increase the toxicity	Major
Modafinil+Clopidogrel	Decrease the effect of Clopidogrel	Major
Modafinil+Atorvastatin	Decrease the effect of Atorvastatin	Major
Modafinil+Budesonide	Decrease the effect of Budesonide	Major
Hydrocortisone+Atorvastatin	Decrease the effect of Atorvastatin	Major
Atorvastatin+Diltiazem	Increase the risk of rhabdomyolysis	Major
Diltiazem+Nebivolol	Increase the risk of hypotension	Major
Atorvastatin+Pantoprazole	Decrease the effect of Atorvastatin	Major
Sodium Bicarbonate+Ofloxacin	Decrease the level of Ofloxacin	Major
Ofloxacin+Ondansetron	QT interval prolongation	Major
Sodium Bicarbonate+Gabapentin	Decrease the level of Gabapentin	Major
Aspirin+Bisoprolol	Decrease the effect of Bisoprolol	Major
Calcium+Bisoprolol	Decrease the effect of Bisoprolol	Major
Calcium Acetate+Metoprolol	Decrease the effect of Metoprolol	Major
Prazosin+Metoprolol	Risk of hypotension	Major
Pioglitazone+Atorvastatin	Increase the toxicity of Atorvastatin	Major
Aspirin+Dexamethasone	Either increase the toxicity of other	Major
Amlodipine+Dexamethasone	Steroid antagonize antihypertensive effect of Amlodipine	Major
Metoprolol+Furosemide	Risk of hypotension	Major

CONCLUSION

The present study observed that the dosing of drugs in renal impairment follows the standard guidelines to a greater extend and are comparable with the existing literature. However the presence of renal dysfunction was not considered in dosing of certain renally excreted drugs like Nebivolol, Metformin, Glipizide, Levofloxacin etc. which in-turn can lead to potential risk for adverse drug reactions. This study clearly showed that pharmacist participation in ward rounds, prescription chart review, evaluation of drug dosing based on eGFR or creatinine clearance and immediate concurrent feedback mechanism may cause substantial reduction of

inappropriate drug regimens, thereby improving drug safety in patients with renal impairment.

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