Dosage Adjustment of Renally Eliminated Drugs in Patients with Chronic Kidney Disease at Tertiary Care Teaching Hospital in Nepal

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Title Dosage adjustment of Renally Eliminated Drugs in Patients with Chronic Kidney Disease at a Tertiary Care Teaching Hospital in Nepal

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ABSTRACT

The present study was carried out to investigate the appropriateness of dosage adjustments of the drugs that are nephrotoxic and / or metabolized or eliminated by the kidney in patients with impaired renal function during hospital stay, as well as at hospital discharge. All medications records of the patients, admitted between October, 2012 and March, 2013 at Tribhuvan University Teaching Hospital (TUTH) in Nepal were studied retrospectively. All patients with renal clearance ≤ 50 ml/min/1.73 m^2 were included for the analysis. Data with respect to patients, clinical, laboratory findings, medications and their dose were extracted from the patient's medical file.

In hospitalized patients, there were total 1133 items of medications for 118 renal impaired patients. Of them 639 were characterized for toxic and/or metabolite or eliminated (TEM) medications. Among them, 267 medications were considered for dosage adjustments and 26 were imperative to use with caution. Dosage adjustments were done in 213 (79.78%) prescriptions. According to the degree of renal impairments, adjustments were overlooked in 21 (7.86%) and 33 (12.35%) in moderate and severe renal dysfunction cases, respectively. Appropriateness of dosage adjustments were significantly different in metronidazole

($P < 0.02$), SMZ-TMP ($P < 0.04$) and meropenem ($P < 0.03$) in patients with moderate renal impairments cases compared with those of the severe renal impaired cases.

Similarly, at hospital discharge, there were total 848 items of prescription drugs for 116 impaired renal patients. Of them 404 were designated as toxic and / or Metabolized or eliminated (TEM) medications. Dosage adjustments according to renal dysfunctions were necessary in 135 prescriptions and 28 prescriptions deemed to use with caution. Among those, dose adjustments were performed in 108 (80%) medications. According to the degree of renal impairments, dosage adjustments were ignored in 14 (10.37%) and 13 (9.62%) in moderate and severe cases, respectively.

This results show a clear clinical need to improve the prescriptions process for patients with impaired renal function. It deemed critical to initiate further studies to reveal the cause of dosing errors and to in-depth investigate why clinicians have chosen certain dosages despite the patient's renal impairment. In light of the study findings, we advocate a guideline solely based on the renal drugs that are frequently prescribed at this hospital. Moreover, we urge to implement these guidelines in a dynamic alert computing system in the hospital setting which would serve the clinicians to easy and regular assess of laboratory data comfortably. It would also assist to continuously and comprehensively recognize patients at risk and appropriately adjust drug dosing which ultimately contribute to provide pharmaceutical care in patients with impaired renal function.

Key words- Creatinine clearance, dose adjustment, renal impairment

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LIST OF ABBREVIATIONS AND SYMBOLS

ACE	Angiotensin-converting enzyme
ADR	Adverse drug reaction
ADE	Adverse drug event
ABW	Actual body weight
b.i.d.	Twice a day
CrCl	Creatinine Clearance
CKD	Chronic kidney disease
CNS	Central nervous system
CI	Contraindicated drugs
DM	Diabetes mellitus
DS	Double strength
DRPs	Drug related problems
eGFR	Estimated Glomerular filtration rate
HTN	Hypertension
hr	Hour
IHD	Ischaemic heart disease
IBW	Ideal body weight
MDRD	Modification of diet in renal disease
LMW	Low molecular weight
mL	Milliliter
mg	Milligram
NSAIDs	Non steroidal anti-inflammatory drugs

LIST OF ABBREVIATIONS AND SYMBOLS (continued)

q.i.d.	Four times a day
q.d.	Everyday
q.o.d.	Every other day
SCr	Serum creatinine
SD	Standard deviation
SMZ-TMP	Sulfamethoxazole-Trimethoprim
TEM	Toxic, metabolite and / or eliminated through kidney
TB	Tuberculosis
TUTH	Tribhuvan University Teaching Hospital
t.i.d.	Three times a day
Vd	Volume of distribution
χ^2	Chi square

CHAPTER I

INTRODUCTION

1.1 Background

Renal insufficiency is one of the common problem in hospitalized patients, and is associated with an increase in hospitalization morbidity and mortality [1]. An increase in serum creatinine more than 0.5 mg/dL has been associated with a 6.5-fold increase in the odds of death, a 3.5-days increase in length of stay, and nearly 7500 USD in extra hospital costs [2]. In patients with renal disease, as well as in patients with advanced age, there are depletion in glomerular filtration rate [3]. Drugs that are primarily excreted via kidneys, a reduction in GFR will directly reduce the amount of drug excretion leading to the 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 [4]. Thus, a dosage adjustment is likely to be necessary for safe and effective use in such a patient where the kidney function is impaired and the drug or its active metabolites exhibit a narrow therapeutic index and when excretion and / or metabolism occurs primarily via kidneys.

Several studies have established that the incidence of adverse drug events is much higher in patients with chronic kidney diseases than those without renal insufficiency. Moreover, it has been documented that the drug related problem in patients with renal impairment is mostly due to the medication dosing errors [5]. Adverse consequences for dosing errors may be mild or severe. For instance, patients with severe renal insufficiency receiving allopurinol appear to experience a life threatening toxicity syndrome consisting of erythematous, disquamative skin rash, hepatitis, fever, eosinophilia and worsening of renal insufficiency which occur in patient receiving standard dose (200-400 mg/day). In a review of 72 cases receiving alloppurinol, 8 died [6]. The elimination half-life of the active metabolite oxipurinol

is approximately 24 hours but this time frame can prolong to 125 hours in renal failure. Similarly, lactic acidosis from metformin carries a mortality of ≤ 50% and typically occurs in patients with one or more risk factors including renal insufficiency, severe cardiac failure, severe liver disease, high doses and age >80 years [7]. Many antimicrobial agents used in patients with chronic kidney disease accumulate in the body. Excessive serum levels of injectable penicillin G or carbenicillin may be associated with neuromuscular toxicity, myoclonus, seizures, or coma [8]. Imipenem/cilastatin can accumulate in patients with chronic kidney disease, causing seizures if doses are not reduced [9]. Nitrofurantoin has a toxic metabolite that can accumulate in patients with chronic kidney disease, causing peripheral neuritis [10]. In the same way, metabolites of meperidine (normeperidine), dextropropoxyphene, morphine, tramadol, and codeine can accumulate in patients with chronic kidney disease, causing central nervous system and respiratory adverse effects [11, 12]. The severe muscle weakness and tenderness seen in patient receiving clofibrate are associated with excessive accumulation of free acid metabolite of clofibrate. Accumulation of free and acetylated sulfonamide in patient with renal insufficiency is associated with the increase toxic side effect including severe nausea, and vomiting [10]. In a case study, a high serum concentration of acyclovir and reduced drug clearance was associated with neurotoxicity. A meta analysis of prospective study [13] has shown that adverse drug reactions are responsible for about 7% of all hospital admissions. However, most of the drug related problems (50-73%) are detectable and preventable [14], often caused by the medication dosing error [15]. Drug induced nephrotoxicity and adverse effect can be reduced by adjusting the dosing of renally excreted drug according to the patient's estimated glomerular filtration rate (eGFR) but it is often found to be neglected by prescribers. The various studies have shown that, in renal impaired patients, 20-30 % of drug prescriptions and 5-85 % of the drugs requiring dosage adjustments have not properly adjusted [16-18]. In Nepal, One study documented that the overall prevalence of CKD is 10.6% in urban areas [19]. Data from India also suggest that the prevalence rate of CKD could vary almost 5-fold between rural and urban populations [20].

