"DOSAGE INDIVIDUALIZATION OF ANTI MICROBIALS AND CARDIOVASCULAR DRUGS IN PATIENTS WITH CHRONIC RENAL DYSFUNCTION"

Project submitted to

The Tamil Nadu Dr. M.G.R. Medical University, Chennai
In partial fulfilment of the award of Degree of

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Submitted by

SARAYU B

Under the Guidance of

Dr. A.S. Manjula Devi, M. Pharm., Ph.D.,
Associate Professor
Department of Pharmacy Practice

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COLLEGE OF PHARMACY

SRI RAMAKRISHNA INSTITUTE OF PARAMEDICAL SCIENCES

COIMBATORE - 641 044

Certificates

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in Sri Ramakrishna Hospital, Coimbatore, attached to the College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore, which is affiliated to The Tamil Nadu Dr. M.G.R Medical University, Chennai, under my direct supervision and guidance to my fullest satisfaction.

Dr. A.S. Manjula Devi, M. Pharm., Ph.D.,
Associate Professor,
Department of Pharmacy Practice,
College of Pharmacy,
SRIPMS,
Coimbatore - 641 044.

Place: Coimbatore
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Dr. S. Sriram, M.Pharm., Ph.D.,
Professor and Head
Department of Pharmacy Practice,
College of Pharmacy,
SRIPMS,
Coimbatore- 641 044.

Place: *Coimbatore*
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Dr. T. K Ravi, M. Pharm., Ph.D., FAGE,
Principal,
College of Pharmacy,
SRIPMS,
Coimbatore- 641 044.

Place: Coimbatore
Date:

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CONTENTS

ABBREVIATIONS

ABW	–	Actual Body Weight
ACE	–	Angiotensin Converting Enzyme
ADRs	–	Adverse Drug Reactions
APD	–	Acute Pulmonary Disease
ARB	–	Angiotensin Receptor Blocker
BD	–	Twice Daily
BNF	–	British National Formulary
CAPD	–	Continuous Ambulatory Peritoneal Dialysis
CCF	–	Congestive Cardiac Failure
CG	–	Cockcroft-Gault
CHF	–	Congestive Heart Failure
CKD	–	Chronic Kidney Disease
ClCr	–	Creatinine Clearance
CRF	–	Chronic Renal Failure
CVA	–	Cerebrovascular Accident
CVD	–	Cardio Vascular Disease
DCI	–	Dialysis Clinic, Inc
DM	–	Maintenance Dose
DRPs	–	Drug Related Problems
eGFR	–	Estimated Glomerular Filtration Rate
ESRD	–	End Stage Renal Disease
GFR	–	Glomerular Filtration Rate
HD	–	Heamodialysis
IBW	–	Ideal Body Weight
IHD	–	Ischaemic Heart Disease

IV	–	Intravenous
KDOQI	–	Kidney Disease Outcomes Quality Initiative
KF	–	Kidney Function
LBW	–	Lean Body Weight
LRTI	–	Lower Respiratory tract Infection
MDRD	–	Modification of Diet in Renal Disease
NAPQI	–	N-acetyl-P-benzoquinoneimine
NFK	–	National Kidney Foundation
NSAIDs	–	Non Steroidal Anti-inflammatory Drugs
NTI	–	Narrow Therapeutic Index
OD	–	Once Daily
PDR	–	Physician Desk Reference
PO	–	Per Oral
RI	–	Renal Impairment
RF	–	Renal Failure
RRT	–	Renal Replacement Therapy
SD	–	Standard Deviation
TDM	–	Therapeutic Drug Monitoring
TID	–	Thrice Daily
τ	–	Dosing Interval
q.8.h	–	Every Eight Hours
q.6.h	–	Every Six Hours
q.12.h	–	Every Twelve Hours
UTI	–	Urinary Tract Infection
WHO	–	World Health Organisation

ABSTRACT

BACKGROUND

Chronic kidney disease is a common and progressive illness that may be harmful and may have deleterious effects. Inappropriate dosing in patients with renal dysfunction can cause toxicity or ineffective therapy. Dose adjustment in patients with renal failure reduces both the cost of the drug therapy and the risk of ADRs.

OBJECTIVE

- To understand the prescribing pattern of antimicrobials and cardiovascular drugs in patients with renal function impairment.

- To understand drug dosage individualization of all renally excreted antimicrobials and cardiovascular drugs that necessitates dosage adjustment in patients with renal function impairment**.**

DESIGN

Prospective descriptive study

STUDY DURATION

9 months (from December 2018 to August 2018)

SETTING

A 700 bedded multi-specialty tertiary care teaching hospital

PATIENTS

All in patients with estimated serum creatinine value more than 1.7mg/dL (Normal range: 0.8 – 1.2 mg/dL), prescribed with at least one antimicrobial drug or cardiovascular drug or both were included in the study.

METHOD

Clinical and demographic details of the eligible patients were collected in a structured proforma after obtaining approval from the Institutional Review Board. Creatinine clearance or estimated glomerular filtration rate of the patient were calculated using Cockroft-Gault equation and Modified Diet in Renal Disease equation respectively with the help of Micromedex calculators. The dose of all drugs with potential nephrotoxicity or renally excreted drugs was evaluated using

the published drug dosing guidelines. When necessary the new dosages or dosing intervals were optimized to the patient's individual degree of renal impairment using relevant equations.

RESULTS

20 patients had moderate renal impairment while 46 had severe and 37 had end stage renal dysfunction. 1016 drugs in 103 patients were evaluated in the present study with an average of 10 drugs per patient. Of these 1016 studied drugs 98 (9.64%) required dose adjustment where 244 (24.01%) were adjusted and 83 (8.16%) were not adjusted. It was found also that most of the drugs requiring dose adjustment were antibiotics (41.77%) followed by antihypertensives (13.67%). Major category of errors identified were overdose (61.53%) and wrong frequency of administration (23.07%). About 15.38% of the drugs were to be avoided strictly. It was also found that 13.12% of prescribed drugs had interaction. The most common interaction was identified as Pantaprazole vs Torsemide and was found in 4.17% of patients. Nephrotoxic drug interactions were observed in 2.79% of patients. Around 1.84% of drugs had narrow therapeutic index. These were prescribed in 13.5% of patients. Prazosin (2%) theophylline (8%) and Digoxin (4%) were the drugs with narrow therapeutic index.

CONCLUSION

Recommended dosage guidelines in renally impaired patients were followed in 82.6% of prescriptions whereas only 17.39% were found to be deviated. Findings of the present study revealed that the overall consistency was good when compared with similar studies reported.

INTRODUCTION

The most important contribution of the kidney to overall maintenance of body homeostasis is the urinary excretion of water, endogenous substances and toxins. Through the combined processes of glomerular filtration, tubular secretion, and tubular reabsorption, the nephron, as the functional unit of the kidney, maintains balance between input and output of water and solutes from the body. Thus the kidney is the key organ responsible for maintenance of homeostasis.[1] this is represented as:

Renal deficiency can be caused by inadequate blood flow to the kidney, renal

Rate of excretion = rate of filtration + rate of secretion - rate of reabsorption

and systemic diseases and disorders related to the urinary tract obstruction. The major manifestations of altered kidney function are the effects on excretion of metabolic wastes and on maintenance of Na +, K + water, and acid-base balance. Failure to excrete urea and other metabolic wastes adequately, manifested as progressive elevation of blood urea nitrogen (BUN) and serum creatinine. In the absence of adequate renal clearance of excessive amounts of water, Na+, K+, or acids may result in water, electrolyte and acids-base abnormalities that can be life-threatening. Generally speaking, the renal deficiency includes also the endocrine and metabolic dysfunction.

The two principle organs are responsible for the elimination of drugs and their metabolites from the body are the liver and kidney.[2] Kidney does the major work of the urinary system. Functions of the kidney include the following

- Regulation of blood ionic composition
- Regulation of blood pH
- Regulation of blood volume
- Regulation of blood pressure
- Maintenance of blood osmolarity

- Production of hormones
- Regulation of blood glucose level
- Excretion waste and foreign substances.[3]

Kidney disease is defined as the presence of kidney damage or a reduction in GFR for a period of three months or longer. Kidney disease is increasingly recognised as a significant health issue in the population.[4] In particular, older patients are at a higher risk of developing advanced disease and related decline in renal function and the use of multiple medications to treat comorbid conditions. Chronic kidney disease can affect glomerular blood flow and filtration, tubular secretion and reabsorption and renal bio activation and metabolism. Drug absorption, bioavailability, protein binding, distribution volume, and non-renal clearance (metabolism) also can be altered in these patients.[5]

Renal failure is used primarily to denote failure excretory function of kidneys, leading to retention of nitrogenous waste products of metabolism. Various other aspects of renal function may fail at the same time, including the regulation of fluid and electrolyte status and the endocrine function of the kidney. Renal failure can be divided according to clinical presentation into acute renal failure (ARF) and chronic renal failure (CRF).[6] The severe condition (end-stage) of both is named as uremia. ARF is a heterogeneous group of disorders, which is characterized by a sudden (within hours to days) deterioration of renal function and usually associated with oliguria (< 400ml per day in (adult) or anuria (< 100ml per day in adult) resulting in accumulation in the blood of nitrogenous wastes that would normally be excreted in the urine. The patient presents with a rapidly rising blood urea nitrogen and serum creatinine. Other compounds including uric acid, phosphate, and sulphates are also accumulated. Glomerular filtration rate (GFR) decrease plays a central role in pathogenesis of ARF. Most of the patients with ARF present oliguria, which is named as oliguric type of ARF. The ARF without oliguria is named as non-oliguric type of ARF. Acute renal failure may be observed in patients with previously normal renal function or patients whose prior renal function was impaired but stable. Urine volume may be

normal at any time in mild forms of acute renal failure, the diminished urine volume is commonly but not always seen. Some patients may be anuric, some may be oliguric.

The incidences of prevalence of kidney failure are rising and the outcomes are poor. The kidney provides the final common pathway for execration of most drugs and their metabolites. Inappropriate dosing in patients with chronic kidney disease can cause toxicity or ineffective therapy. The major outcomes of CKD regardless to cause include progression to kidney failure, complications of decreased kidney function and CVD. Increasing evidence indicates that some of these adverse outcomes can be prevented or delayed by early detection and treatment. Unfortunately, CKD is under diagnosed and under treated, resulting in lost opportunities for prevention, in part because of lack of agreement on a definition and classification of stages in the progression of chronic kidney disease and a lack of uniform application of simple tests for detection and evaluation.

Renal dysfunction can affect the pharmacokinetic and pharmacodynamics action of drug. Dosage adjustment in renal failure is critical because drug or its active metabolites can accumulate and additional morbidity and cost. In many drugs like aminoglycosides antibiotics, H2 receptor antagonists, ACE inhibitors, Digoxin, Lithium are eliminated primarily unchanged through the kidney. Dosage adjustment in renal failure can easily be achieved by estimating the creatinine clearance based on serum creatinine, age, weight, gender; calculating the individual elimination capacity for a given drug; and adjusting dose and/or dosing interval. Dosage adjustment in patients with renal failure reduces the risk of adverse drug reactions

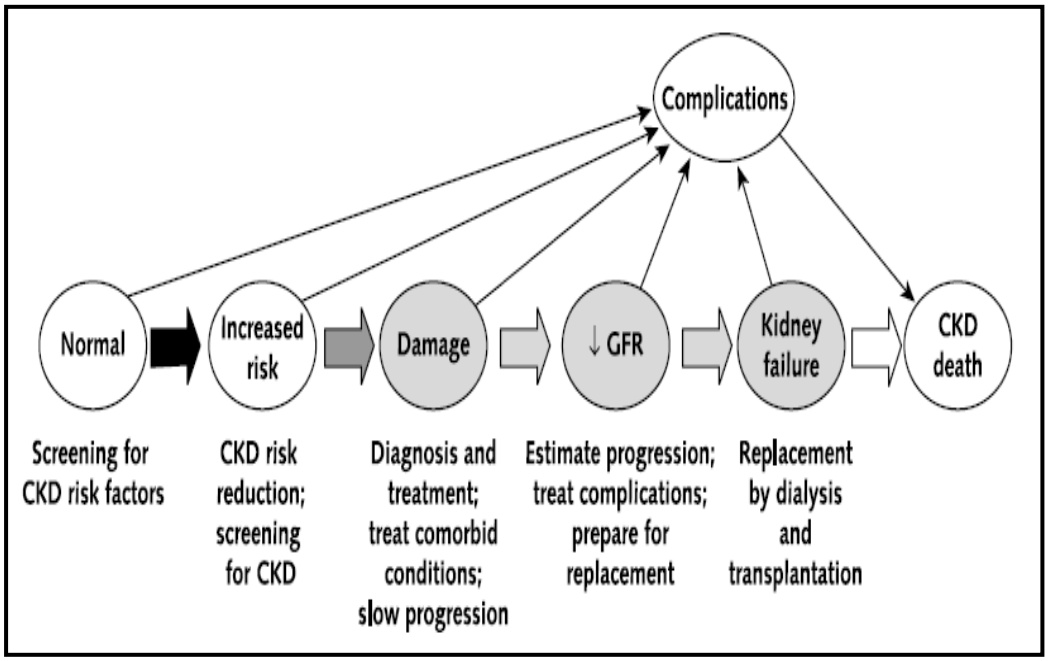
Risk factors for the chronic kidney disease and its outcomes[7]

S.No	Risk factors	Definition	Examples
1.	Susceptibility factors	Increase susceptibility to kidney damage	Older age, family history of CKD, reduction in kidney mass, low birth weight, low

			income or education
2.	Initiation factors	Directly initiate kidney damage	Diabetes, high blood pressure, autoimmune disease, systemic infections, urinary stones, lower urinary tract obstruction, drug toxicity
3.	Progressive factors	Cause worsening kidney damage and faster decline in kidney function after initiation of kidney damage	Higher level of proteinuria, higher blood pressure, poor glycemic control in diabetes, smoking
4.	End – stage factor	Increase morbidity and mortality in kidney failure	Lower dialysis dose, temporary vascular access, anemia, low serum albumin level, late referral

Patient diagnosed with severe renal impairment and patient in dialysis are followed closely by nephrologist in specialized nephrology department. 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. Studies have suggested that care provided by multi-disciplinary nephrology teams may improve patient outcome. However, in most patients with mild to moderate RI the reduced function may not have been diagnosed and these patients are managed in general practice and in general hospitals. The necessity of dose adjustment or drug avoidance is probably under estimated in clinical practice.[8]

INITIATION AND PROGRESSION OF CHRONIC KIDNEY DISEASE (CKD) AND THERAPEUTIC INTERVENTIONS.[7]



LABORATORY EVALUATION OF RENAL FUNCTION

Kidney function is assessed by a variety of tests and procedures that can be done to evaluate how well kidneys are functioning. These tests are done on urine as well as blood samples. Many conditions can affect the ability of the kidneys to carry out their vital function. The extent of loss of renal function is judged by calculating creatinine clearance which is a useful measure of glomerular filtration rate. According to the reduction in creatinine clearance value the patients are categorised into mild moderate and severe renal impairment.