High prevalence of CKD and the large number of drugs with mainly renal elimination suggest that physicians should consider renal function when prescribing [21, 22]. Particularly, drugs that have a narrow therapeutic index, or parent drugs or active metabolie are primarily excreted by the kidneys, should require a reduction in the maintenance dose and/or an increase in the dose interval to prevent the potential adverse drug events and improve the therapeutic outcome. However, there are a lack of large-scale studies, which identify the medications most commonly overdosed in Nepal

The present study was conducted to determine the degree of renal impairment and the proportion of toxic and / or metabolite or eliminated (TEM) drugs prescribed and subsequently to investigate whether dosage adjustments was made appropriately in those patients accordingly, and further to determine the potential adverse consequences at inappropriate dose.

1.2 Rationale of the study

Inappropriate dosing in hospitalized patients may take account into several considerations. Sometimes prescriber may not review the test for renal function before prescribing. References to guide dosage adjustment in renal impairment may not be freely available in the hospital wards. The hospital laboratory does not routinely test the renal function and clinicians have to calculate eGFR themselves before prescribing. Sometimes prescribers use only SCr as an indicator of renal function and conclude that some patients had normal renal function despite calculated glomerular filtration rate were less than normal.

While failure of dosage adjustment occurs in the hospitalized patients, the inappropriate use of medications results in drug related problem in patients with renal impairment [23], longer hospitalization, and extra treatment costs, consequently increasing overall morbidity and mortality rate. On the other hand, the various studies have documented that dosage adjustment in patients with renal failure reduces the rate of adverse drug event, reduces the cost of drug therapy and improves the overall delivery of health care. Despites, the importance of dosage adjustment in patients

with CKD, such adjustments are sometimes found to be ignored [17]. The studies conducted in developed countries have consistently shown that approximately 20-30% [17, 18] of hospitalized patients have overdosing problems and their adverse consequence are considerable. In Nepal, these data have not been addressed properly. To date, there are no comprehensive studies for the dosing of renally excreted drugs in Nepalese hospital setting. However, it is likely that the problems could be significantly considerable due to high prevalence [19] of chronic kidney disease. Therefore, the information obtained from the present study could be helpful to know the prescribing pattern of drugs in chronic kidney disease patients as well as the consequences from the dosing errors in such patients in hospital setting practice. Moreover, the outcome of the study could guide the systemic management for dosage adjustments in renal impaired patients in Nepal. Subsequently, the prescribing pattern of toxic and /or metabolite or eliminated (TEM) medications in this study may provide insight for the development of dosing guideline and the implementation of such guideline in the hospital setting could be promising to individualize drug therapy, contributing to drug safety, and optimize pharmaceutical care for all kidney patients.

1.3 Objectives of the study

Primary objective

To evaluate the appropriateness of dosage adjustment of toxic and/or metabolite or eliminated (TEM) medications in a patients with impaired renal function.

Secondary objective

To determine the incidence of adverse drug reaction (ADR) from non-optimal dose.

CHAPTER II

REVIEW OF LITERATURES

2.1 Effect of Chronic Kidney Disease on Pharmacokinetics

Renal dysfunction induces alteration in pathophysiology and its' changes could alter medications pharmacodynamic. Several pharmacokinetic parameters are adversely affected in chronic kidney disease (CKD), secondary leading to a reduced oral absorption, glomerular filtration rate, altered tubular secretion, reabsorption and changes in intestinal, hepatic and renal metabolism [24]. Therefore, the clearance of drugs eliminated primarily by this mechanism is decreased, and guided dosing should be considered when these drugs are prescribed to patients with impaired renal functions. Patients with severe renal insufficiency can enhance accumulation of metabolites which can contribute to undesirable pharmacologic activity or toxicity.

2.2 Effects on Absorption

Increased gastric pH is a common manifestation in CKD and its etiology is multifactorial. For medications (e.g., furosemide, ketoconazole) that are best absorbed in an acidic environment, drug dissolution and ionization are often reduced by increased gastric pH, resulting in reduced bioavailability [25]. Also, the ingestion of cation-containing antacids (e.g., calcium, magnesium), aluminum hydroxide, sodium polystyrene sulfonate and iron may reduce drug absorption because of chelation with other medications, resulting in the formation of insoluble compounds. The Fluoroquinolones and Tetracyclines classes of drugs are highly susceptible to chelate formation in patients with renal insufficiency [25, 26]. Renal insufficiency is associated with decreased intestinal CYP450 activity. This altered activity is thought to be secondary to diminished CYP450 gene expression. CKD

induced reductions in intestinal CYP450 biotransformation have a profound effect on drug absorption by increasing overall oral bioavailability [27].

2.3 Effects on Drug Distribution

CKD-induced alterations in protein binding are associated with many clinical implications. Medications that are acidic, such as barbiturates, cephalosporins, furosemide, penicillins, phenytoin, salicylates, valproate and warfarin are profoundly affected by reduced protein binding. Acidic drugs are bound to albumin, plasma concentrations of which are often decreased in uremic patients. Hypoalbuminemia and altered plasma protein binding due to the competition for binding affinity sites by other drugs, metabolites, and accumulating endogenous substances may displace medications from plasma protein binding sites leading to increased levels of free concentrations of drugs. Conversely, alkaline drugs (e.g., propranolol, morphine, oxazepam, vancomycin) bind primarily to non-albumin plasma proteins, such as α1- acid glycoprotein. α1-acid glycoprotein is an acute-phase protein whose plasma concentrations are often elevated in renal dysfunction. For this reason, free fraction of alkaline drugs in CKD patients may be reduced (e.g., propranolol) [27, 28]. CKD-induced changes in body composition, such as increased total-body water and adipose tissue and decreased muscle mass, can have a profound effect on hydrophilic drugs (e.g., pravastatin, fluvastatin, morphine, codeine). Oedema and ascites is expected to increase the volume of distribution (Vd) of hydrophilic compounds such as vancomycin. This change in volume of distribution (Vd) may result in reduced serum concentrations. In contrast, muscle wasting and increased adipose tissue may reduce volume of distribution and may result in increased serum concentrations of hydrophilic medications [25].

2.4 Effect on Drug Metabolism

In general, phase I hydrolysis and reduction reactions are slow in chronic kidney disease. Phase II metabolic reactions are also affected by renal dysfunction. Acetylation (e.g., dapsone, hydralazine, isoniazid, procainamide),

glucuronidation (e.g., acetaminophen, morphine, lorazepam, oxazepam, naproxen), sulfation (e.g., acetaminophen, minoxidil, dopamine, albuterol), and methylation (e.g., dobutamine, dopamine, 6-mercaptopurine) are all slow in patients with chronic kidney disease. Alteration in both phases of metabolism results in increased serum drug concentrations. Ordinarily, the kidneys have nearly 15% of the metabolic function of the liver, with most of the metabolic enzymes located in the renal cortex. Renal metabolism is obviously reduced in cases with renal insufficiency. Reduction in the overall metabolic rate results in increased parent compound concentrations, potentially increasing the incidence of adverse events [24, 29].

2.5 Effect on Drug Elimination

The renal excretion of drugs depends on glomerular filtration rate, renal tubular secretion and reabsorption. The glomerular elimination of drugs depends on several factors, including the molecular weight and protein binding. Drugs bound to albumin are not filtered. In this situation, the filtration rate of these drugs is directly proportional to their free plasma concentrations. In CKD, medication elimination by glomerular filtration is decreased, resulting in a prolonged free drug elimination half-life. As the medication elimination decrease, biological active or toxic metabolite accumulates in the body. For example; the opioid analgesic meperidine undergoes biotransformation to normeperidine. Normeperidine, which is renally eliminated, has little analgesic activity but it has central nervous system stimulation and accumulation of such drug in the body, secondary to renal dysfunction lead to convulsion [30].