The standard indicators of renal function are serum levels of urea nitrogen and creatinine: this ratio is normally about 10:1. This ratio may increase when renal perfusion or urine flow is decreased, as in the urinary tract obstruction or dehydration. The most reliable single indicator of glomerular function is serum levels of creatinine. For example serum creatinine increasing from 0.5mg/dl to 1mg/dl represents 50% reduction in GFR.

Serum creatinine is a by-product of creatinine metabolism in muscle. It is filtered in the glomeruli, but not reabsorbed in the tubules. Therefore, blood values depend closely on GFR. Normal creatinine level is proportional to muscle mass. For example, small woman – 0.5mg/dl, man – 1mg/dl and muscular man – 11.4mg/dl

- If value doubles, GFR and renal function probably have fallen to half of normal state.
- If value triples, it suggested 75% loss of renal function.
- Values of 10mg/100ml suggests 90% loss of renal function

Creatinine clearance: For 24 hours urine. Normal results: 90-139ml/min for adults and 80-125ml/min for females.[9]

The NKF-KDOQI clinical practice guideline advocates using the traditional Cockcroft - Gault equation or Modification of Diet in Renal Disease (MDRD) study equation for routine estimation of GFR. However, in patients with a GFR lower than 60ml/min/1.73m^2 the MDRD equation has been shown to be superior to the Cockcroft - Gault equation.

Because the production and excretion of creatinine declines with age, normal serum creatinine values may not represent normal renal function in older patients. The MDRD equation has been shown to be the best method for detecting a GFR lower than 90ml/min/1.73m^2 [5]

Renal drug clearance [2]

Three processes that can potentially contribute to the renal clearance of a drug are glomerular filtration, tubular secretion and tubular reabsorption. Approximately 20 -25 % of cardiac output or 1.1L of blood per min goes to the kidneys. Of this volume, approximately 10% is filtered at the glomerulus. Large circulating molecules, such as albumin and α1- acid glycoprotein to which many drugs are reversibly bound, are normally not filtered to any appreciable extent at the glomerulus. Consequently, only unbound drug in plasma water is excreted by glomerular filtration. Glomerular filtration is a low clearance process.

Active tubular secretion is another efficient mechanism for extracting substances from the circulation and secreting them into the tubular lumen. Renal clearance by tubular secretion can be perfusion rate limited or capacity rate limited. The renal proximal tubule is the primary site of active transport for a wide variety of substrates including organic anions/ cations, peptides and nucleosides.

Tubular reabsorption, which takes place by passive diffusion, may also influence the renal excretion of drugs. The extensive reabsorption of filtered water along the renal tubule- from 120 ml of plasma water filtered per min to only 1 to 2 ml/min arriving in the collecting tubules and bladder as urine is a driving force for to tubular reabsorption. Factors that control the tubular reabsorption of drugs are urine pH, degree of ionisation of drugs and their metabolites, urinary flow rate, lipophilicity and pKa.

Effect of renal dysfunction on pharmacokinetic process[2]

Absorption

Drugs are most frequently administered orally. Both the rate and extent of absorption from the GI tract influence the drug plasma concentration- time profile. The rate of absorption is assessed by measuring Tmax, the time at which the maximum plasma concentration (Cmax) occurs. Tmax has been shown to be slightly increased for a number of drugs when administered orally to patients with severe renal dysfunction. The longer T_{max} may be due to reduced gastric emptying in these patients or simply to a longer plasma elimination half-life of the drug. Extent of oral absorption is best assessed by comparing the area under the plasma drug concentration- time curve (AUC) following oral and IV administration. In patients with renal dysfunction do not measure absolute oral bioavailability but simply determine pharmacokinetic parameters such as plasma clearance, Vd and plasma half-life following oral administration of the drug. Patients with renal disease are treated with many medications some of which may alter the absorption of other concomitantly administered drugs. For example hyperphosphatemia is an important component of the bone disease seen in chronic renal failure and many

of these patients take phosphate binders may interact with certain drugs like fluroquinolones, thereby reducing their extent of absorption.

Distribution

The plasma protein binding of many acidic drugs is decreased in patients with renal dysfunction. Several mechanisms decreased plasma binding, including hypoalbuminemia, the accumulation of endogenous substances which competitively displace acidic drugs from their binding sites on albumin, and a conformational change of the binding sites on the albumin molecule. While acidic drugs usually bind to plasma albumin, basic drugs in general have a high affinity for α_1-acid glycoprotein but often also bind to albumin and lipoproteins. Although the plasma binding of basic drugs appears to be generally unaffected in patients with chronic renal disease, it may be increased for some drugs (e.g., bepridil, disopyramide) because α_1-acid glycoprotein is an acute phase protein that is elevated in certain patients with renal disease, such as in renal transplant patients and patients on haemodialysis.

The volume of distribution of several drugs is significantly increased in patients with severe renal dysfunction. An increased volume of distribution may be the result of fluid overload, decreased protein binding, or altered tissue binding. The volume of distribution of a few drugs, such as digoxin, pindolol, and ethambutol, is decreased in patients with ESRD probably due to a decrease in their tissue binding.

Metabolism

Drugs which are mostly or completely eliminated from the body by non-renal mechanisms may accumulate in patients with renal dysfunction if their dosage regimen is not adjusted. Pharmacokinetic studies in patients with renal dysfunction have shown that non-renal clearance is reduced for many drugs, especially in ESRD, providing indirect evidence that the metabolism of these drugs is impaired in these patients. Recently, the effect of renal dysfunction on drug-metabolizing enzymes has been directly demonstrated. Dowling et al.

used the erythromycin breath test (EBT) to assess hepatic CYP3A activity in patients with ESRD undergoing long-term hemodialysis three times weekly. The EBT following intravenous administration of C-erythromycin has been extensively used to measure in vivo hepatic cytochrome 450 (CYP)3 A activity, although the outcome of the test may also be affected by the activity of hepatic uptake and efflux transporters such as OATP and P-gp. The results of this study showed that patients with ESRD had a 28% lower base line hepatic EBT value despite adequate dialysis compared to age-matched healthy control subjects. Likewise, Dreisbach et al. measured the plasma warfarin S/R ratio in patients with ESRD. The idea that renal dysfunction could differentially affect the activity of various drug- metabolizing enzymes. A study reveals that, although the overall plasma clearance of antipyrine, amarker substance completely eliminated by metabolism catalyzed by several CYP450 isoenzymes, was not different in patients with chronic renal failure compared to healthy control subjects, the formation clearance of one of the metabolites, nor antipyrine, was decreased on average by 50% in the renal patients.

Many in vivo and in vitro studies on acute and chronic renal failure subjects, it shows a down-regulation of the activity of not only CYP450 enzymes but also other drug-metabolizing enzymes, such as N-acetyl transferase. In contrast, the activity of UDP- glucuronosyl transferases 1A and 2B seem to be preserved. Uremic toxins that accumulate in the body in chronic renal failure have been implicated in these alterations in drug-metabolizing enzyme activity.

Many drugs and/or their phase I metabolites are eliminated by glucuronidation. These glucuronides are very polar and are efficiently excreted by renal mechanisms such as tubular secretion. Acyl glucuronides, i.e., glucuronide conjugates of compounds containing a carboxylic acid group, are not stable at physiological pH and are susceptible to hydrolysis by amyriad of catalysts, including β-glucuronidases, non-specific esterases, serum albumin, and hydroxideions. In patients with renal dysfunction, glucuronide conjugates

generally accumulate in the plasma. In the case of plasma accumulation of acyl glucuronides of carboxylic acid drugs, this will inevitably lead to their systemic hydrolysis and, consequently, reduced plasma clearance of the parent compound. Systemic hydrolysis of acyl glucuronides has been shown to be the cause of accumulation of several carboxylic acid drugs in patients with renal dysfunction. For example, the aryl propionic acid non-steroidal anti-inflammatory drug ketoprofen has a significantly reduced plasma clearance in patients with renal dysfunction because of the compromised capacity to excrete ketoprofen acyl glucuronide in urine which results in enhanced regeneration of the parent drug by hydrolysis.

Impaired drug metabolism has been shown in patients with severe renal dysfunction (see below) and may be the cause of a significant increase in oral bioavailabity in these patients due to reduced presystemic elimination. One of the first well- documented examples of increased plasma drug concentrations due to decreased first-pass metabolism is propoxyphene. Propoxyphene is subject to pronounced pre- systemic biotransformation after oral administration. In functionally anephric patients, the AUC of propoxyphene and its major metabolite, nor pro-poxyphene, was shown to be approximately two fold higher than that of healthy control subjects. The increase in the AUC of propoxyphene is very likely the result of reduced pre-systemic metabolism in the anephric patients. Nor pro- poxyphene is normally eliminated renally and, therefore, accumulates when renal function is impaired. Like pro- poxyphene, nor-propoxyphene can depress cardiac conduction, and its accumulation can contribute to the cardiac toxicity.

Accumulation of active metabolites:

Many drugs are eliminated from the body by metabolism. The metabolites thus formed are often thought of as inactive waste products, which is certainly not always the case. In many other cases, both the parent compound and its metabolite(s) are active. The duration and intensity of the pharmacological responses are dependent on the time course so fall active substances in the

body. Drug metabolites are usually eliminated by further metabolism and/or renal excretion. Consequently, metabolites, especially polar phase II conjugates such as glucuronides and sulfates, often accumulate in patients with renal dysfunction. When adjusting the dosage of a drug in these patients, the altered pharmacokinetics of all active species of the drug molecule has to be considered.

Morphine is a good example illustrating the significance of the accumulation of drug metabolites in patients with renal dysfunction.

Elimination

Metabolism is the major mechanism for the elimination of drugs from the body. Relatively few drugs are eliminated almost entirely unchanged by the kidneys. The plasma clearance of a drug is the pharmacokinetic parameter that best describes the capacity of a patient to eliminate that drug substance. Drug plasma clearance (CL) is generally considered to be the sum of a renal and non-renal component.

Renal Excretion

Depending on the etiology of renal dysfunction, the normal histology of the glomeruli and the tubules may be differentially affected. However, according to the intact nephron hypothesis, the function of all segments of a diseased nephron is assumed to be equally affected. Consequently, it is assumed that, regardless of the intra renal path ways of excretion, i.e., filtration, secretion, and reabsorption, the loss of excretory function in the diseased kidney can be quantified by GFR, a measure of glomerular function. Although it has been shown in rat models of acute renal failure that glomerular filtration and tubular secretion by the anionic and cationic pathways are not equally affected, the renal clearance of most drugs in patients appears to vary indirect proportion to GFR or to a measure of GFR, such as estimated creatinine clearance, regardless of the intra renal mechanism involved in their urinary excretion. For example, the plasma clearance of memantine has been shown to increase indirect proportion to CL_{CR}, as estimated by the Cockroft–Gault method. When there is no renal function,

some plasma clearance remains: this is the non-renal clearance. Dosage adjustment of memantine in patients with impaired renal function will be based on the relationship between memantine plasma clearance and CL_{cr} in the studied patient sample. As pointed out before, the intact nephron hypothesis has been questioned by some researchers who believe that a better method to quantify renal function for dosage adjustment purposes may be based on the cocktail approach.

Altered pharmacodynamics in renal disease [2]

Chronic renal failure can affect multiple organ systems and, the response to a given drug may change even though the drug's pharmacokinetics is not dramatically altered. For example, furosemide reaches its site of action via tubular secretion. Patients with chronic renal failure exhibit an increased maximal response when the dose is adjusted to the functional status of the kidneys. To achieve an adequate diuretic response, plasma furosemide concentrations must be in- creased by administering larger doses so that adequate amounts of drug reach the site of action. Adjusting the furosemide dose in a patient with renal dysfunction to maintain normal plasma concentrations would not be appropriate because of the altered pharmacodynamic response of furosemide in chronic renal failure.

Several studies of enoxaparin in patients with varying degrees of renal failure have shown that anti-Xa clearance decreases with the degree of renal function. As a result, dosage reduction is recommended in patients with severe renal impairment (i.e., $ClCr<30 ml min^{-1}$).

The effect of renal dysfunction on the pharmacodynamics responses of drugs has not been well studied. However, the examples of furosemide and enoxaparin show that ideally integrated PK/PD studies are needed to evaluate the necessity of dosage adjustment in renal dysfunction.

Principles of Dose Adjustment in Renal Impairment [2]

The level of renal function below which the dose of a drug must be reduced depends on the proportion of a drug eliminated by renal excretion and its toxicity.

For many drugs with only minor or no dose related side effects very precise modification of the dose regimen is unnecessary and a simple scheme for dose reduction is sufficient.

For more toxic drugs with a small safety margin dose regimens based on glomerular filtration rate should be used. When both efficacy and toxicity are closely related to plasma – drug concentration, recommended regimens should be regarded only as a guide to initial treatment. Subsequent doses must be adjusted according to clinical response and plasma – drug concentration.