2.6 Drug Related Problems (DRPs) and Adverse Drug Reaction (ADR) Associated with Non-optimal Dose in Patients with Impaired Renal Function

The drug related problems are defined according to the definition of pharmaceutical care net work in Europe [31] “An event or circumstance involving drug therapy that actually or potentially interferes with patient health cares”. The

drug related problem which was compiled according to modified version of Strand et al., [32] is shown in table 1.

Table 1 Classification of drugs related problems

1	The need for additional drug
2	Unnecessary drug
3	Non optimal drug including drug formulation
4	Non optimal dosing including optimal dosing schedule
5	No further need for the drug
6	Drug-drug interaction
7	Adverse effect being experienced (ADR)
8	Need for laboratory test. e.g., therapeutic drug monitoring, laboratory value, microbiology
9	Medical chart error (e.g., dose not stated)
10	Compliance problem
11	Patient education required (giving patient information on physician request e.g., to avoid non-compliances)
12	Information therapy discussion (regarding a specific regimen for a patients)
13	Others

Adverse drug reaction remains a common problem in patient with renal impairment [33]. The accumulation of parents drugs and active or toxic metabolites could lead to unexpected drug reaction. The study have shown that most frequently reported drug related problem owing to dose related problem was 35.1%) [34]. Drug toxicity manifested by overdose is shown in table 2.

2.7 Dosage Adjustment

Initial Dose: The initial drug dose for a patients with renal failure is the same as that for the patient with normal renal function provided that the extracellular fluid volume of the patient is normal. However, in case of substantial edema or ascites is present, a large initial dose may be necessary. Conversely dehydrated and severely debilitated patients may require smaller initial dose[30].

Maintenance dose: After the initial dose, subsequent dosages may need to be modified in patients with diminished renal function. Published guidelines suggest methods for maintenance dosing adjustments in two ways; i. dose reduction ii. lengthening the dosing interval, or both. Dose reduction involves reducing each dose while maintaining the normal dosing interval. This approach maintains more constant drug concentrations, but it is associated with a higher risk of toxicities if the dosing interval is inadequate to allow for drug elimination. Normal dosage is maintained with the extended interval method, but the dosing interval is lengthened to allow time for drug elimination before redosing. Lengthening the dosing interval has been associated with a lower risk of toxicities but a higher risk of sub-therapeutic drug concentrations, especially towards the end of the dosing interval. According to the Drug Prescribing in Renal Failure; Dosing Guidelines for Adults, the guidelines are divided into three broad GFR categories [30].

i. Less than 10 mL per minute per 1.73 m^2

ii. 10 to 50 mL per minute per 1.73 m^2

iii. More than 50 mL per minute per 1.73 m^2.

2.8 Estimation of Glomerular Filtration Rate and Creatinine Clearance

Dosages of drugs cleared renally are based on renal function and are calculated as GFR or creatinine clearance. These calculations are valid only when renal function is stable and the serum creatinine level is constant. The K/DOQI clinical practice guideline [35] advocates using the traditional Cockcroft-Gault

equation or the Modification of Diet in Renal Disease (MDRD) study equation (full or abbreviated) for routine estimation of Glomerular Filtration Rate (GFR). However, in patients with a Glomerular Filtration Rate (GFR) lower than 60 mL per minute per 1.73 m^2, the MDRD equation has been shown to be superior to the Cockcroft-Gault equation [36] 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 90 mL per minute per 1.73 m^2 in older patients.

Cockroft- Gault equation **[37].**

If male

Creatinine Clearance (Cl_{Cr}) : $$\frac{(140\text{-age}) \times \text{weight}}{72 \times SCr}$$

If female

Creatinine clearance (Cl_{Cr}) : $$\frac{(140\text{-age}) \times \text{weight} \times 0.85}{72 \times SCr}$$

Where CrClis expressed in millilitres per minute, age in years, weight in kilograms and serum creatinine (SCr) in milligrams per deciliter

Estimated GFR using MDRD4 study equation **[38]:**

Male

eGFR : $186 \times (Scr)^{-1.154} \times (age)^{-0.203}$

(x 1.212 if the male is black)

Female

eGFR : $186 \times (Scr)^{-1.154} \times (age)^{-0.203} \times 0.742$

(x 1.212 if the female is black)

Where eGFR is expressed in milliliters per minute per 1.73 m^2, age in years and serum creatinine (SCr) in milligrams per deciliter.

2.9 Drugs Requiring Dosage Adjustment in Renal Impaired Patients

Analgesic Agents:

Most of the analgesic drugs are eliminated by hepatic metabolism. They require a little dosage adjustment in renal impairment patients. The drugs that need dosage adjustment are listed in table 2.

Table 2 Drugs that require dosage adjustment or contraindicated or need special precaution in patients with renal impairment

Medication	**Adjustment for Renal Failure**			**Toxicity due to over-dose**
	GFR, mL/min			
	>50	**10-50**	**<10**	
	Narcotics and Narcotics Antagonistics			
Codeine	100%	75%	75 %	CNS and Respiratory ADR
Morphine	100 %	75 %	50 %	CNS and Respiratory ADR
Methadone	100 %	100 %	50-75 %	Respiratory depression

Table 2 Drugs that require dosage adjustment or contraindicated or need special precaution in patients with renal impairment (continued)

Medication	**Adjustment for Renal Failure**			**Toxicity due to over-dose**
	GFR, mL/min			
	>50	**10-50**	**<10**	
	Angiotensin- Converting Enzyme (ACE) Inhibitors			
Captopril	100 %	75 %	50 %	Increase Serum Creatinine
Enalapril	100 %	50-100 %	25 %	-
Lisinopril	100 %	50-75 %	25- 50 %	-
Ramipril	100%	25-50 %	25 %	-
	B-blockers			
Atenolol	50-100 mg q 24 hr	25-50 mg q 24 hr	25 mg q 24 hr	Respiratory depression
Bosoprolol	100%	100%	505%	Respiratory depression
Procainamide	100%	50 %	25%	SLE symptom
Antihypertensive and Cardiovascular Agents				

Antihypertensive and cardiovascular drugs are most prescribed drugs in patient with renal impairment. Narrow therapeutic range and individual variability response have made the use of these drugs more complicated in this kind of patients. Some of these drugs and their metabolite accumulate in patients with renal insufficiency. For safe use of the drugs to prevent from the potential adverse effect, the guideline has recommended the dosing adjustment. The drugs requiring dosing adjustment are listed in table 2.