Renal failure declines with age, many elderly patients have renal impairment but, because of reduced muscle mass, this may not be indicated by a raised serum creatinine. It is wise to assume at least mild impairment of renal function when prescribing for the elderly.

The total daily maintenance dose of a drug can be reduced either by reducing the size of the individual doses or by increasing the interval between doses. For some drugs, although the size of the maintenance dose is reduced it is important to give a loading dose if an immediate effect is required. This is because it takes about five times the half – life of the drug to achieve steady – state plasma concentrations. Because the plasma half – life drugs excreted by the kidney is prolonged in renal impairment it can take many doses for the reduced dosage to achieve a therapeutic plasma concentration. The loading dose should usually be the same size as the initial dose for a patient with normal renal function. Nephrotoxic drugs should, if possible, be avoided in patients with renal disease because the consequences of nephrotoxicity are likely to be more serious when renal reserve already reduced.

Dosage Adjustment in Patients with Renal Dysfunction

Adjustment of the usual drug dosage regimen may be necessary in

patients with renal dysfunction to avoid excessive accumulation of the drug and/or its active metabolite(s) which could result in serious adverse reactions. A dosage regimen is characterized by the maintenance dose (DM) and the dosing interval (τ). The goal is to derive an equation that allows estimation of the maintenance dosing regimen in a patient with renal dysfunction based on a measure of his/her kidney function (KF). The objective is to adjust the usual dosage regimen, by reducing the maintenance dose and/or prolonging the dosing interval, to avoid accumulation of the drug (and/or its active metabolites) in the patient with impaired kidney function.

LITERATURE REVIEW

Md Aslam Ali Hashmi et al[54] (2017) performed a study on Antibiotics requiring dosage adjustment in community acquired pneumonia patients with renal impairment. A prospective and observational study was carried out in a Tertiary care hospital. All community-acquired pneumonia patients with mild to moderate renal impairment were included. The Cockroft-gault formula or MDRD equation was used to calculate creatinine clearance. The mean creatinine clearance values were calculated by t-test and chi-square test was used to test categorical variables. The odds ratio and relative risk were estimated to test the association between antibiotics requiring dosage adjustment and mortality. The proportions of antibiotics requiring adjustment in Community acquired pneumonia patients with renal impairment were high in the present study. It was concluded that large randomized studies particularly focusing on in-hospital mortality of the patients with renal impairment is warranted.

Alok Kumar et al[55] (2016) performed a study on Evaluation of Antibiotic Dose Adjustment in Patients with Renal Insufficiency in a Tertiary Care Centre. The study is retrospective and cross sectional. Records of all patients with renal dysfunction in any department where nephrology unit was consulted were screened. Inclusion criteria were eGFR of < 60ml/minute, age>16 years and administration of at least 1 antibiotic. Prescribed dosage of the drug was compared with dosage recommended by guidelines to assess appropriateness of dose in renal dysfunction. GFR was calculated by Cockcroft Gault equation. This study showed that there was no adjustment done in drug doses in 63% patients with renal insufficiency and 23.9% got adjustment for some drugs. 24 patients (9.9%) developed adverse drug reaction attributable to excessive doses. There is need to create awareness among physicians for drug dose adjustment in renal dysfunction.

Henok Getachew et al[49] (2015) performed a study on Drug dosage adjustment in hospitalized patients with renal impairment at Tikur Anbessa Specialized hospital, Addis Ababa, Ethiopia. A prospective cross-sectional study was carried out in the internal medicine wards. All patients with creatinine clearance ≤59 ml/min admitted to hospital between April and July, 2016 were included in the analysis. 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. The findings indicate that dosing errors were common among hospitalized patients with renal impairment. Improving the quality of drug prescription in patients with renal impairment could be of importance for improving the quality of care.

Fanak Fahimi*a* et al[50] (2012) determined the number of prescribed antibiotics being adjusted and assessed dosing of antibiotics based on the patient's renal function according to distinguished guidelines. The study was conducted at a 446-bed university hospital. One hundred and fifty patients admitted through different wards of the hospital were included in the study. Demographic data were extracted and creatinine clearance was calculated using either Cockcroft- Gault (C&G) or Modification of Diet in Renal Disease (MDRD) formula. In patients with creatinine clearances less than 50 mL/min, antibiotic dosages were compared with guideline dose recommendations to judge whether they were correctly adjusted. Two hundreds and ninety-one instructions (79.9%) of 364 antibiotic prescriptions required dosage adjustment based on the patient's renal condition. These adjustments were rationally performed in 43.7% and 61.4% of prescriptions, according to the two guidelines used. Ciprofloxacin (29.1% of cases), and vancomycin (33.6% of cases), were the most inappropriately prescribed antibiotics in terms of dose administration, and concluded that the drug dosing adjustments should be emphasized in patients with renal dysfunction. Failure to do so may lead to higher morbidity and mortality as well as therapeutic

costs. Estimating creatinine clearance prior to drug ordering and use of a reliable dosing guideline is highly recommended.

Abdul rah man M[51] (2012) the study was conducted to determine whether dose adjustment was taken into account or not when prescribing drugs in patients with renal impairment. A retrospective chart review was performed and included 98 adult in-patients, diagnosed with renal impairment based on clinical evaluation and laboratory data, in King Abdul-Aziz University Hospital (KAUH), Jeddah, Saudi Arabia, who was admitted to the hospital from September 2005 to January 2011. Data of the patients were noted and recorded including baseline demographics, clinical data, laboratory data, renal state, treatment data and medications. The current study confirms that dosage adjustment has to be done for renal impairment when prescribing drugs. Continuous medical education and collaboration with clinical pharmacist should be encouraged for quality improvement in patients with renal impairment.

Sepideh Emami, Hamid Riazi Esfahani[52] (2012) conducted the present observational study was performed on drugs requiring dose adjustment in kidney disease to assess the frequency and potential consequences of overlooked dosage adjustment in hospitalized patients. Medication records and data of 142 patients were collected on random basis. Selected patients with elevated serum creatinine who were prescribed at least one drug needing dose adjustment were kept for further study. Eight hundred and thirty drug orders were evaluated in which dose adjustment was required in 193 (23.2%) of cases. Proper dose adjustments were performed in 88 (45.5%) of cases and not performed in 105(54.4%) orders. According to the study, dose adjustment in renal dysfunction shows a great need for pharmacist involvement in the process to improve drug dosing and avoid adverse drug reactions. Sub-grouping patients according to kidney function and following established dosing guidelines is recommended.

Alahdal and Ahmed[10] (2011) determined whether appropriate dose adjustment was taken into account or not by the physicians when prescribing drug in patients with renal impairment. Retrospective study was performed which includes 98 adult in-patients, diagnosed with renal impairment based on clinical evaluation and laboratory data. 502 drugs were investigated in the present study with an average of six drugs per patient. Of these 502 drugs, 196(39%) required dose adjustment where 92(46.9%) were adjusted and 104(53.1%) were not adjusted. So this study confirms that physicians still do not take into account sufficiently patient's renal function when prescribing drugs. Continuous medical education with clinical pharmacist should be encouraged for quality improvement in patients with renal impairment.

Verbeeck and Flora[2] (2009) described about the pharmacokinetics and dosage adjustment in patients with renal dysfunction. In patients with kidney dysfunction, the activity of several drug metabolizing enzymes, drug transporters and 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. In a patient with renal dysfunction the normal dosage regimen of a drug should be adjusted to get therapeutic effects. Dosage adjustment was estimated on the basis of GFR (glomerular filtration rate) or CrCl (creatinine clearance) using MDRD (modification of diet in renal disease) or Cockroft-Gault formula. Thus this study stated that a pharmacokinetic study should be carried out during the development phase of a new drug that is likely to be used in patients with renal dysfunction and appropriate dosing should be done to reduce toxicity and to get effective therapy.

Hassan et.al.[11] (2008) studied the rate of inappropriate dosing in patients with CKD in a nephrology unit and evaluated the impact on dose adjustment; adverse drug events and drug cost. The authors suggested that appropriate drug

selection and dosing for patients with chronic kidney disease is important to avoid unwanted drug effects and ensure patient outcomes.

Libiszewski[12] **(2008)** described the development of a drug dosage adjustment service for patients with renal impairment. The dosage of nephrotoxic drugs such as gentamicin should ideally be adjusted when they were administered to patients with varying degrees of renal impairment. Such an adjustment of dosage should be estimated with a knowledge of the plasma levels of the drug. Until regular monitoring of drug levels in plasma was routinely available. A service for dosage adjustment of nephrotoxic drugs had been provided in the Macclesfield Health District since December 1977 and has been well received by prescribers in the hospitals. The use of a flow chart scheme for the adjustment of individual dosage for routine use is described. About 80% of the requests were for dosage adjustments of gentamicin in renal failure. It is advocated that such a service can be provided by hospital pharmacists without difficulty and should be encouraged as part of the patient services.

Roblin et al[13] **(2008)** evaluated if Cockcroft and Gault (CG) estimated glomerular filtration rate (eGFR) might be replaced by abbreviated MDRD eGFR for drug dose adjustment. CG eGFR was 61 mL/min vs. 78 mL/min/1.73 m^2 for MDRD ($p < 0.0001$). CG-MDRD difference ranged from − 93 to + 34 mL/min, influenced by patient age, weight, and gender ($p < 0.001$). Authors suggested that CG eGFR cannot be easily replaced by abbreviated MDRD eGFR for drug dose adjustment[12].

Philipneri et al[14] **(2008)** developed a guideline for management of chronic kidney disease (CKD). K/DOQI-consistent measurements of parathyroid hormone (7.1 vs. 0.6%, $P = 0.0002$), phosphorus (38.2 vs. 1.9%, $P < 0.0001$) and quantified urinary protein (23.8 vs. 9.4%, $P = 0.008$) were more common among CKD patients with or without nephrology referral in the administrative data. Nephrology referral correlated with increased likelihood of testing for parathyroid hormone and phosphorus after adjustment for baseline patient factors.

Use of ACEi/ARB medications was more common among patients with nephrology contact (50.0 vs. 30.0%; $P = 0.008$) but appeared largely driven by higher comorbidity burden. The literature review demonstrated similar practice patterns. Authors concluded that Delivery of CKD care may be monitored by administrative data. There was any opportunity for improvement in CKD guideline adherence in practice.

Munar et al[5] **(2007)** reported 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. 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.

Cavanaugh[15] **(2007)** mentioned that Chronic kidney disease (CKD) was common and can be found in up to 23% of patients with diabetes. The recommended haemoglobin A1C goal for these patients is also < 7.0%. Medication therapy for diabetes may require dose adjustments or may be contraindicated in patients with CKD. Assessment and management of comorbid diseases, including hypertension, hyperlipidemia, anemia, hyperphosphatemia, and hyperparathyroidism, was important in the care of patients with diabetes and CKD. Multidisciplinary care may provide the optimal system for maximizing care of these complex patients.

Marr[16] **(2007)** prepared a guideline for Antibiotic dosing in renal impairment.

Shyam et al[17] **(2007)** reported the need of national action plan for minimizing the progression of CKD. Author suggested that a Government-supported programme should be initiated for the large expanding ESRD population. Simultaneously efforts should be made to plan and initiate a

prevention/control program for CKD. To pick up CKD at an early stage, steps should be initiated to promote methodology for standardization and estimation of glomerular filtration rate (GFR) rather than serum creatinine in clinical laboratories. Such data would prompt and enable physicians to pick up CKD at an earlier stage, improve the opportunity for early referral of CKD patients to nephrologists to minimize progression of CKD.

Blix et al[4] (2006) investigated the use of renal risk drugs in renally impaired patients in general hospitals and analysed the relationship to demographic factors, risk factors and occurrence of drug-related problems. Of the 808 included patients, 293 (36%) had normal renal function (stage 1), 314 (39%) had mild RI (stage 2), 160 (20%) had moderate RI (stage 3), 35 (4%) had severe RI (stage 4) and six (0.7%) had kidney failure (stage 5). Mean number of drugs used per patient in patients with RI (stages 3, 4 and 5) and patients evaluated to have adequate renal function relative to drug therapy (stages 1 and 2). All but six patients with RI stages 3, 4 and 5 used two or more renal risk drugs. 124 (62%) of the patients with RI stages 3, 4 and 5 had DRPs linked to the renal risk drugs, and 26% of the renal risk drugs were associated with DRPs. In patients with reduced renal function, renal risk drugs were widely used and often in combination. DRPs were frequently associated with the use of renal risk drugs.

Dijk et al[18] (2006) analysed the incidence of required versus implemented dosage adjustments according to guidelines in patients with renal insufficiency at discharge and evaluated specific determinants responsible for the percentage of overlooked dosage adjustments. At discharge, 237 of 647 (36.6%) patients had a calculated creatinine clearance less than 51 mL/min/1.73 m^2. Dosage adjustment based on renal function was necessary in 411 of 1718 (23.9%) of prescriptions. These adjustments were performed in 242 (58.9%) prescriptions and not performed in 169 (41.1%) cases. The risk of not adjusting the dosage was significantly associated with drugs producing severe consequences when dosing guidelines were overlooked ($p < 0.05$). In patients with a calculated creatinine

clearance less than 51 mL/min/1.73 m^2, dosing according to their renal function can be improved; an alert system could help prescribers and pharmacists to adapt drug dosage in patients with renal impairment.

Joshi[9] **(2006)** marked variability in drug responsiveness especially in critically ill patients admitted in the Intensive care units. In order to obtain therapeutic effectiveness with in pharmacokinetic parameters related to therapeutic dose, it is always desirable to monitor and to maintain drug dose adjustment in such a way especially in presence of organ failure like renal failure, hepatic failure or any other clinical situation necessitating Therapeutic Drug Monitoring (TDM) so that one can use safe and effective drug therapy with least toxicity due to inaccurate and invalid drug doses.