Table 2 Drugs that require dosage adjustment or contraindicated or need special precaution in patients with renal impairment (continued)

Medication	Adjustment for Renal Failure			Toxicity due to over-dose
	GFR, mL/min			
	>50	**10-50**	**<10**	
		Cardiac Glycoside		
Digitoxin	100%	100%	50-75%	Digitoxin toxicity
Digoxin	100%	25-75%	10-25%	Digitoxin toxicity
		Diuretic		
Acetazolamide	Q 6 hr	Q 12hr	Avoid	Impaired mental alertness, Respiratory acidosis

Table 2 Drugs that require dosage adjustment or contraindicated or need special precaution in patients with renal impairment (continued)

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Medication	Adjustment for Renal Failure			Toxicity due to over-dose
	GFR, mL/min			
	>50	10-50	<10	
Diuretic (continued)				
Amiloride	100%	50%	avoid	Rise in K, Metabolic / Respiratory acidosis
Chlorthalidone	Q 24 hr	Q 24 hr	avoid	Precipitation of gout in CKD
Spironolactone	Q6-12 hr	Q 12-24 h	avoid	Hyperkalemia, Gyenecomastia
Thiazide	100%	100%	avoid	Precipitation of gout in CKD
Aminoglycosides				
Amikacin	100% Q 12 -72 hr	100% Q 24-72 hr	100% Q 48-72 hr	Worsening of renal function / Ototoxicity
Gentamicin	100% 8-24 hr	100% 12-48 hr	100% 48-72 hr	Worsening of renal function / Ototoxicity

Table 2 Drugs that require dosage adjustment or contraindicated or need special precaution in patients with renal impairment (continued)

Medication	Adjustment for Renal Failure			Toxicity due to over-dose
	GFR, mL/min			
	>50	10-50	<10	
	Cephalosporins			
Cefadroxil	Q 12 hr	Q 12-24 hr	Q 36 hr	seizure
Cefazolin	100%	100%	50%	seizure
Cefepime	100%	50-100%	25050%	Seizure
Cefotaxime	Q 6 hr	Q6-12 hr	Q 24 hr	seizure
Cefoxitin	Q 6-8 hr	Q 8-12 h	Q 24-48hr	Seizure
Cephalexin	Q 6-8 hr	Q 8-12 hr	Q12-24 hr	Seizure
Cefpodoxime	Q 12 hr	Q 24 hr	Q 24 hr	seizure
	Macrolides			
Clarithromycin	100%	50-100%	50%	

Table 2 Drugs that require dosage adjustment or contraindicated or need special precaution in patients with renal impairment (continued)

Medication	Adjustment for Renal Failure			Toxicity due to over-dose
	GFR, mL/min			
	>50	10-50	<10	
		Miscellaneous		
Ertapenem	100%	100%	50%	seizure
Imipenem	100%	50%	25%	Seizure
Meropenem	100%	100% Q 12 hr	100% Q 24 hr	seizure
Sulfamethoxazole	Q 12 hr	Q 18hr	Q 24 hr	
Trimethoprim	Q 12 hr	Q 12 hr	Q 24 hr	
Vancomycin	1 g Q 12-24 hr	1g Q24-96 hr	1g Q 4-7 d	
		Penicillins		
Amoxicillin	Q8h	Q8-12 hr	Q24 hr	

Table 2 Drugs that require dosage adjustment or contraindicated or need special precaution in patients with renal impairment (continued)

Medication	Adjustment for Renal Failure			Toxicity due to over-dose
	GFR, mL/min			
	>50	10-50	<10	
	Penicillins			
Ampicillin	Q 6 hr	Q 6-12 hr	Q 12-24 hr	
Penicillin G	100%	75%	25-50%	Myoclonus seizure
Piperacillin	Q 6 hr	Q 6-12 hr	Q 12 hr	Neurotoxicity
Piperacillin Tazobactam	100%	2.25 g Q 6 hr (q 8 hr if CrCl < 20)	2.25 g Q 8 hr	Neurotoxicity
	Quinolones			
Ciprofloxacin	100%	50-75%	50%	Seizure
Levofloxacin	100%	250-750 mg q 24-48 hr (500-750 mg initial dose	250-500 mg q 48 hr (500 mg initial dose)	-
Norfloxacin	Q 12 hr	Q 12-24 hr	400 mg q 24 hr	

Table 2 Drugs that require dosage adjustment or contraindicated or need special precaution in patients with renal impairment (continued)

Medication	Adjustment for Renal Failure			Toxicity due to over-dose
	GFR, mL/min			
	>50	10-50	<10	
Antifungal				
Amphotericin B	Q 24 hr	Q 24 hr	Q 24 hr	Decrease renal function,
Fluconazole	100%	50%	50%	BUN increased, SCr increased,
Flucytosine	Q 12 hr	Q 12-24 hr	Q 24 -48 hr	
Itraconazole	100%	100%	50%	
Antimycobacterial Agents				
Ethambutol	Q 24 hr	Q 24-36 hr	Q 48 hr	Nephritis, Ototoxicity
Ethionamide	100%	100%	50%	
Para-amino salicylate sodium	100%	50-75%	50%	
Pyrazinamide	100%	100%	50%	Precipitate the gout

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Table 2 Drugs that require dosage adjustment or contraindicated or need special precaution in patients with renal impairment (continued)

Medication	Adjustment for Renal Failure			Toxicity due to over-dose
	GFR, mL/min			
	>50	10-50	<10	
Antiviral Agents				
Avacavir/Lamivudine	1 tab daily	Use individual drug		
Avacavir/Lamivudine /Zidovudine	100%	Avoid	avoid	
Acyclovir	100%	100%	50%	Renal failure
Amantadine	Q 12 hr	Q24-48 hr	Q 7 days	
Ganciclovir	50% Q12-24 hr	25-50% Q24 hr	25% 3x/week	
Lamivudine	100%	50-150 mg Q 24 hr (full first dose)	25-50 mg Q24 hr 50 mg first dose	

Table 2 Drugs that require dosage adjustment or contraindicated or need special precaution in patients with renal impairment (continued)

Medication	Adjustment for Renal Failure			Toxicity due to over-dose
	GFR, mL/min			
	>50	10-50	<10	
	Antiviral Agents (continued)			
Lamivudine/Zidovudine	100%	Avoid	avoid	
Zidovudine	100%	100%	100 mg q 8hr	
	Anticonvulsant Agents			
Amantadine	Q 12 hr	Q24-48 hr	Q 7 days	
Ganciclovir	50% Q12-24 hr	25-50% Q24 hr	25% 3x / week	
Lamivudine	100%	50-150 mg Q 24 hr (full first dose)	25-50 mg Q24 hr 50 mg first dose	
lamotrigine	100%	75%	100 mg qod	
Phenobarbital	Q 8-12 hr	Q 8-12 hr	Q 12-16 hr	Oliguria

Table 2 Drugs that require dosage adjustment or contraindicated or need special precaution in patients with renal impairment (continued)

Medication	Adjustment for Renal Failure			Toxicity due to over-dose
	GFR, mL/min			
	>50	10-50	<10	
Antihistamines				
Cetrizine	5 mg qd	5 mg qd	5 mg qd	
Fexofenadine	Q 12 hr	Q 12-24 hr	Q 24 hr	
Hydroxyzine	100%	50%	50%	
Ranitidine	75%	150 mg Q12-24 hr	75-150 mg Q 24 hr	SCr increased
Cetrizine	5 mg qd	5 mg qd	5 mg qd	
Arthritis and Gout Agents				
Allopurinol	75%	50%	25%	Interstitial nephritis
Colchicine	100%	50-100%	25%	

Table 2 Drugs that require dosage adjustment or contraindicated or need special precaution in patients with renal impairment (continued)

Medication	**Adjustment for Renal Failure**			**Toxicity due to over-dose**
	GFR, mL/min			
	>50	**10-50**	**<10**	
Arthritis and Gout Agents (continued)				
Probencid	100%	avoid	avoid	Nephritic syndrome, renal colic
Diclofenac sodium	50-100%	25-50%	25%	Abnormal renal function
Bronchodilators				
Terbutaline	100%	50%	50%	
Hypoglycemic Agents				
Acarbose	50-100%	avoid	avoid	Worsen renal function
Gliclazide	50-100%	avoid	avoid	-

Table 2 Drugs that require dosage adjustment or contraindicated or need special precaution in patients with renal impairment (continued)

Medication	Adjustment for Renal Failure			Toxicity due to over-dose
	GFR, mL/min			
	>50	10-50	<10	
Hypoglycemic Agents (continued)				
Metformin	50%	25%	Avoid	
Insulin	100%	75%	50%	
Gliclazide	50-100%	avoid	avoid	Lactic acidosis
Hypolipidemic Agents				
Gemfibrozil	100%	75%	50%	Worsening of renal function
Antiemetic Agents				
Metochloprapamide	100%	75%	50%	

Table 2 Drugs that require dosage adjustment or contraindicated or need special precaution in patients with renal impairment (continued)

Medication	Adjustment for Renal Failure			Toxicity due to over-dose
	GFR, mL/min			
	>50	**10-50**	**<10**	
	Sedative, Hypnotive and other Drugs Used in Psychiatric			
Chlordiazepoxide	100%	100%	50%	
Midazolam	100%	100%	50%	
Lithium carbonate	100%	50-75%	25-50%	Nephrotic syndrome

2.10 Framework of Dosage Adjustment in Renal Insufficiency Patients

The following outline provides a stepwise approach to assist physician in prescribing drug therapy in patients with impaired renal function (Table 3).