Levey et al[19] **2006** described the performance of the revised 4-variable MDRD Study equation and compare it with the performance of the 6-variable MDRD Study and Cockcroft–Gault equations. Mean measured GFR was 39.8 mL/min per 1.73 m^2 (SD, 21.2) Accuracy and precision of the revised 4-variable equation were similar to those of the original 6-variable equation and better than in the Cockcroft–Gault equation, even when the latter was corrected for bias, with 90%, 91%, 60%, and 83% of estimates within 30% of measured GFR, respectively. Differences between measured and estimated GFR were greater for all equations when the estimated GFR was 60 mL/min per 1.73 m^2 or greater. The 4-variable MDRD Study equation provides reasonably accurate GFR estimates in patients with chronic kidney disease and a measured GFR of less than 90 mL/min per 1.73 m^2.

Vidal et al[20] **(2005)** compared four sources of drug information regarding adjustment of dose for renal function. The four sources differed in their recommendations for adjustments of dosage and dosing interval. They vary in their definitions of renal impairment; some were qualitative and remain unclear. All sources provide only a general description; the methods on which the advice is based and references for original data are rarely presented. The remarkable

variation in definitions and recommendations, along with scarce details of the methods used to reach this advice, maid the available sources of drug information ill-suited for clinical use. Authors noted that advice on drug prescription, dose and dosing interval, contraindications, and adverse effects should be evidence based.

Ricci et al[21] **(2005)** observed the practice patterns in the management of acute renal failure in the critically ill patient. More than 200 different definitions of ARF and about 90 RRT start criteria were reported. In 10% of centres all forms of renal replacement techniques were available, and in 70% of cases two or more different techniques were available: absolute analysis of different techniques showed that continuous renal replacement therapies were utilized by 511 specialists (91%), intermittent haemodialysis by 387 (69%) and sustained low efficiency dialysis by 136 (24%). Treatment prescription showed significant differences among specialists, 60% of intensives being uncertain on RRT dose prescription compared to 40% of nephrologists (P = 0.002). New classifications such as RIFLE criteria might improve well-known uncertainty about ARF definition. Different RRT techniques are available in most centres, but a general lack of treatment dose standardization is noted. Non-renal indications to RRT still need to find a definitive role in routine practice.

Ararwal et al[22] **(2005)** mentioned that Chronic renal failure (CRF) is a debilitating condition responsible for high morbidity and mortality and was a financial burden on government and society. Because of its costs and the complexity of its treatment, proper care is available to very few patients in India. A community-based study has not been done to determine the prevalence of CRF in India. Results. A total of 4972 persons were contacted for the study. Their mean age was 42±13 years; 56% were males. Out of the 4972 who were initially approached, 4712 agreed to give the blood sample, and thus were included for the evaluation of CRF. CRF was found in 37 of them. Thus, the prevalence of CRF in that adult population was 0.785% or 7852/million. In conclusion, the prevalence of CRF in India makes it a serious problem in need of urgent efforts to control it.

Bailie et al[23] **(2004)** evaluated the analgesic prescription patterns among hemodialysis patients. Our results highlight that analgesics may be underprescribed in the hemodialysis population. With respect to prevention of chronic kidney damage, the National Kidney Foundation's position paper suggests acetaminophen as the nonnarcotic agent of choice for episodic use, although habitual use, and use of combination analgesic products, should be discouraged. It is possible, although uncertain, that this recommendation has lead to a more cautious use of analgesics in general in patients with kidney disease and resulted in potential under-prescription. The safest approach to the management of pain in dialysis patients may be the use of short courses of analgesics, where possible. Extra vigilance is warranted for potential adverse effects of all analgesics in dialysis patients. The extreme variability in facility practice suggests that patients and clinicians should be educated about the need to appropriately prescribe analgesics. Patients should understand that optimal pain management was an acceptable expectation, and clinicians should examine reasons for any reluctance on their part to prescribe analgesics. The refinement of existing World Health Organization guidelines regarding analgesic use in dialysis patients may be necessary to improve pain management and quality of life for this population. Changes might be necessary to reflect appropriate choices of analgesics, statements about combination products, and perhaps education about methods for assessment of appropriate analgesia.

Nurko[25] **(2004)** published Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Most patients with advanced chronic kidney disease (CKD) develop hypertension. Most classes of antihypertensive medication can be used to treat patients with CKD. The general approach for prescribing drugs in CKD had been either to decrease the maintenance dose without changing dosing intervals, or to keep the usual dose but prolong the dosing intervals, or use of a combination of these interventions. Each drug should be evaluated individually.

Manley et al[26] **(2004)** compared haemodialysis (HD) patient medication prescribing patterns between the Dialysis Clinic, Inc. (DCI) database and the United States Renal Data System report. There were 128 477 medication orders categorized in 10 474 patients. DCI patient demographics were similar to present USRDS patients except for fewer Hispanics (P<0.001). Patients were prescribed 12.3±5.0 (median 12) different medications (2.6±1.4 clinic medications and 10.0±4.5 home medications). This is higher than reported by USRDS (median 9 medications). Patient age did not influence number of medications used (P = 0.54). DM patients were prescribed more medications than non-DM (13.3±5.0 DM *vs* 11.6±4.8 non-DM; P<0.00001). The data suggested that medication prescribing patterns in HD patients have changed. The audit identified appropriate and questionable prescribing patterns. Various prescribing patterns identified areas for improvement in care (e.g. increased use of aspirin, beta-blockers and hyperlipidaemia medications) and areas requiring further investigation (e.g. high use of anti-acid, benzodiazepine and non-aluminum/non-calcium phosphate-binding medications).

Salamon et al[41] **(2003)** determined the frequency and potential consequences of lack of dosage adjustment in hospitalized patients with renal impairment. 202 order sheets were completed for 164 patients. They totalled 1469 lines of prescription, 85% of which were TEM medications, with guidelines for dosage adjustment for 71% of them (n=886). Of these 886 prescriptions, 34% were inappropriate, 14% being contraindicated and 20% with inappropriate dosage given the patient's renal function. Among the 202 order sheets, 75% included at least one appropriate prescription. 63% included at least 1 prescription with potentially adverse consequences, 3% of these had potential fatal or severe consequences. The study confirmed that physicians do not take into account sufficiently patient renal function when prescribing. Improving the quality of drug prescription in patients with renal impairment could be of importance for improving the quality of life.

Levey et al[7] **(2003)** evaluated the usage of the Guidelines for Chronic KidneyDisease: Evaluation, Classification, and Stratification in US population and reported that Chronic kidney disease affects approximately 11% of the U.S. adult population (20 million people from 1988 to 1994). The prevalence of earlier stages of disease (10.8%) is more than 100 times greater than the prevalence of kidney failure (0.1%). Adverse outcomes of chronic kidney disease, including loss of kidney function and development of kidney failure and CVD, can often be prevented or delayed through early detection and treatment. In particular, physicians should consider using interventions to slow the progression of kidney disease in all patients with chronic kidney disease and should place patients with chronic kidney disease in the highest-risk group for CVD risk factor reduction and other treatments for CVD.

Pillans et al[27] **(2002)** observed whether appropriate dosage adjustments were made in patients with significant renal impairment for drugs with a high fractional renal clearance. Doses were found to be inappropriately high in 105 (42.2%) of 249 admission prescriptions of the targeted drugs. Doses were appropriately reduced in hospital in 32 patients (30.4%). Seventy-three (29.3%) prescriptions were continued with excessive doses. Only 34 prescriptions for the target drugs were initiated in hospital, of which 88.2% were appropriately dosed. A significant percentage of patients with renal impairment are admitted to hospital on inappro priately high doses of drugs, with a high fractional renal excretion and low therapeutic index. Doses are appropriately reduced in hospital in some patients but there is still room for improvement.

Falconnier et al[8] **(2001)** examined the impact of immediate concurrent feedback on dose adjustment in patients with renal failure. Overall, 17% of the patients had atleast 1 estimated creatinine clearance ≤50 mL/min. In the intervention group, the dose of 81% of renally eliminated drugs was adjusted to renal function, compared with 33% in the control group. The propotion of doses renally eliminated drugs adjusted to renal function can be substantially increased

by immediate concurrent feedback. This saves drug costs and has the potential to prevent adverse drug reactions.

Chertow et al[28] **(2001)** explained a system application for adjustment for dose and frequency in patients with renal insufficiency. A total of 7490 patients were found to have some degree of renal insufficiency. In this group, 97151 orders were written on renally cleared or nephrotoxic medications, of which 14440 (15%) had at least 1 dosing parameter modified by the computer based on renal function. The fraction of prescriptions deemed appropriate during the intervention vs control periods by dose was 67% vs 54% (*P*=.001) and by frequency was 59% vs 35% (*P*=.001). Guided medication dosing for inpatients with renal insufficiency appears to result in improved dose and frequency choices. This intervention demonstrates a way in which computer-based decision support systems can improve care.

Sturmer et al[29] **(2001)** evaluated the interference of Nonsteroidal anti-inflammatory drugs (NSAIDs) on renal function, but little is known about the effects of the half-life of these agents, or the use of other medications, on renal function. The result of the use of NSAIDs with a half-life of 4 or more hours (OR = 2.6; 95% CI: 1.2 to 5.7). Patients who used diuretics with NSAIDs (OR = 3.7; 95% CI: 1.7 to 8.3) or without NSAIDs (OR = 3.5; 95% CI: 1.6 to 7.6) had a higher risk of impaired renal function than did patients using NSAIDs alone (OR = 1.6) or none of these drugs (reference). A similar but less pronounced pattern was observed for ACE inhibitors. NSAID-associated impaired renal function seems to be mainly the result of compounds with intermediate-long half-life. It was evidenced that the adverse effects of diuretics and ACE inhibitors on renal function were greater in those who also used NSAIDs.

SCOPE OF STUDY

Kidney disease is a common, progressive illness that is becoming a global public health problem. Kidney disease rank third amongst life threatening disease after cancer and cardiac ailments. Older patients were at higher risk of developing a decline in renal function and the use of multiple medications to treat comorbid conditions. Indeed, the incidence of chronic kidney disease (CKD) is increasing alarmingly in most industrialized countries. For e.g. the prevalence of CKD among the Indian adult population was recently estimated to be > 13% (>25 million adults), and the number of patients with ESRD alone has risen from 209,000 in 1991 to 472,000 in 2004 whereas glomerulonephritis was one of the leading causes of kidney disease several decades ago.[2]

Chronic kidney disease can affect glomerular blood flow and filtration, tubular secretion and reabsorption and renal bio activation and metabolism. Drug absorption, bioavailability, protein binding, distribution volume, and non-renal clearance (metabolism) also can be altered in this patients.[5]

The adjustment of drug dosage to individual patient requirements can maximize therapeutic efficacy and minimize the adverse drug reactions. Dosages of drugs cleared renally are based on the renal function. The calculations are valid only when renal function is stable and serum creatinine level is constant. A dose adjustment in renal failure is especially critical because parent compounds or active metabolites can accumulate and cause additional morbidity and costs.

CKD is a progressive condition marked by deteriorating kidney function. The GFR which is most frequently estimated by using the equation Cockroft-Gault that incorporates serum creatinine concentration along with demographic data is the most commonly used index of overall kidney function.

The need for appropriate dose reduction in patients with renal failure is illustrated by earlier studies in which ranitidine-associated central nervous system (CNS) adverse drug reaction occurred more frequently in patients with renal impairment and the incidence of imipenem/cilastatin – associated seizures was reduced after dosage adjustment to renal function.[8] Munepa et al.[32] reported 37.6% of potential dosing errors in the drugs prescribed for azotemic patients in

the medical wards of KholKaen hospital Thailand. Literature reveals that only few studies have assessed drug prescriptions and dosage adjustments in renal impairment.[8]

Renal dysfunction affects more than just the renal clearance of drugs and /or active metabolites. A general guideline for administering drugs to patients with renal dysfunction is that when *fe* (fraction of the drug excreted unchanged in the urine) is >0.3, a dosage adjustment is most likely required at least in patients with severe renal impairment (ClCr<30mLmin^{-1}. Also, patients with chronic renal failure have serious health problems and require multiple medications. Obviously, extra cautions warranted when prescribing drugs with narrow therapeutic index.[2]

Many drugs which are prescribed to renal impaired patients like cephalosporins, aminoglycosides, fluroquinolones, beta-blockers, diuretics and hypoglycemic agents are eliminated primarily unchanged through the renal route. These drugs will create complications due to drug accumulation and should be adjusted to optimize the therapy. Dose adjustment in renal impairment can easily be achieved by estimating creatinine clearance based on serum creatinine; and adjusting dose and/or dose interval. Dose adjustment in patients with renal failure reduce both the cost of the drug therapy and the risk of adverse drug reaction.[8]

Literature reveals that only few studies have assessed drug prescriptions and dosage adjustments in renal impairment, hence the proposed study entitled **"Dosage individualization of anti microbials and cardiovascular drugs in patients with chronic renal dysfunction"** with the following objectives have been undertaken.

OBJECTIVES

The aims of the present study are,

- To understand the prescribing pattern of antimicrobials and cardiovascular drugs in patients with renal function impairment.

- To understand drug dosage individualization of all renally excreted antimicrobials and cardiovascular drugs that necessitates dosage adjustment in patients with renal function impairment.

PLAN OF THE STUDY

The proposed study entitled **"Dosage individualization of anti microbials and cardiovascular drugs in patients with chronic renal dysfunction"** was planned and carried out as given below,

Phase 1 (December 2018)

- ✓ Identification of research problem and scope of the study.
- ✓ Preparation of study protocol.
- ✓ Obtaining consent from the hospital authorities.
- ✓ Literature survey

Phase 2 (January 2018 to July 2018)

- ✓ Design of structured proforma.
- ✓ Patient selection, inclusion/exclusion criteria.
- ✓ Data retrieval from general medicine department.
- ✓ Estimating renal function status, evaluation of drug dosage appropriateness of all potentially nephrotoxic/ renally eliminated drugs.
- ✓ Drug dosage adjustments.

Phase 3 (August 2018)

- ✓ Data analysis.
- ✓ Report submission.

METHODOLOGY

Study design: Prospective descriptive study.

Study site: General medicine department of a 700 bedded multispecialty tertiary care teaching hospital.

Study period: 9 months (December 2017– August 2018).

Inclusion Criteria: Patients with estimated serum creatinine value more than 1.7mg/dL (Normal range: 0.8 – 1.2 mg/dL), prescribed with at least one antimicrobial drug or cardiovascular drug or both are included in the study.[37]

Exclusion Criteria: Patients with estimated serum creatinine value more than 1.7mg/dL but with no antimicrobial drug or cardiovascular drug in the prescription are excluded from the study. Patients who are not willing to participate in study are excluded.

Major outcome measure: The number or percentage of antimicrobial and cardiovascular drug dosage regimens adjusted to renal function.

Methods: The study protocol was approved by institutional review board (Annexure-I). Patients with impaired renal function were identified based on laboratory data and clinical evaluation. Verbal consent was obtained from each subject before initiating the study. Structured proforma (Annexure-II) were used to collect various clinical and demographic details of the patient such as age, gender, body weight, length of hospital stay, primary diagnosis, serum urea and creatinine levels. Treatment data including prescribed drugs, dosages, frequency and route of administration were also recorded.

For all prescribed drugs, the fraction of the bioavailable dose which is eliminated extra-renally (Q_0) was obtained from literature. Dose adjustments was considered mandatory for those drugs with at least 70% of bioavailable, active form of drug is eliminated by the kidney in unchanged form ($Q_0 \leq 0.3$) as well as other potentially nephrotoxic drugs for which dose adjustment is recommended in the literature.

Creatinine clearance was calculated by using Cockroft-Gault equation.[40]

$$\mathbf{CrCl} = \frac{(140 - \text{age}) \times \text{Weight in kg}}{\text{Sr. Cr} \times 72}$$

Instead of creatinine clearance, GFR was calculated by using Modification of Diet in Renal Disease (MDRD) whenever patient's weight was not available.[37]

$$\mathbf{GFR} = 186.3 \times (\text{Serum creatinine})^{-1.154} \times (\text{Age})^{-0.203} \times 0.742(\text{Female})$$

For obese patients for whom actual body weight (ABW) was more than 120% ideal body weight (IBW), the dosing weight was calculated[40] before using Cockroft-Gault equation.

$$IBW\ for\ male\ patients = [Height\ (cm) - 80] \times 0.7$$

$$IBW\ for\ female\ patients = [Height\ (cm) - 70] \times 0.6$$

$$Dosing\ Weight = (ABW - IBW) \times 0.4 + IBW$$

Creatinine clearance, eGFR and IBW were calculated using Micromedex software.[REF] After determining the degree of renal insufficiency the patients was classified according to their stages of renal impairment as recommended by National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI)[43] and Food Drug Administration (FDA).[4]

Stage	Description	eGFR(mL/min/1.73m^2)	CLcr(mL/min
1	Control (normal)	≥ 90	≥ 90
2	Mild decrease in GFR	60 – 89	60 - 89
3	Moderate decrease in GFR	30 – 59	30 – 59
4	Severe decrease in GFR	15 – 29	15 – 29
5	End Stage Renal Disease (ESRD)	<15 not on dialysis	<15 not on dialysis
		Requiring dialysis	Requiring dialysis

After estimating creatinine clearance the dose of the medication of interest was then evaluated using the published drug dosing guidelines for the patient's individual degree of renal impairment.[40,45,46] Each medication was then categorized as either 'dose adjusted' if its dosing was found within the target range or 'dose not adjusted' if the prescribed dose exceeded the relevant dose threshold.

When necessary, the new dosages or dosing intervals were accurately estimated by using the following formula: [44]

$$\text{New Dose} = \frac{\text{Patient's CrCl} \times \text{Normal Dose}}{\text{Normal CrCl}}$$

$$\text{New Dosing Interval} = \frac{\text{Normal CrCl} \times \text{Normal Dose}}{\text{Patient's CrCl}}$$

RESULTS

A total of 1016 drugs in 103 patients were evaluated in the present study with a mean of 10.13 ± 3.26 drugs per patient. The mean age of the study population was 58.42 ± 12.69(range 32 to 83yrs) with 70.87% male patients. Their mean Serum creatinine level was 5.48 mg% ± 3.04 (range 2.0 to 8.2 mg/dl) and mean creatinine clearance was 18.51mg/ml ± 10.05(range 8.47 to 34.8 ml/min). Demographic details of these patients are shown in Table 1. Most of the patients (54.36%) were in the late adulthood (51-65yrs) and followed by adulthood (13.5%) which is shown in Table 2. The major diagnoses were renal failure (96.0%), hypertension (58.0%) and diabetes mellitus (34%). About 84% of patients had multiple co-morbidities. Table 3 shows the major diagnosis of all the patients.

The stage distributions of renal impairment as per FDA are shown in Table 4; none of the patients selected had mild renal impairment; 13 had moderate, 17 had severe renal impairment and 20 had end stage renal dysfunction (ESRD).

It was found that 17.59% of the prescribed drugs were renally eliminated with at least 70% of the drugs in unchanged form (ie. $Q_0<0.3$) or potentially nephrotoxic. On an average each patient with a renal failure received about 2 renally eliminated drug ($Q<0.3$) or nephrotoxic drugs.

Vitamins and mineral supplements were most commonly prescribed (84%). The major drug category prescribed was antibiotics (13.04%), antihypertensives (11.07%) and antiulcer drugs (9.29%). The prescribing patterns of renally eliminated drugs are shown in Table 5 to 27. About 16% of patients were prescribed with 13 drugs and 12.24% with 12 drugs each. Figure 1 illustrated the number of drugs prescribed per patients.

Among the 1016 evaluated drugs, 98 (9.64%) required dose adjustments. Of these dose of 244 (24.01%) were adjusted at the time of prescribing and 83 (8.16%) were not adjusted. The prescribed drugs with dosages not adjusted and those with contraindications in renal impairment are detailed in Table 28.

Major category of errors identified were overdose (61.53%), and wrong frequency of administration (23.07%). About 8% of the drugs were to be avoided strictly in renal impairment as per the available evidences. (Table 29) Further 95% of the patients needed dosage adjustment for at least one drug prescribed.

It was found that 29.85% of prescribed drugs had drug-drug interactions. The most common interacting drugs were identified as torsemide vs. pantoprazole and ceftriaxone vs. torsemide. These were found in 4.17% and 2.78% of patients respectively. Interactions which can directly affect kidney function were also observed in 4 cases. (Table 30)

Out of 1016 drugs prescribed 13.59% of drugs had narrow therapeutic index. These were prescribed in 18% of patients. Theophylline (7.76%), digoxin (3.88%), prazosin (1.94%) and amikacin (4.85%) were the drugs with narrow therapeutic index (Table 31).

Table 1: Demographic Data

S.No	Parameters	Value
1.	N	103
2.	Age	32-84years
3.	Male, n (%)	73(70.87%)
4.	Female (%)	30 (29.12%)
5.	Body Weight	52-74kg
6.	Serum creatinine	2.8-8.7mg/dL
7.	Creatinine clearance	8.51mg/ml-35.6mg/ml

Table 2: Age distribution (N=103)

S.No	Age (years)	No. of patients	Percentage (%)
1.	Adolescents (13-18yrs)	NIL	NIL
2.	Early adulthood (19-35yrs)	3	2.9%
3.	Adulthood (36-50yrs)	14	13.5%
4.	Late adulthood (51-65yrs)	56	54.3%
5.	Young old (66-74yrs)	29	28.1%
6.	Old (75-84yrs)	1	0.9%
7.	Old old >85yrs	NIL	NIL

Table 3: Clinical conditions of patients (N=103)

S. No.	Clinical conditions	No. of Patients	Percentage (%)
1.	Renal Failure	98	95.14%
2.	Hypertension	84	81.55%
3.	Diabetes Mellitus	85	82.52%
4.	Pott's spine	12	11.65%
5.	COPD	8	7.76%
6.	Gout	5	4.85%
7.	CAD	6	5.82%
8.	CVD	9	8.73%
9.	CHF	42	40.77%
10.	Asthma	12	11.65%
11.	Anemia	2	1.94%
12.	Hypothyroidism	2	1.94%
13.	CVA	4	3.88%
14.	IHD	1	0.97%

Table 4: Stages of Renal impairment (N=103)

Stages	No. of Patients	Percentage (%)
Normal (>80ml/min)	0	0
Mild (60 – 79ml/min)	0	0
Moderate (30 – 49ml/min)	20	19.41%
Severe (15 – 29ml/min)	46	44.66%
ESRD (<15ml/min)	37	35.92%

Table 5: Prescribing pattern of renally eliminated drugs (N=1016)

No.	Category	Total Drugs	Percentage (%)	No. of Patients	Percentage (%)
1.	Vitamins & minerals	87	8.56%	42	40.77%
2.	Antibiotics	76	7.48%	40	38.83%
3.	Antihypertensives	69	6.79%	42	40.77%
4.	Antiulcer	57	5.61%	41	39.80%
5.	Antiasthmatic	42	4.13%	28	27.18%
6.	Analgesics	44	4.33%	22	21.35%
7.	Antidiabetics	43	4.23%	27	26.21%
8.	Diuretics	41	4.03%	23	22.33%
9.	Antiemetics	38	3.74%	24	23.30%
10.	Hematopoietic Agents	26	2.55%	15	14.56%
11.	Sedatives	21	2.06%	13	7.76%
12.	Anticoagulants	21	2.06%	19	10.67%
13.	Uricosuric agents	19	1.87%	12	11.65%
14.	Anti Hyperlipidemic	9	0.88%	9	8.73%
15.	Laxatives	8	0.78%	8	7.76%
16.	Anticonvulsants +Antianxiety	6	0.59%	6	5.82%
17.	Cortisones	5	0.49%	5	4.85%
18.	Antianginal	16	1.57%	7	6.79%
19.	Hepatoprotective	4	0.39%	4	3.88%
20.	Antiallergic	3	0.29%	3	2.91%
21.	Antidiarrheal	1	%	1	0.97%
22.	Cardiac glycosides	4	0.39%	4	3.88%

Table 6: Antihypertensives prescribed (N=196)

S. No.	Drugs	Dosing Regimen	No. of Patients	Percentage (%)
1.	Amlodipine	2.5 mg OD/ 5mg OD	37	18.87%
2.	Nebivolol	2.5 mg OD/5mg OD	22	11.22%
3.	Metoprolol	25mg OD/ 50mg OD	30	15.30%
4.	Telmisartan	20mg OD/ 40mg OD	27	13.77%
5.	Ramipril	2.5mg OD/5mg OD	4	2.04%
6.	Carvedilol	3.125mg OD/ 12.5mg OD/25mg OD	1	0.51%
7.	Nifedipine	2.5 mg OD/ 5mg OD	18	9.18%
8.	Metolazone	5mg OD	1	0.51%
9.	Clonidine	100mcg OD	1	0.51%
10.	Atenolol	25mg OD/ 50mg OD	1	0.51%
11.	Prazosin	2.5mg OD	8	4.08%
12.	Clinidipine	5mg OD, 10mg OD	32	16.32%
13.	Slidenafil	20mg BD	14	7.14%

Table 7: Antiulcer drugs prescribed, (N=57)

S.No	Drugs	Dosing Regimen	No. of Patients	Percentage (%)
1	Pantoprazole	40 mg OD	49	85.96%
2	Sucralfate	500mg/5ml BD	2	3.50%
3	Rabeprazole	20mg BD	2	3.50%
4	Esomeprazole	20 mg BD	4	7.01%

Table 8: Antibiotics prescribed (N=138)

S. No.	Drugs	Dosing Regimen	No. of Patients	Percentage (%)
1.	Ceftriaxone	1g BD	30	21.73%
2.	Meropenem	1gm BD	16	11.59%
3.	Ornidazole	500mg OD	1	0.72%
4.	Piperacillin + tazobactum	4.5g OD	29	21.01%
5.	Ceftriaxone + Sulbactum	1.5g OD	16	11.59%
6.	Ofloxacin	200mg OD	4	2.89%
7.	Pyrazinamide	500mg BD	12	8.69%
8.	Levofloxacin	500mg OD	5	3.62%
9.	Amoxicillin + clavulnate	625mg OD	1	0.72%
10.	Ciprofloxacin	500mg OD	5	3.62%
11.	Amikacin	250mg OD	5	3.62%
12.	Cefipime + Tazobactum	1.5mg OD	1	0.72%
13.	Rifampicin +Isoniazid	400mg OD	13	9.42%

Table 9: Diuretics prescribed (N=76)

S.No	Drugs	Dosing Regimen	No. of Patients	Percentage (%)
1.	Furosemide	40mg OD	27	35.52%
2.	Torsemide	10mg BD	23	30.26%
3.	Spirinolactone	25mg OD/ 50 mgOD	17	22.36%
4.	Metalazone	2.5mg OD	7	9.21%
5.	Hydrochlorthiazide	12.5mg OD	2	2.63%

Table 10: Antiasthmatic drugs prescribed (N=42)

S.No	Drugs	Dosing Regimen	No. of Patients	Percentage (%)
1.	Salbutamol / Albuterol	100mcg/puff	22	52.38%
2.	Theophylline+ Etofylline	100mg BD	5	11.90%
3.	Ipratropium Br	20mcg/puff	4	9.52%
4.	Doxofylline	400mg OD	3	7.14%
5.	Budesonide	200mcg/puff	4	9.52%
6.	Monteleukast	10mg BD	2	4.76%
7.	Bromhexine	4mg/ml	1	2.38%
8.	Ambroxol	30mg/5ml	1	2.38%

Table 11: Analgesics Prescribed (N=44)

S.No	Drugs	Dosing Regimen	No. of Patients	Percentage (%)
1.	Paracetamol	650mg TDS	26	59.09%
2.	Tramadol	50mg/75mg BD	7	15.90%
3.	Aspirin	75mg OD	6	13.63%
4.	Diclofenac	75mg/100mg BD	5	11.36%