Table 3 Framework of dosage adjustment in patients with renal insufficiency [39]

Step 1	Take history and perform physical examination	Record current medications, including over-the-counter drugs, recreational drugs, alcohol use. Drug allergies & sensitivities should be noted. Physical examination should include the following: height, weight, extra-cellular volume status (jugular venous pulse, blood pressure & heart rate with orthostatic changes, edema, ascites, lung crackles) & look for signs of chronic liver disease.
Step 2	Determine the degree of renal insufficiency	Measure serum creatinine. Order 24-hour urine collection or calculate creatinine clearance.
Step 3	Review the medication list	Ensure that all drugs are still required and that new medications have specific indications. Evaluate for potential drug interactions.
Step 4	Choose less nephrotoxic drugs	If the use of nephrotoxic drugs cannot be avoided without patient morbidity or mortality then therapeutic drug monitoring or monitoring of renal function is mandatory.
Step 5	Select loading doses	These are usually the same for patients with both normal and abnormal renal function.

Table 3 Frame work of dosage adjustment in patients with renal insufficiency (Continued)

Step 6	Select a maintenance regimen	Either reduce the dose of the drug and maintain the usual dosing interval or maintain the drug dose and extend the interval. Remember to titrate the dose of the drug to patient effect, if applicable. For example, antihypertensives are dosed based upon blood pressure control, whereas antimicrobials are not adjusted according to response.
Step 7	Monitor drug levels	≤ Monitor drug levels if monitoring is available to guide further therapy
Step 8	Reassess	Reassess the patient to evaluate drug effectiveness & the need for ongoing therapy. If nephrotoxic drugs are used, remember to check the patient's serum creatinine & creatinine clearance again.

2.11 Studies on Drug Dosage Adjustment

A very few studies have been conducted in developed as well as other developing countries regarding the dose adjustment. However, to date, there are no existing data addressing the dose adjustment practice in Nepalese hospital setting.

In a prospective study [40] of hospital acquired renal insufficiency patients in USA, 2216 patient were evaluated to determine the iatrogenic factors to the development of renal insufficiency in hospitals. Of 2,216 patients at risk, some degree of renal insufficiency developed in 4.9%. Decreased renal perfusion, postoperative renal insufficiency, radiographic contrast media, and aminoglycosides accounted for 79 percent of the episodes. Iatrogenic factors, broadly defined, accounted for 55% of all episodes. In a recent biopsy study in 104 patients with acute chronic renal failure,

about 35% appeared to be drug-related [41]. In a prospective study covering 886 prescriptions, Solomon revealed that 34% were inappropriate, 14% being contraindicated, and 20% with inappropriate given with patients renal function [17]. Similarly, data analysis of 4 years prescriptions at a Tertiary Teaching Hospital in South Korea found that considering the patient's renal function, 5.3% of drug doses were excessive. The overdose rate in the patients with moderate to severe renal insufficiency was 28.2. Of 56 drugs studied, 10 drugs, including ranitidine, amoxicillin, and piperacillin / tazobactam, involved in 85.4% of the overdoses [18]. Likewise, a study done in Princess Alexandra Hospital, Brisbane, Queensland, Australia on 249 admission prescriptions by Pillans et al, [16] revealed that 24.2 % dosages were inappropriately used and 29.3 % prescriptions were continued with excessive dosages. Drug-related problems can result in an increase in morbidity and mortality, as well as an increase in the cost of healthcare. Inappropriate use of medications can increase adverse drug effects that may be reflected by excessive length of hospital stay, and excessive healthcare utilization and cost [42].

In a case-control study covering 17,828 patients, Chertow et al. [43] revealed that the inappropriate order rate of nephrotoxic or renally cleared medication for renally impaired patient in a hospital was 70%.

A retrospective, cross-sectional study done by Decloedt et al., [44] reported that, out of 615 prescription entries for the 97 patients with renal impairment, dosage adjustment was required in 19% (117/615) of total prescription entries and only 32 % (37/117) entries of these prescription were correctly adjusted. Of 97 patients 69 received one or more drugs that require dosage adjustment. All drugs doses were correctly adjusted in 12% (8/69) of patients. Most importantly, in the majority of patients 59 % (41/69), no drugs doses were correctly adjusted.

CHAPTER III

METHODS

3.1 Study Site

Tribhuvan University Teaching Hospital (TUTH)

Tribhuvan University Teaching Hospital, located in the capital city-Kathmandu occupying more than 450 beds was established in 1984 with support from Japan International Co-operation Agency (JICA). Tribhuvan University Hospital is currently the largest hospital in country, providing new tertiary level health service to the Nepalese people. This hospital is affiliated with Institute of Medicine and involves in teaching as well as research activities.

3.2 Study Design

This was a retrospective, cross-sectional, descriptive study, where all medication (toxic and / or metabolite or eliminated, TEM) records of the patients who had been admitted between October, 2012 to March, 2013 were studied.

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Study variables

- Patient's age
- Patient's sex
- Patient's weight
- Patients' Hospital days
- Total number of drug prescribed during hospital stay
- Total number of drugs prescribed at hospital discharge
- Serum creatinine
- Serum creatinine clearance

3.3 Sampling Frame and Sampling Method:

All the renal impaired patients admitted during the period of one year and the patients that met the inclusion criteria were identified by checking the admission register book and listed out from the admission record files in the computer. The Hospital / In-patient Numbers of patients were then noted. Among 310 medical files provided, one hundred and eighteen patients, diagnosed as chronic kidney disease by doctors were met the inclusion criteria and considered for further evaluation. Thereafter, two hundred and ninety-three TEM drugs, requiring dosage adjustments were extracted for further evaluation..

3.4 Inclusion Criteria

Patients :

All chronic kidney disease patients with renal impairment, defined as an estimated glomerular filtration rate (eGFR) $\leq$ 50 ml per minute per 1.73 m^2, who received treatment in the medical ward for at least 1 day after a serum creatinine test performed were enrolled.

Drugs :

All classes of drugs, mainly toxic and / or metabolite or eliminated (TEM) through kidney that were given to the patients on daily basis, which were prescribed at least one day after the measurement of serum creatinine.