Table 12: Antidiabetic drugs prescribed (N=65)

S.No	Drugs	Dosing Regimen	No. of Patients	Percentage (%)
1.	Insulin	10-15 U	25	38.46%
2.	Metformin	250mg/500mgOD	9	13.84%
3.	Linagliptin	5mg OD	23	35.38%
4.	Glipizide	2.5mg OD	7	10.76%
5.	Pioglitazone	100mg OD	1	1.53%

Table 13: Antiemetics Prescribed (N=67)

S.No	Drugs	Dosing Regimen	No. of Patients	Percentage (%)
1.	Ramosetron	0.3mg TDS	6	8.95%
2.	Ondansetron	4mg BD	49	73.13%
3.	Domperidone	30mg BD	11	16.41%
4.	Betahistine	10mg BD	1	1.49%

Table 14: Laxatives prescribed (N=10)

S.No	Drugs	Dosing Regimen	No. of Patients	Percentage (%)
1.	Lactulose	3.35g/5ml	6	60%
2.	Bisacodyl	5mg /ml	4	40%

Table 15: Sedatives prescribed (N=16)

S.No	Drugs	Dosing Regimen	No. of Patients	Percentage (%)
1.	Alprazolam	0.25mg/0.5mg HS	4	25%
2.	Clonazepam	0.25mg/1mg HS	6	37.5%
3.	Clobazam	5mg HS	5	31.25%
4.	Lorazepam	1mg/2mg HS	1	6.25%

Table 16: Anticoagulants prescribed (N=68)

S.No	Drugs	Dosing Regimen	No. of Patients	Percentage (%)
1.	Clopidogrel	75mg/150mg OD	28	41.17%
2.	Enoxaparin	40mg	20	29.41%
3.	Heparin	5000IU	20	29.41%

Table 17: Anticonvulsants prescribed (N=6)

S.No	Drugs	Dosing Regimen	No. of Patients	Percentage (%)
1.	Chlordiazepoxide	10mg BD	1	16.66%
2.	Pregabilin	150mg OD	5	83.33%

Table 18: Corticosteroids Prescribed (N = 5)

S.No	Drugs	Dosing Regimen	No. of Patients	Percentage (%)
1.	Hydrocortisone	100mg BD	2	40%

2.	Methyl prednisolone	10mg BD	2	40%
3.	Deflazacort	1mg/ 6mg BD	1	20%

Table 19: Antiallergic drugs prescribed (N=3)

S.No	Drugs	Dosing Regimen	No. of Patients	Percentage (%)
1.	Hydroxazine	25mg OD	1	33.33%
2.	Levocitrizine	5mg OD	2	66.66%

Table 20: Hematopoetic agents prescribed (N=26)

S.No	Drugs	Dosing Regimen	No. of Patients	Percentage (%)
1.	Folic acid	5mg BD	17	65.38%
2.	Ferrous Ascorbate	600mg OD	6	23.07%
3.	Ferrous Fumarate	600mg OD	3	11.53%

Table 21: Urecosuric agents prescribed (N =33)

S.No	Drugs	Dosing Regimen	No. of Patients	Percentage (%)
1.	Febuxostat	40mg BD	32	96.96%
2.	Allopurinol	100mg BD	1	3.03%

Table 22: Antihyperlipidemics prescribed (N=58)

S. No.	Drugs	Dosing Regimen	No. of Patients	Percentage (%)
1.	Atorvastatin	10mg/20mg OD	36	62.06%
2.	Rosuvastatin	5mg/10mg OD	13	22.41%

Table 23: Hepatoprotective prescribed (N=43)

S. No.	Drugs	Dosing Regimen	No. of Patients	Percentage (%)
1.	Silymarin	70mg/140mg BD	22	51.16%
2.	Ursodeoxycholic acid	300mg OD	21	48.83%

Table 24: Antianginals prescribed (N =40)

S. No	Drugs	Dosing Regimen	No. of Patients	Percentage (%)
1.	Isosorbide mono nitrate	5mg/10mg OD	22	55%
2.	Trimetazidine	35mg BD	18	45%

Table 25: Antidiarrhoeals prescribed (N= 3)

S.No	Drugs	Dosing Regimen	No. of Patients	Percentage (%)
1.	Racecadotril	100mg OD	3	100%

Table 26: Vitamins & Minerals prescribed (N=135)

S.No	Drugs	No. of Patients	Percentage (%)
1.	Multivitamin	57	42.22%
2.	Mecobalamin	32	23.70%
3.	Sodium Bicarbonate	11	8.14%
4.	Alfacalcidol	2	1.48%
5.	Calcium Carbonate	9	6.66%
6.	Calcium Gluconate	1	0.74%
7.	Calcium + D3	3	2.22%
8.	Calcitriol	18	13.33%
9.	Potassium chloride	1	0.74%
10	Calcium Acetate	1	0.74%

Table 27: Cardioglycosides prescribed (N=4)

S. No	Drugs	Dosing Regimen	No. of Patients	Percentage (%)
1.	Digoxin	0.25mg OD	4	100%

Table 28: Miscellaneous (N=121)

S.No	Drugs	No. of Patients	Percentage (%)
1.	Alpha Ketoanalogue	27	22.31%
2.	Preprobiotics	22	18.18%
3.	Chloroquine	1	0.82%
4.	Lactic acid	21	17.35%
5.	Sevelamer carbonate	1	0.82%
6.	Doxepin	1	0.82%
7.	Dimethicone + Pancretin	1	0.82%
8.	Thyroxine	2	1.65%
9.	Clotrimazole	1	0.82%
10.	N-acetyl Cystine + Taurine	3	2.47%
11.	Buclizine	1	0.82%
12.	Ursodeoxycholic acid	3	2.47%
13.	Geroz o	15	12.39%
14.	Tranexamic acid	1	0.82%
15.	Lanthanum carbonate	1	0.82%
16.	Calcitrol	33	27.27%
17.	Serratiopeptidase	1	0.82%
18.	Dextromatharpan	21	17.35%
19.	Sodium dihydrogen citrate	1	0.82%
20.	Albendazole	1	0.82%
21.	EPOETIN 4000IU	12	9.91%

Fig: 1: NO. OF DRUGS PRESCRIBED PER PATIENT

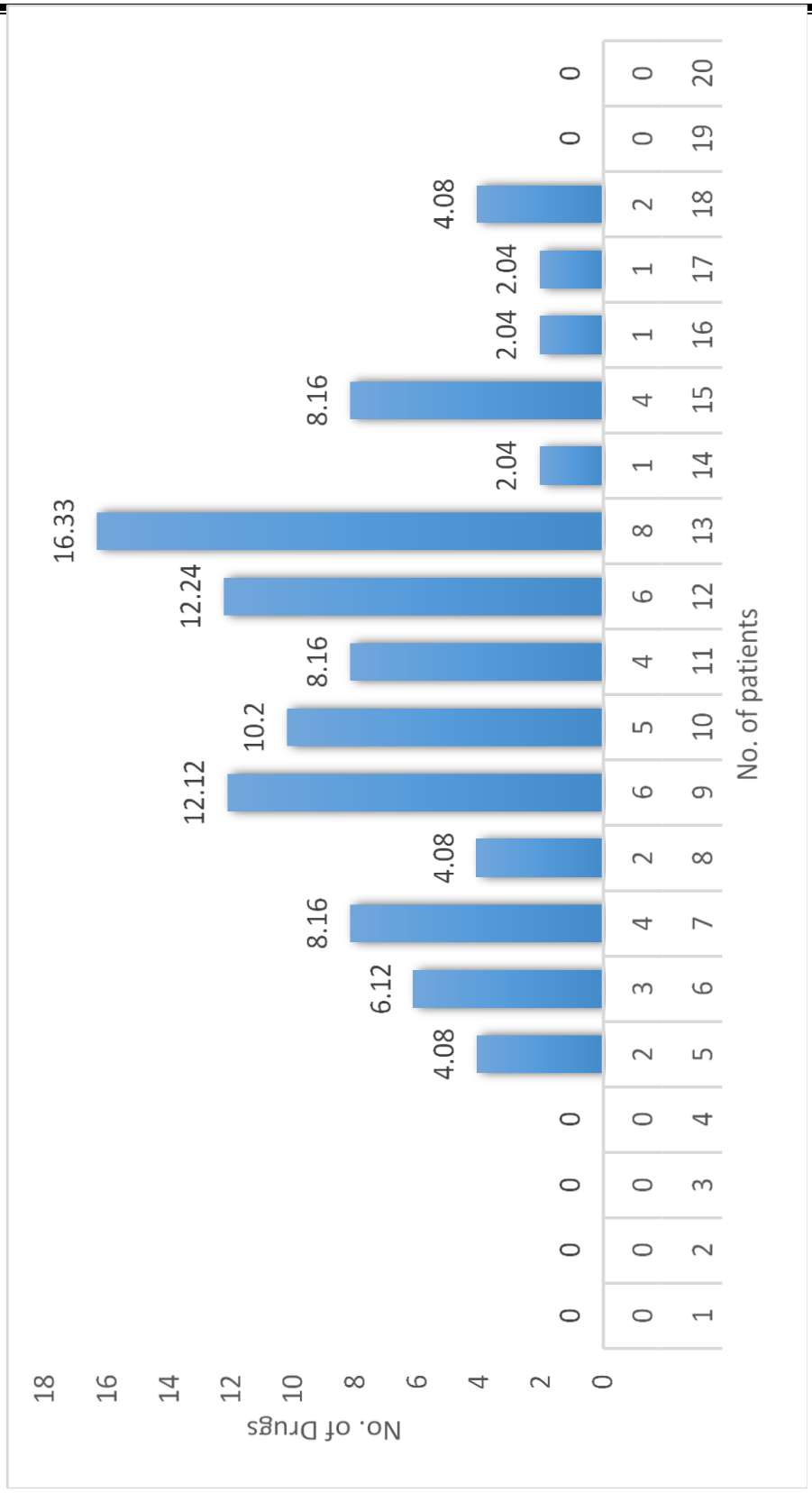


Table 28: Renally Eliminated antimicrobials and cardiovascular drugs with Adjusted Doses, (N=88)

SL no	Drugs prescribed	No.of patients (%)				Prescribed Dose	Adjusted Dose
		30-59ml/min	15-29ml/min	<15ml/min	Inference		
1.	Cefoperazone	-	2(2.22)	-	Overdose	1gm BD	1g OD
2.	Piperazillin	-	2(2.22)	3(3.33)	Wrong Frequency	4g BD	3g BD
3.	Garamaycin	1(1.11)	-	-	Wrong Frequency	80mg q24h	80mg q36h
4.	Amoxicillin	-	1(1.11)	-	Overdose	1g BD	500 mg BD/ 1gOD
5.	Ofloxacin	-	2(2.22)	2(2.22)	Overdose	200mg OD	100 mg OD
6.	Cefepime	-	-	1(1.11)	Overdose	1g BD	500mg BD/1gOD
7.	Ciprofloxacin	-	-	1(1.11)	Overdose	500mg OD	400mg od
8.	Levofloxacin	-	2(2.22)	1(1.11)	Overdose	500mg OD	1g x 3times/week
9.	Amikacin	-	-	1(1.11)	Overdose	500mg BD	500mg x3 times/week
10.	Ceftriaxone	-	2(2.22)	9(10)	Overdose	1g OD	22mg -290 mg
11.	Tazobactum	-	2(2.22)	3(3.33)	Wrong Frequency	500mg BD	250mg BD
12.	Ramipril	-	2(2.22)	1(1.11)	Overdose	5mg BD	2.5mg BD

14.	Spironolactone	1(1.11)	-	4(4.44)	Contraindicated	25mg BD	Avoid
15.	Eplerenone	-	1(1.11)	-	Contraindicated	25mg OD	Avoid
16.	Hydrochlorthiazide	-	1(1.11)	-	Contraindicated	12.5mg OD	Avoid
17.	Rosuvastatin	1(1.11)	2(2.22)	1(1.11)	Overdose	10mg BD	5mg OD

Table 29: Types of errors identified (N=52)

S. No	Type of error	No. of Patients	Percentage (%)
1.	Overdose	32	61.53%
2.	Wrong frequency	12	23.07%
3.	Contraindicated	8	15.38%

Table 30: Drug interactions of Antimicrobials and cardiovascular drugs, (N=66)

S.No	Drugs	Interaction	% of Interactions	Severity
1	Furosemide + Metoprolol	Increase the risk of hyperkalemia	1.39	Major
2	Metoprolol + Spironolactone	Increase risk of hyperkalemia	1.39	Major
3	Theophylline + Pantoprazole	Increase the effects of theophylline	1.39	Moderate
4	Theophylline + Tramadol	Increased risk of seizures	1.39	Major
5	Ondansetron + Tramadol	Decreased analgesic efficacy of tramadol	1.39	Moderate
6	Hydrocortisone + Doxofylline	Decrease the effect of theophylline	1.39	Major
7	Ceftriaxone + Torsemide	Increase risk of kidney failure	2.79	Major
8	Propoxifen + Clobazam	Increase CNS side effects	1.39	Major
9	Clopidogrel + Pantoprazole	Decrease effect of clopidogrel	1.39	Moderate
10	Clotrimazole + Atorvastatin	Increase the blood levels of atorvastatin	1.39	Moderate
11	Metoprolol + Calcium carbonate	Decrease the effects of metoprolol	1.39	Major

12	Metoprolol + Amlodipine	Reduction heart rate,cardiac contractility	1.39	Major
13	Doxepin + Propoxyphene	Increase the effects other medication	1.39	Major
14	Propoxyphene + Hydroxyzine	Increase the effects such as dizziness, confusion, drowsiness	1.39	Major
15	**Ceftriaxone + Calcium gluconate**	**Results in formation crystals in blood stream**	**1.39**	**Contraindi -cated**
16	Amlodipine + Calcium acetate	Decreases the effect of amlodipine	1.39	Moderate
17	Amlodipine + nebivolol	Lowering the blood pressure	1.39	Moderate
18	Alprazolam +Isosorbidemonotitrate	Lowering blood pressure	1.39	Moderate
19	Alprazolam + tramadol	Increase the effects like dizziness,confusion	1.39	Moderate
20	Insulin + Torsemide	Decrease efficacy of insulin	1.39	Minor
21	Alprazolam + Spiranolactone	Lowering the blood pressure	1.39	Moderate
22	Calcium carbonate + Amlodipine	Decreases the effects of amlodipine	1.39	Moderate
23	Magnesium carbonate + Ferrous ascorbate	Decrease iron bioavailability	1.39	Minor
24	Insulin + Clonidine	Results in hypo or hyperglycemia	1.39	Minor
25	Theophylline + nebivolol	Increase the effect of theophylline	1.39	Major
26	Furosemide + Pantoprazole	Results in hypomagnesemia	2.78	Minor
27	Ceftriaxone + calcium	Precipitation in lungs & kidney	1.39	Major
28	Nebivolol +calcium	Decreases the effects of nebivolol	1.39	Major
29	Carvedilol + Torsemide	Serum potassium level is altered	1.39	Moderate
30	Calcium acetate + Carvedilol	Decrease the effect of carvedilol	1.39	Moderate
31	Prazosin + Clinidipine	Increase chance of hypotension	1.39	Minor
32	Chloroquine + Ondansetron	Increased risk of QT interval prolongation	1.39	Major
33	Isoniazid + Rifamipicin	Results in hepatotoxicity	1.39	Major

34	Potassium chloride + Spiranolactone	Results in hyperkalemia	1.39	Major
35	Clopidogrel + Torsemide	Increased risk of torsemide toxicity	1.39	Moderate
36	Moxifloxacin + Sucralfate	Decreased moxifloxacin effectiveness	1.39	Moderate
37	Levofloxacin + diclofenac	Increased risk of seizure	1.39	Moderate
38	Tramadol + Levofloxacin	Increased risk of seizures	1.39	Major
39	Amikacin + diclofenac	Increased chance of kidney damage	1.39	Moderate
40	Amikacin + Pantoprazole	Hypomagnesemia	1.39	Moderate
41	Ondansetron + Levofloxacin	Increased risk of arrhythmia	1.39	Moderate
42	Ciprofloxacin + Sodium bicarbonate	Increased risk of stone formation	1.39	Major
43	Ciprofloxacin + lactulose	Increased risk of arrhythmi	1.39	Minor
45	Ondansetron + Tramadol	Decreased effect of Tramadol	2.78	Minor
46	Amlodipine + Diclofenac	Decreased effect of amlodipine	1.39	Minor
47	Atenolol + Diclofenac	decreased effect of atenolol	1.39	Major
48	Torsemide + Pantoprazole	Hypomagnesemia	4.17	Minor
49	Aspirin + Hydrocortisone	Aspirin effect gets reduced	1.39	Major
50	Salbutamol + Toresemide	Hypokalemia	1.39	Major
51	Ceftriaxone + Furosemide	Increase chance of kidney damage	2.78	Minor

52	Albuterol + Carvedilol	Inhibits activity of albuterol	1.39	Major
53	Levofloxacin + Insulin	Increased effect of insulin	1.39	Major
54	Prochlorperazine + Levofloxacin	Increased QT interval	1.39	Major
55	**Clopidogrel + Rabeprazole**	**Inhibits activity of clopidogrel.**	**1.39**	**Contraindicated**
56	Metformin + Nebivolol	Hypoglycemia	1.39	Minor
57	**Calcium Gluconate + Ceftriaxone**	**Fatal particulate precipitate in lungs and kidney**	**1.39**	**Contraindicated**
58	Furosemide + Ketorolac	Decreased diuresis	1.39	Major
59	Spironolactone + Telmisartan	Hyperkalemia	1.39	Moderate
60	Furosemide + Metoprolol	Hypotention	1.39	Major
61	Atorvastatin + pantoprazole	Increased risk of myopathy	1.39	Minor
62	Furosemide + Nebivolol	Hypotension	1.39	Major
63	Hydrocortisone + Nebivolol	Hypotension	1.39	Minor
64	Alprazolam + Nebivolol	Hypotension	1.39	Minor
65	Aspirin + Amlodipine	Hypertention	1.39	Minor
66	Hydrocortisone + amlodipine	Hypertension	1.39	Minor

Table 31: Antimicrobials and cardiovascular drugs with narrow therapeutic index (N=103)

S.No	NTI Drugs	No. of Patients	Percentage (%)
1.	Amikacin	5	4.85%
2.	Theophylline	8	7.76%
3.	Digoxin	4	3.88%
4.	Prazosin	2	1.94%
	Total	**19**	**18.44%**

DISCUSSION

Kidney plays vital physiological functions and it acts as the major excretory organ in the human body. Renal function can be assessed by various tests and procedures that will help evaluate the kidney function. Drug therapy in the presence of renal diseases requires to be individualized. Some drugs are to be avoided and some others may require dose adjustments in order to avoid drug toxicity.

The major test which can be performed to assess the renal function is the estimation of serum creatinine in urine as well as blood. Creatinine is a by-product of muscle metabolism in the body and it is primarily eliminated through glomerular filtration. Thus the accumulation of creatinine in blood indicates abnormal or diminished renal function.[47]

The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF KDOQI) advocates the use of creatinine clearance (CrCl) and estimated glomerular filtration rate (eGFR) for calculating the individualized dose. Once the CrCl or eGFR is estimated CKD is classified into five stages proposed by KDOQI and approved by FDA. Estimation of GFR is done with the help of Modification of Diet in Renal Disease (MDRD) equation and CrCl by Cockroft-Gault equation. [(Roger K.)]The Cockroft-Gault equation is still most often used for estimating GFR in pharmacokinetic studies and for drug dosage adjustments, although some studies have shown the MDRD equation to be more accurate for estimating GFR. [24]

About 506 drugs were evaluated in terms of dosage appropriateness in patients with renal impairment and 21.14% required dose adjustments. Of these dose of 3.75% were adjusted at the time of prescribing and 17.39% were not adjusted. The major categories of errors found in these unadjusted drugs were overdose, wrong frequency and inappropriate drug choice. Falconnier ET al[8] reported 17% of inappropriate prescriptions which was almost comparable to the present study. A similar study [48] carried out in the nephrology department of the same study site showed only 7% inappropriateness. This may be due to the fact

that the drugs were prescribed by nephrologists whereas in the present study patients with renal impairment were managed in the general practice or general medicine department. Moreover, multiple co-morbidities of the study population and polypharmacy were the major reasons to expose them to various categories of drugs which can easily lead to dosing errors.

The study revealed that most of the dosage errors were seen with antibiotic containing prescriptions followed by antihypertensives. The major drug categories for which drug dosage adjustments were recommended based on the available evidence are discussed below.

ANTIBIOTICS

A CRF case with UTI was prescribed with amoxicillin 1g twice daily. But literature (Micromedex) reveals that in severe renal impairment the maximum tolerated dose of amoxicillin is 1g per day. If accumulation of this drug occurs common side effects like epigastric distress, crystalluria, nephritis etc. would aggravate and result in complications like oral thrush, vaginal yeast infection etc. Hence for this patient a reduced dose of 500mg BD/ 1g OD of amoxicillin or an alternate therapy with dose adjusted ciprofloxacin was recommended.

Garamycin was prescribed for a patient with venous ulcer at a dose of 80 mg q12h which will lead to accumulation of drug and can even cause resistance. As per the literature [40] the adjusted dose of garamycin in patients having moderate renal failure should be the normal dose given at every 36 hrs.

Also, another antibiotic called cefepime was prescribed for prophylaxis of secondary infection with a dose of 1 g given two times daily. In this condition the half-life of cepfepime will tend to increase fivefold and will lead to accumulation of drug. This results in increased chance of severe ADR like toxic epidermal necrolysis, encephalopathy and seizures. Hence, 500 mg BD or 1 g OD was recommended.

Another cephalosporin which required dose individualization was cefperazone whose usual dose is 2g twice daily but in decreased renal function its

level in plasma tend to increase and cause severe ADR like Steven-Johnson syndrome, epidermal necrolysis etc. Hence the dose should be adjusted to 1 gm per day to minimize such complications. Cefexime which does not require any adjustment can be a safe and suitable alternative.

Fluroquinolones such as levofloxacin, and ciprofloxacin were prescribed for various infections at a dose of 500 mg once daily. The treatment continued for several days during the hospital stay. In situation of impaired renal function the serum concentration of drug will increase rapidly and tend to cause toxicity. It worsens the renal function as well as it affects the liver. Thus it became mandatory to adjust the dose to 1 g repeated three times per week for levofloxacin and 400mg once daily (max) for ciprofloxacin so that the drug concentration will remain in therapeutic range.

Ofloxacin, which is another fluroquinolone requires dose individualization as it causes increased risk of tendonitis and tendon rupture if administered in normal adult doses for patients having renal failure. Thus it is recommended to give half the usual dose to minimize toxicity.

Amikacin, an aminoglycoside antibiotic was administered for symptoms of mycobacterial infection with a dose of 500 mg twice daily for a patient who was in end stage renal diseases (ESRD).In such a condition, the dose of amikacin should be adjusted to avoid complications like nephrotoxicity and ototoxicity. The modified dose in this case was 500mg repeated three times a week.

ANTIHYPERTENSIVES

The current study documented few CRF patients receiving nebivolol, a cardioselective beta-blocker, at a dose of 5 mg OD and angiotensin converting enzyme inhibitor, rampril 5mg BD. Nebivolol is a nephrotoxic drug which causes reduced renal blood flow and reduced renal function which will further enhance the deleterious effect on renal function. The proposed dose of nebivolol in CRF cases is 2.5 mg once daily so that nephrotoxic effects are minimized. [25]

ACE inhibitors like ramipril is also considered nephrotoxic drug and in most SHT cases it was administered as 5mg twice daily dosage. But international indices [40] suggests that maximum tolerated dose of ramipril in RF patients is 2.5 mg up to a maximum of 5mg per day.

DIURETICS

Few cases with comorbidities like SHT, CHF and CRF were treated with potassium sparing diuretics like spironolactone and eplerenone for edema as well to reduce systemic blood pressure. But for a CRF patient these drugs are recommended to be avoided from pharmacotherapy.

A case of past medical history having SHT was continued on hydrochlorthiazide 12.5 mg once daily which should be avoided in renal impairment as the cumulative effect of thiazide in body will precipitate azotemia which will further impair the renal function.[40]

ANTIDIABETICS

Metformin is a drug frequently prescribed in T_2DM at a dose of 500mg once daily. In renal impairment the elimination of metformin and its metabolites diminishes, leading to drug accumulation. This precipitates fatal condition like lactic acidosis and hence the use of metformin in renal failure patients is contraindicated.

Another antidiabetic drug of interest is glipizide which is usually prescribed at a dose of 2.5 mg twice daily. At this dose accumulation is common in renal impaired patients and will end up in hypoglycemic coma which is very severe. Hence it is not recommended to be continued in therapy for RF patients.

ANALGESICS

Tapendalol 50mg thrice daily was prescribed in a case having CrCl< 30ml/min. The Area Under the Curve (AUC) of tapendalol is higher and lead to nephrotoxicity in such cases. So tapendalol use should be avoided in renal failure.

In renal impairment the elimination of paracetamol is profoundly diminished which will lead to accumulation of NAPQI, a toxic metabolite of paracetamol in renal tissues and it may lead to complete organ damage. So it is advised to increase the dosing interval of paracetamol to minimize the toxic effects.

ANTIHYPERLIPIDEMICS

Rosuvastatin 10mg daily was prescribed in a case with hyperlipidemia and severe renal impairment. Overdosage of rosuvastatin due to reduced elimination can cause breakdown of skeletal muscle tissues (rhabdomylosis) and can aggravate the renal failure conditions. As per the literature, 5mg daily of rosuvastatin is recommended in renal impairment or it can be alternated with atorvastatin 10mg/20mg OD which is found to be rather safe in renal failure.

OTHER DRUGS

In one case of CRF potassium chloride was prescribed which may cause hyperkalemia and related cardiac complications like tachyarrhythmia. So the use of KCl should be avoided in such conditions. An important anticoagulant enoxaparin will have increased exposure in the body as the elimination of drug is drastically reduced in renal failure. This can cause fatal haemorrhagic complications and hence the dose should be titrated to optimize the blood thinning and reduce problems. [40]

CONCLUSION

The present study was carried out in order to understand the prescribing pattern of drugs in patients with renal impairment and to evaluate them in terms of dosage appropriateness. Modification of Diet in Renal Disease and Cockroft-Gault formula was used to calculate patient's eGFR or creatinine clearance and dosage appropriateness was then assessed using published drug dosing guidelines and relevant equations. 1016 drugs in 103 patients were evaluated in the present study with an average of 10 drugs per patient. Of these 1016 studied drugs, 98 (9.64%) required dose adjustment where 244 (24.01%) were adjusted and 83 (8.16%) were not adjusted. It was found also that most of the drugs requiring dose adjustment were antibiotics (41.77%) followed by antihypertensives (13.67%). Major types of errors identified were overdosage and wrong frequency of administration. About 15.38% of drugs were to be avoided. However the current study observed that the prescribed drug dosage follows the recommended guidelines to a greater extent and are comparable with the existing literature. Continued collaboration with clinical pharmacist should be encouraged for improving therapeutic outcome in patients with renal impairment.

FUTURE OUTLOOK

Further studies are needed in order to assess the impact of pharmacist intervention on improving drug dosage adjustment in patients with renal impairment. The present study may be extended to the other department of the hospital.