3.5 Exclusion Criteria

Population:

i. Patients with unstable renal function (acute kidney injury)
ii. Acute renal failure on chronic kidney disease

Drugs: The following categories of prescribed drugs were excluded

i. Drugs that were prescribed as a SOS or PRN (if required)
ii. All classes of drugs which were prescribed in a STAT dose.
iii. Drugs in a topical dosage form

3.6 Sample size calculation:

Unit: The sampling unit of the study was drugs

$N = (z/e)^2 (\pi) (1- \pi)$

Z: 1.96 at 0.05 type I error

E = 5% (Acceptable error in the estimation of appropriateness of dosage adjustments)

π =25 % (Appropriateness of dosage adjustment from previous study) [16]

$N=(1.96/0.05)^2 \{(0.25 (1-0.25)\}$

=288 drugs

Sample size: 293 drugs (To optimize the sample size)

3.7 Data Collection Tools and Technique:

Data were collected in an data collection form (Appendix A). All the medical records of renal impaired patients were noted down via record book from medical record section.

3.8 Extraction of Drugs Details:

Medications with potential nephrotoxicity and / or elimination through renal excretion or metabolism were designated as TEM medications. Drugs details were extracted from the prescriptions charts on the day that clinical note indicated that the renal functions were reviewed.

3.9 Clinical Interpretation

Renal Risk Drugs and Categorization

Several classes of drugs including renal elimination, are recommended to be used with cautions in patients with renal impairment. These drugs are named as renal risk drugs. Renal risk drugs are further categorized in to three groups:

i. Drugs for which dosage adjustments are recommended
ii. Drugs to be used with caution
iii. Drugs to be avoided in renal impairment.

Extraction and Interpretation of Serum Creatinine (SCr) Value from Laboratory Data

- Patient's serum creatinine value was evaluated on each visit
- Creatinine measured values were extracted from the laboratory data.
- If serum creatinine values measured in a number of times on the same day, the highest serum creatinine value was considered as a reference to estimate the renal status of patients .
- If no serum creatinine value was measured on the prescription day, the nearest previous creatinine value before the starting of the really eliminated drug was taken to estimate the creatine clearance.
- Patients creatinine clearance was calculated on each visit.
- For the patients who had more than three serum creatinine values measured, serum creatinine that represents the closest in time before starting the renally eliminated drug(s), was taken as a reference for the estimation of renal status.
- The 1-day dose of a prescribed drug was calculated by multiplying the unit dose (mg) and frequency. The recommended 1-day dose (mg) for the patient's estimated creatinine clearance was selected from the renal dosing reference (e.g., Drug Prescribing in Renal Failure, The Sandford Guide to Antimicrobial Therapy, 2012.). An overdose was identified by comparing the 1-day dose of a prescribed drug with the maximally recommended dose for 1-day

Method for Estimation of Creatinine Clearance from Serum Creatinine and Grading of Renal Impairment.

Renal failure in this study was defined as the creatinine clearance less than 50 ml/min/1.73 m^2 and was subdivided in to 3 categories: Mild (30-50 ml/min/1.73m^2), moderate (10-29 ml/min/1.73m^2) and severe (10 ml/min/1.73m^2). The rationale of selecting 50 ml/min/1.73m^2 is the relationship between the creatinine clearance and plasma concentration (or half life or area under the curve) of drug eliminated predominantly via the kidney is exponential, plasma concentration

increases markedly when creatinine clearance falls below 50 ml/min/1.73m^2 and in this circumstances, need dose adjustment. The serum creatinine concentration, closest in time of TEM prescription was extracted from the laboratory data and serum creatinine clearance was calculated by the *Modification of diet in renal disease (MDRD4)* .

Estimation of Glomerular Filtration Rate (GFR) by Creatinine Clearance

The renal clearance of the endogenously produced creatinine is the most commonly used for the estimation of the GFR in the hospitalized patient. Creatinine, a product of protein metabolism, is primarily produced in the liver, pancreas, and kidneys and is actively transported into muscle tissue proportionally to muscle mass. Creatinine is passively filtered by glomerulous proportionately to the GFR, although 10 to 40% of the total creatinine found in urine is a result of active renal tubular secretion [45, 46].

A. Formulas to Estimate Creatinine Clearance (CrCl) in Adults:

There are many equations for rapid estimation of CrCl but the two major well-validated and commonly used equations for adult patients when SCr is steady state are the Cockroft-Gault equation and Jelliffe equation. The Cockroft-Gault equation is now commonly included in drug product labeling (package inserts) for individualizing drug dosage for renally cleared drug.

The Cockroft-Gault (table 4) and Jelliffe equation (table 5) work reasonably well for most adults with serum creatinine at steady state because they allow for declining muscle mass (and creatinine production) often associated with reduced weight and advancing age and are adjusted for the average smaller muscle mass of female. On the other hand, the Jelliffe equation is reasonable accurate for use when height and weight are not available in average size patient. The accuracy of these equations in predicting Cl_{Cr} is often limited in patients with various disease state or conditions like elderly, the malnourished, the obese, patients with amputation or

spinal cord injury, those with chronic renal insufficiency, acutely changing renal function, those with liver disease, critically ill patients and pediatric patients.

Table 4 Cockroft-Gault Equation [47]

If male	Creatinine Clearance (CrCl) :	$\frac{(140\text{-age}) \times \text{weight}}{72 \times \text{SCr}}$
If female	Creatinine Clearance (CrCl) :	$\frac{(140\text{-age}) \times \text{weight} \times 0.85}{72 \times \text{SCr}}$

Where CrCl is expressed in milliliters per minute, age in years, weight in kilograms and serum creatinine (SCr) in milligrams per deciliter. Since, creatinine, is produced in the liver, pancreas, and kidneys and is actively transported into muscle tissue proportionally to muscle mass, weight in the Cockroft-Gault equation is preferably ideal body weight (IBW) or actual body weight (ABW) if it is less than actual body weight).

IBW (males) (Kg) : 50 + [2.3(H-60)]

IBW (female) (kg) : 45.5 + [2.3(H-60)]

Where H is height in inches or

IBW (males) (Kg): 50+[0.9 (H-152)]

IBW (female) (kg): 45.5 + [0.9 (H-152)]

Where H is height in centimeters (cm)

Table 5 Jellife equation [48]

If male

Estimated Creatinine Clearance (CrCl)

$$\frac{98\text{-}0.8\ (\text{age-}20\ ) \times \text{BSA/mL/min/}1.73\text{m}^2}{(\text{SCr})}$$

If female

Estimated Creatinine Clearance (CrCl)

$$\frac{98 - 0.8\ (\text{age-}20\ ) \times 0.90\ \text{BSA/ mL/min/}1.73\text{m}^2}{(\text{SCr})}$$

In Jelliffe equation, the CrCl is normalized to body surface area by dividing the patient's BSA by 1.73 and multiplying BSA to CrCl from Jelliffe equation will be CrCl for dosage adjustment.

Body Surface Area Calculation:

BSA (m^2): $W^{0.5378}$ X $H^{0.3964}$ X 0.024265

Where W is weight (kg)

H is height (inch)

Estimation of Renal status Using MDRD4 Study equation

The National Kidney Disease Education Program (NKDEP) is currently recommending eGFR (estimated GFR) reporting along with serum creatinine to aid in the detection, evaluation and management of patients with chronic kidney disease. They recommend reporting exact equal value for eGFR of 60 ml/min/1.73 m^2 and below, but for value above 60 mL/min/1.73 m^2 they recommend reporting it as "> 60 mL/min/1.73 m^2." The rationales for this are :

i. The equation was more extensively studied in patients with chronic kidney disease
ii. The imprecision of creatinine assay have the greatest effect on near normal renal function and
iii. Quantification of GFR below 60mL/min/1.73 m^2 has more clinical implication from a disease progression point of view.

However, this abbreviated MDRD equation has not been validated in many population group including children, the elderly (>70 year). This equation is not weight based but is affected by obesity and other factors that affect creatinine production[49]. Abbreviated MDRD equation is presented in table 6 and table7.

Table 6 Abbreviated MDRD study equation [38]

Male	eGFR: 186 x (Scr) $^{-1.154}$ x (age) $^{-0.203}$ (x 1.212 if the male is black)
Female	eGFR: 186 x (Scr) $^{-1.154}$ x (age) $^{-0.203}$ x 0.742 (x 1.212 if the female is black)

Where eGFR is expressed in milliliters per minute per 1.73m², age in years and serum creatinine (SCr) in milligrams per deciliter.

Table 7 MDRD study equation in Nepalese population [50]

Male	eGFR: 186 x (Scr) $^{-1.154}$ x (age) $^{-0.203}$
Female	eGFR: 186 x (Scr) $^{-1.154}$ x (age) $^{-0.203}$ x 0.742

Where, eGFR is expressed in milliliters per minute per 1.73m², age in years and serum creatinine (SCr) in milligrams per deciliter.

Assessment of Appropriate and Inappropriate Dose

Medications with potential nephrotoxicity and / or elimination through renal excretion or metabolism were designated as TEM medications. 'Appropriateness' of the dosage of any TEM medications was defined as "the dosages were suitable based on the patient's CrCl." Prescriptions of any TEM medications were judged 'inappropriate' when the dosages prescribed were not in compliance with the adjustment required with regard to the patient's CrCl.

References Used for the Renal Drug Dosage Adjustment:

To assess the need of dosage adjustment, the following books/guideline were applied.

i. Drug Prescribing in Renal Failure [30]
ii. Online information from Micromedex Healthcare Service
iii. The Sanford Guide to Antimicrobial Therapy, 2012

Furthermore, in a case when guidelines differed from each other, either lowest percentage of reduction from the usual dose or the minimal interval prolongation were applied to minimize the overestimation.

Assessing Adverse Drug Reaction (ADR) in Patients Associated with Non-optimal Dose

Adverse drug reactions owing to overdose were assessed by evaluating patients medical history, medications charts and laboratory values using Naranjo's algorithm [51]. If the patients experience adverse drug reactions (ADR) caused by other reasons other than adverse drug reactions were also assessed accordingly.

The Naranjo's Scale: The Naranjo algorithm, or Naranjo drug related probability Scale, or Naranjo Nomogram is a questionnaire designed by Naranjo et al. for determining the likelihood of whether an ADR (adverse drug reaction) is actually due to the drug rather than the result of other factors. Probability is assigned as definite, probable, possible or doubtful. Values obtained from this algorithm are sometimes rated by many assessors to verify the validity of author's conclusions regarding adverse drug reactions. The Naronjo's Algorithm is shown in table 8.

Table 8 The Naranjo's Algorithm

	Question	Yes	No	Do not score know
1	Are there previous conclusive reports on this reaction?	+1	0	0
2	Did the ADR appear after the suspected drug was administered?	+2	-1	0
3	Did the ADR improved when the drug was removed or a specific antagonist was administered?	+1	0	0

Table 8 The Naranjo's Algorithm (continued)

	Question	Yes	No	Do not know	score
4	Did the ADR reappear when the drug was readministered?	+2	-1		
5	Are there alternative cause that could on their own have the reaction?	-1	+2	0	
6	Did the reaction reappear when the placebo was given?	-1	+1	0	
7	Was the drug detected in the blood (or other fluids) in concentration known to be toxic?	+1	0	0	
8	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9	Did the patient have similar reaction to the same or similar drug in any previous exposure?	+1	0	0	
10	Was the adverse event confirmed by the objective evidence?	+1	0	0	

Total Score:…….

Naranjo total scores of 9 or 10 indicate that an event is "definitely" an ADR; scores of 5-8 rate the likelihood as "probable"; scores of 1-4 are "possible"; and scores of less than 1 are "doubtful."

3.10 Statistical Analysis

A. Descriptive Analysis:

In this study, the numerical data e.g., age, body weight, creatinine value (mg/dL), hospital stay days and total drugs prescribed per prescription were presented as mean ± SD. Also, frequency of the most prescribed drugs, frequency of the contraindicated drugs, and overdose rate were summarized as percentage (%) value.

Age, Weight and Serum Creatinine of the Patients:

The age group of the patients were categorized as

a. > 18-39 year

b. ≥ 40 year

The age, weight and serum creatinine of the patients were presented as mean ± SD

Creatinine Clearance (CrCl): The creatinine clearance of the patient were categorized as

a. 10-50 ml/min (Mild to moderate CKD)

b. <10 ml/min (Severe CKD)

Total hospital stay days: The total hospital stay days was presented in mean ± SD.

Analysis of Appropriateness of Dose Adjustment

i. Appropriateness of Adjusted Dose Rate :

$$\frac{\text{No. of adjust dose} \times 100\ \%}{\text{Total no. of drugs}}$$

ii. Overdose Rate (in percentage)

$$\frac{\text{No. of over dose} \times 100\ \%}{\text{Total no. of drugs}}$$

iii. Analysis of Frequency Contraindicated Drugs (%)

$$\frac{\text{No. of contraindicated drug} \times 100\ \%}{\text{Total no. of drugs}}$$

B. Analysis of Categorical Data

Chi-square test: In the present study, Chi-square test was applied to depict the relationship between categorical data of renal status and dosage adjustment. Ninety five percentage confidential intervals (CI) was used to find out the association

between different variable such as dose adjustment and renal status. A *p*-value less than 0.05 was considered statistically significant.

3.11 Ethical Issue

The study protocol was ethically approved by National Health Research Council (NHRC), Nepal and the approval was made by the hospital authorities prior to conduct the study.

3.12 Validity Test

The validity of dosage adjustments, using Kappa test, was done to measure the agreement of dosage adjustments made by two independent clinical experts in 82 medications, prescribed for 20 renal impaired cases. The measurement of agreement (K) value 0.817, asymptotic standard error; 0.126, approximate significant level; 0.000, shown by the Kappa test depicted that there is high agreement of dosage adjustments done by two individual experts.

CHAPTER IV

RESULTS

4.1 Demographic Data of the Study Population

Demographic data of all 118 hospital admissions patients are shown in table 9. The mean age and the mean body weight were 47.47 years (range, 18-66) and 56.28 kg (range, 41-71), respectively. Among these population, 77 (65.25%) were male whereas, 41 (34.75%) were female. The mean hospitalization days was 11.44 ± 9.72 days (range, 3-53).

Hypertension was the major underlying disease of these patients, encompassing 60% of the subjects followed by diabetes mellitus (7.6%). Both hypertension and diabetes mellitus were encountered in 27.12% of total cases. Others (CHF, IHD, stroke, TB) were found in 11.86% of the subjects.

Table 9 Demographic data of the number of hospital admissions of the enrolled patients

Parameters	**Inference**
Age (years), mean ± SD (range)	47.47 ± 15.55 (18-76)
Weight (kgs), mean ± SD (range)	56.28 ± 8.24 (41-71)
Male, n (%)	77 (65.25)
Female, n (%)	41 (34.75)
Length of hospitalization (days), mean ± SD (range)	11.44 ± 9.72 (3-53)
Cases of death during hospitalization, n (%)	2 (1.69)

Table 9 Demographic data of the number of hospital admissions of the enrolled patients (continued)

Underlying disease, n (%)	
HTN	60 (50.85)
DM	9 (7.63)
HTN+DM	32 (27.13)
Others	14 (11.86)

4.2 Biochemical Profile and Severity of Renal Impairment

Biochemical data (serum creatinine) and severity of renal function of the study population are summarized in table 10. In 118 patients considered as having renal impairment, the mean serum creatinine and the mean creatinine clearance were 5.16 mg/dL (range, 2.17-9.80) and 15.05 ± 7.05 mL/min (range, 2.09-32.45), respectively. Most patients belonged to moderate renal function, accounting 74 (63%) of total subjects whereas, 44 (37*%)* were in severe renal impairment.