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ANNEXURE – I

Permission Letter from Hospital

Sri Ramakrishna Hospital

Medical Service : M/s. S.N.R. SONS CHARITABLE TRUST

SRI RAMAKRISHNA HOSPITAL ETHICAL COMMITTEE

395, SAROJINI NAIDU ROAD, SIDHAPUDUR, COIMBATORE - 641 044.
Phone : 0422 - 4500000, 4500201, Grams :"RAMHOSP" Fax : 0422-2240521
E-mail : dean@snrsonstrust.org, website : sriramakrishnahospital.com
Ethics Committee Registration No. ECR/690/Inst/TN/2014

Ethics Committee Chairman

Dr. P. M. Murali, M.Sc.,Ph.D.,D.Sc.,

Ethics Committee Member Secretary

Dr. P. Sukumaran, MS.,M.Ch.,FIACS.,

Ethics Committee Members

Dr. MohanKumar T. MD.,AB.,D.Sc., DPPR.,FCCP., Clinician

Dr. R. Lalitha, DGO., Clinician

Dr. S. Rajagopal, M.Ch., Clinician

Dr. M. Rangasamy, B.E.,M.Sc.(Engg.)Ph.D., Lay Person

Dr. T.K. Ravi, M.Pharm.,Ph.D., Scientific Member

Dr. N. Paramasivan, MBBS., MD.,(Pharmacology) Basic Medical Scientist

Mr. P. R. Ramakrishnan, B.Com.,B.L., Legal Expert

Mrs. Mythili Padmanabhan, M.Sc., Social Scientist

SRH/EC.12-8/2017-18 — 28th December 2017

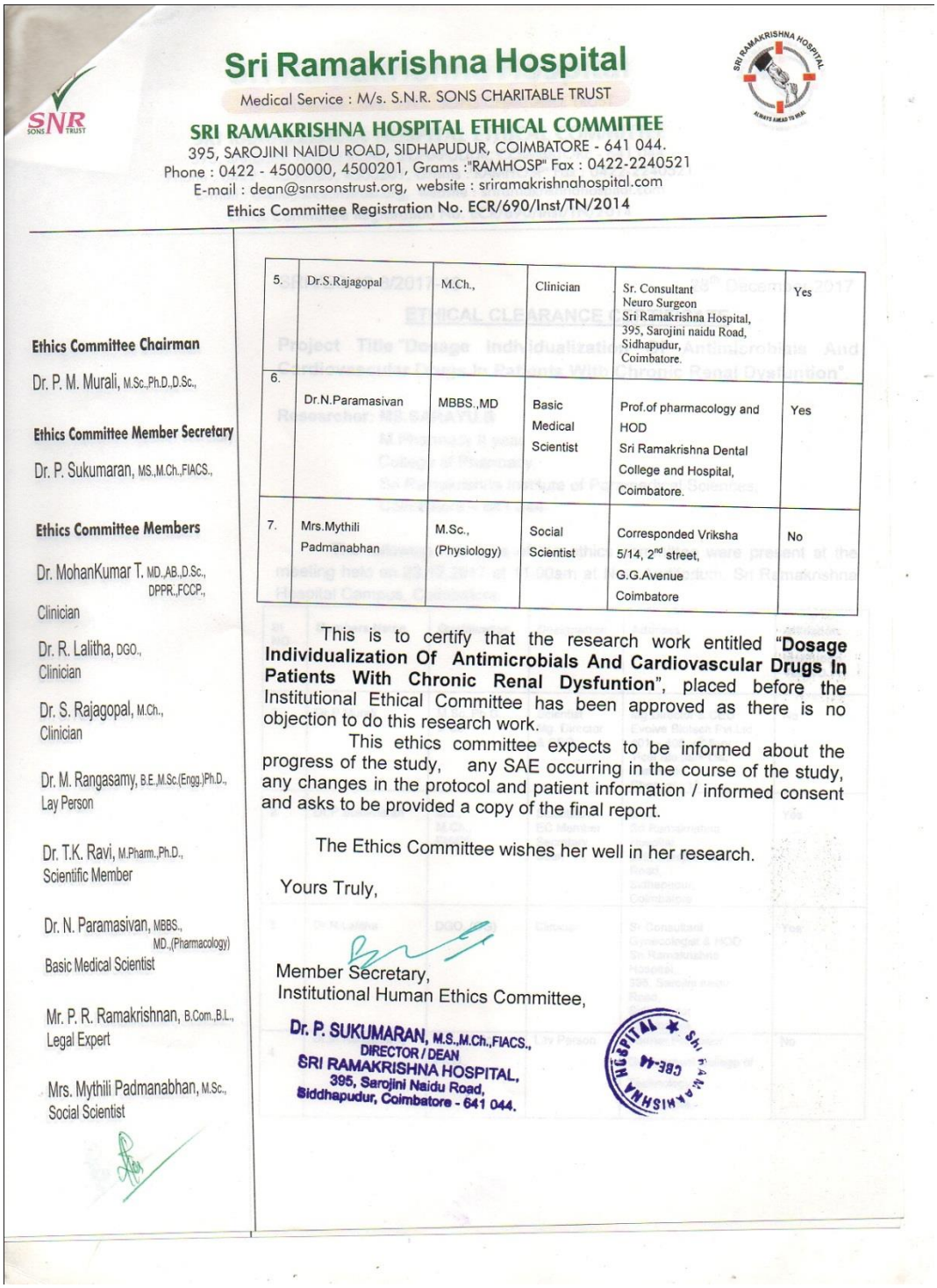
ETHICAL CLEARANCE CERTIFICATE

Project Title:"Dosage Individualization Of Antimicrobials And Cardiovascular Drugs In Patients With Chronic Renal Dysfuntion".

Researcher: MS.SARAYU.B
M.Pharmacy II year
College of Pharmacy,
Sri Ramakrishna Institute of Paramedical Sciences,
Coimbatore – 641 044

The following members of the ethics committee were present at the meeting held on 23.12.2017 at 11.00am at New Auditorium, Sri Ramakrishna Hospital Campus, Coimbatore.

Sl NO	Members Name	Qualification	Designation	Address	Affiliation To the Institution Yes/NO
1.	Dr.P.Murali	M.Sc.,Ph.D., D.Sc	Scientist Mg. Director & CEO	Mg.Director & CEO Evolve Biotech Pvt.Ltd., 401 – 405, 4th floor Ticel Bio park Ltd, Taramani, Chennai - 13	No
2.	Dr.P.Sukumaran	MS., M.Ch., FIACS	Scientific / EC Member Secretary Dean	Dean Sri Ramakrishna Hospital, 395, Sarojini Naidu Road, Sidhapudur, Coimbatore	Yes
3.	Dr.R.Lalitha	DGO.,(OG)	Clinician	Sr.Consultant Gynecologist & HOD Sri Ramakrishna Hospital, 395, Sarojini naidu Road, Sidhapudur, Coimbatore.	Yes
4.	Dr.M.Rangasamy	B.E., M.Sc., Ph.D.,	Lay Person	Former Professor Government College of Technology, Coimbatore.	No



Sri Ramakrishna Hospital

Medical Service : M/s. S.N.R. SONS CHARITABLE TRUST

SRI RAMAKRISHNA HOSPITAL ETHICAL COMMITTEE

395, SAROJINI NAIDU ROAD, SIDHAPUDUR, COIMBATORE - 641 044.
Phone : 0422 - 4500000, 4500201, Grams :"RAMHOSP" Fax : 0422-2240521
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Clinician

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Lay Person

Dr. T.K. Ravi, M.Pharm.,Ph.D.,
Scientific Member

Dr. N. Paramasivan, MBBS., MD.,(Pharmacology)
Basic Medical Scientist

Mr. P. R. Ramakrishnan, B.Com.,B.L.,
Legal Expert

Mrs. Mythili Padmanabhan, M.Sc.,
Social Scientist

5.	Dr.S.Rajagopal	M.Ch.,	Clinician	Sr. Consultant Neuro Surgeon Sri Ramakrishna Hospital, 395, Sarojini naidu Road, Sidhapudur, Coimbatore.	Yes
6.	Dr.N.Paramasivan	MBBS.,MD	Basic Medical Scientist	Prof.of pharmacology and HOD Sri Ramakrishna Dental College and Hospital, Coimbatore.	Yes
7.	Mrs.Mythili Padmanabhan	M.Sc., (Physiology)	Social Scientist	Corresponded Vriksha 5/14, 2nd street, G.G.Avenue Coimbatore	No

This is to certify that the research work entitled "**Dosage Individualization Of Antimicrobials And Cardiovascular Drugs In Patients With Chronic Renal Dysfuntion**", placed before the Institutional Ethical Committee has been approved as there is no objection to do this research work.

This ethics committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information / informed consent and asks to be provided a copy of the final report.

The Ethics Committee wishes her well in her research.

Yours Truly,

Member Secretary,
Institutional Human Ethics Committee,

Dr. P. SUKUMARAN, M.S.,M.Ch.,FIACS.,
DIRECTOR / DEAN
SRI RAMAKRISHNA HOSPITAL,
395, Sarojini Naidu Road,
Siddhapudur, Coimbatore - 641 044.

ANNEXURE – II

Structured Proforma

DEPARTMENT OF PHARMACY PRACTICE
College of Pharmacy, SRIPMS, Coimbatore - 44.

Case No.

DOSAGE INDIVIDUALIZATION OF ANTI MICROBIALS AND CARDIOVASCULAR DRUGS IN PATIENTS WITH CHRONIC RENAL DYSFUNCTION

DATA ENTRY FORM

PATIENT DETAILS

Name	Age	Sex	Wt.	Ht.	BMI	IP No.	Dept.	DOA	DOD
Mr. Parthiban	55	M	59	150		20180957	GM	7.4.18	

REASONS FOR ADMISSION c/o abdominal pain x 5 days, nausea, Body pain

PAST MEDICAL HISTORY K/C/O SHT, DM x 4 years

PAST MEDICATION HISTORY

Vital Signs										
Date	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10
Temp.	N	N	N	N	N	N	N	N	N	N
BP	140/90	140/80	130/80	130/78	130/84	130/80	120/80	120/80	130/84	120/78
Pulse	82	81	81	80	79	78	77	76	77	78

Blood sugar (mg %)										
Day										
F.B.S (70-100)	82									
P.P.S (<140)	110									
R.B.S (70-140)	140									

BLOOD COUNTS

Haemoglobin (g/dl) M:14-18 F:12-14	TLC (cells/cumm) (6000-10000)	ESR (mm/hr) (M<10; F<20)	Differential Leukocyte Count (%)		
10.2			Polymorphs (40-75)	68	
			Lymphocytes(20-45)	40	
Platelets (1-4 lakhs)	Clotting Time(6-11min)	Bleeding Time(1-6min)	Basophils (0-1)	0.8	
2,30,000			Eosinophils (1-6)	4.1	
			Monocytes (2-10)	8.4	

LIVER FUNCTION TESTS							RENAL FUNCTION TESTS			
Total bilirubin (0.1-1.2 mg %)	0.7			Alk. Phosphatase (38-126 U/L)	290		Urea (mg %) (12-35)	112	105	89
							Uric acid (mg %) F-2.4-5.7, M-3.4-7			
P.T Time (12-15 sec)	14			SGPT (9-52U/L)	24		Sr.Creatinine (mg %) (0.4-1.4)	4.8	3.5	2.2

ELECTROLYTES (mEq/l)					URINE EXAMINATION			
Sodium (130-150)	138				Colour	Pale Yellow	Sugar	Nil
Potassium (3.5 – 5.8)	5.4				Bile salts	-ve	WBC	
Chloride (95-105)	99				Bile pigment	-ve	RBC	Nil
Bicarbonate (22-39)	23				Albumin	Nil	Casts	Nil
					Pus cells	4-6	Epithelial cells	2-3

P/E:-

Patient is conscious / oriented / afebrile

P - I - C - C - L E -

BP - 140/90 mmHg Temperature - Normal

Systemic Examination:-

Rs - B/L AE⊕

CVS - S_1S_2⊕

P/A - Soft

CNS - NAD

Discharge Medications:-

Tablet - Pantocid - 40mg P/O 1-0-1
T. Aldactone - 25 mg P/O 1-0-1
T. Teleact - 40mg P/O 0-0-1
C. Becosules - 100mg P/O 0-0-1
T. Multismile - P/O 1-0-0
T. Dytor - 2.5mg P/O 1-0-0

COMORBIDITIES

Hypertension ☑	Dyslipidemia ☐	Cardiovascular risk factors ☐	
Blood disorder ☐	diabetes Mellitus ☑	Asthma ☐	Others ☐

OTHER INVESTIGATIONS:

ECG

DIAGNOSIS:

Chronic Renal failure, Hepatomegaly

DRUGS PRESCRIBED

S.No.	Drugs		Strength	Route of admin.	Days of Treatment									
	T. Name	G. Name			1	2	3	4	5	6	7	8	9	10
01	Inj. Gramocef	Ceftriaxone	1.5gm	IV BD	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
02	T. Multisimile	vit. Supp		P/O 1-0-0	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
03	T. Dytor	Torsemide	2.5mg	P/O 1-0-0	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
04	Inj. Pantocid	Pantaprazole	40mg	IV BD	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
05	Inj. emeset	Ondansetron	4mg	IV S-0-S	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
06	T. Telact	Telmisartan	40mg	P/O 0-0-1	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
07	T. Aldactone	Spironolactone	25mg	P/O 1-0-1	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
08	C. Aurobol	calcitrol	0.25mcg	P/O 1-0-0	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
09	C. Becosules	Vit B complex	100mg	P/O 00-1	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
10														
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DRUG INTERACTIONS

DRUGS	EFFECT	SEVERITY	INFERENCE
Torsemide + Pantaprazole	May result in Hypomagnesemia	Minor	Monitor 'Mg' levels
Spironolactone + Telmisartan (moderate)	May result in hyperkalemia	moderate	Monitor 'K' levels

ANY INTERVENTIONS MADE

NAME OF THE INVESTIGATOR: Sarayu. B

SUBMISSION DATE: 20.4.18

Sarayu. B

Signature of the investigator

Signature of the staff