Table 10 Biochemical profile and severity of renal impairment.

Parameters	**Inference**
Serum creatinine (mg%), mean ± SD: (range)	5.16 ± 1.93 (2.17- 9.80)
Creatinine clearance (mL/min), mean ± SD: (range)	15.10 ± 7.04 (2.09- 32.45)
Renal status	
i. moderate, n (%)	74 (62.71)
ii. severe, n (%)	44 (37.29)

Note, moderate (CrCl < 50 mL/min/1.73 m^2), severe (CrCl < 10 mL/min/1.73 m^2)

4.3 Prescriptions Order Sheet

Details of the prescriptions order sheet including number of medications and the number of drugs requiring dosage adjustment or needed to be used with caution according to the degree of renal impairments are summarized in table 11. It exhibits that there were 1133 orders of prescriptions entries for the 118 hospital admissions patients, an average of 9.60 medications per patient. Among those, a total of 639 medications were characterized for TEM group, and were prescribed with an average of 5.44 ± 1.88 drugs (range: 2-14) per patient. Two hundred and ninety three medications in the prescription, an average of 2.59 TEM medications per patient (range, 1-6) need dosage adjustment or need to be used with caution. According to the degree of renal impairment, 225 and 68 TEM drugs were prescribed in moderate and severe cases, respectively. They all were filled and had a guideline for dosage adjustment.

Table 11 Medications in prescriptions order sheet

Parameters	**inference**
Total no. of medications	1133
Number of medications per patient, *n* ± SD (range)	9.60 ± 2.29 (6-16)
Total number of TEM drugs, *n* : mean (range)	639 : 5.44 ± 1.88 (6-16)
TEM drugs requiring dosage adjustment or usage with precaution, n mean ± (range)	293: 2.59 ± 1.43 (1-6)
Number of patients with TEM drugs	
i. Patients with moderate renal impairment	225
ii. Patients with severe renal impairment	68

Note, Moderate (CrCl < 50 mL/min/1.73 m^2) , Severe (CrCl < 10 mL/min/1.73 m^2)

4.4 Prescribing patterns of medications in hospitalized patients

Details of the various classes of drugs and their appropriateness according to the degree of renal dysfunction of the study patients are summarized in table 12. 79.78% of the medication prescriptions were filled at appropriate dose. Among 118 hospital admissions patient studied, 34 patients received at least one inappropriate medications. The prescriptions were analyzed according to the renal status of each patient. It revealed that, of total 293 TEM medications, 225 drugs were prescribed for the patient with mild to moderate (CrCl 10-50 mL/min) and 68 in severe (CrCl < 10 mL/min) renal impairment patients (Table 11). Data analysis revealed that 7.89% and 12.40% drugs were prescribed at high dose in moderate and severe renal impaired cases, respectively.

It is apparent from the table that atenolol, constituting a total of 10.48% of TEM drugs (28/267), was the most frequently prescribed cardiovascular drugs that required dosage adjustment followed by clonidine 2.99% (8/267), enalapril 2.24 % (6/263), digoxin 1.87% (5/267), enoxaparin 0.8% (3/267), bisoprolol 0.37% (1/267) and tranexamic acid 0.37% (1/267), respectively. Among those drugs 64.94% (9/37) prescription of atenolol, 40% (2/5) of digoxin, were found to be at inappropriate dose followed by clonidine 14.29% (1/8). Tranexamic acid was prescribed in one case and did not conform to guideline for dosage adjustment.

The table demonstrates that among the gastrointestinal drugs including ranitidine 1.87 % (5/267) and metoclopramide 0.74% (2/267). Forty percentage (2/5) of ranitidine prescription was at inappropriate dose, whereas, metocloprapamide were prescribed appropriately in al two cases.

Assessment of medication for arthritis and gout showed that allopurinol 3.37% (9/267) and colchicine 1.12% (3/267) required dosage adjustment. Of them 66% (2/3) of colchicine and 33.33 % (3/9) of allopurinol dosage were not appropriate. (Table 12).

Similarly, 35.20% (94/267) antibiotics were concerned for dosage adjustment. Antibiotics found in the study were cephalosporins 21.34% (57/267),

metronizole 6.74% (18/267), aminoglycosids 6.36% (17/267), antitubercular 6.36% (17/267), penicillin 5.61% (15/267), quinolone, 5.245% (14/267), vancomycin 4.86% (13/267), sulfamethoxazole-trimethoprim 2.99% (8/267), carbapenem 2.24% (6/267), antifungal 1.49 (4/267) and anti-viral 0.74% (2/267).

Amongst those drugs, 85.71% (6/7) of amoxicillin plus clavulanic acid, 85.71% (6/7) cefixime, 60% (3/5) meropenem, 45.45% (5/11) cefepime, 33.33% (1/3) ciprofloxacin, 25% (2/8) levofloxacin, 20 % (1/5) piperacillin-tazobactum, 12.22 % (4/18) metronidazole and 11.11% (1/90) pyrazinamide were prescribed at inappropriate dose. Similarly, a total 62.50 % (5/8) of SMZ-TMP were prescribed in severe renal impairment and all were used at excessive dose.

Lamivudine was prescribed in 3 cases. Each renal impaired cases was rated as appropriate. Appropriateness of dosages adjustments were significantly higher in metronidazole ($P < 0.02$), SMZ-TMP ($P < 0.04$) and meropenem ($P < 0.03$) among patients with moderate compared to those in severe renal impairments.

Table 12 Patterns of appropriate and inappropriate drugs in hospitalized patients

Drugs	**Drug frequency**	**Appropriateness of drug dose according to the severity of renal dysfunction patients**		**Total (%)**	**Appropriateness of drug dose according to the severity of renal dysfunction patients**		**Total (%)**	χ^2 ***(P)***
		Moderate (N)	***Severe (N)***		***Moderate(N)***	***Severe (N)***		
Digoxin	5	1 (20)	2 (40)	3 (60)	0 (0.00)	2 (40)	2 (40.00)	0.36
AML-ATN	9	3 (33.33)	4 (44.44)	7 (77.78)	2 (22.22)	0 (0.00)	2 (22.22)	0.15
Bisoprolol	1	1 (0.00)	0 (0.00)	1 (100)	0 (0.000)	0 (0.00)	0 (0.00)	
MET-RMP	1	1 (0.00)	0 (0.00)	1(100)	0 (0.00)	0(0.00)	0 (0.00)	
Atenolol	28	17 (70.71)	4 (14.29)	21 (75.00)	4 (14.29)	3 (10.71)	7 (25.00)	0.21
Enalapril	6	3 (50.00)	3 (50.00)	6 (100)	0 (0.00)	0 (0.00)	0 (0.00)	
Clonidine	8	2 (25.00)	5 (62.50)	7 (87.50)	0(0.00)	1 (12.50)	1 (14.29	0.17

Note, AML-ATN: Amlodipine-atenolol, MET-ATN: Metoprolol-atenolol, χ^2: chi square

Table 12 Patterns of appropriate and inappropriate drugs in hospitalized patients (continued)

Drugs	**Drug frequency**	**Appropriateness of drug dose according to the severity of renal dysfunction patients**		**Total (%)**	**Appropriateness of drug dose according to the severity of renal dysfunction patients**		**Total (%)**	χ^2 ***(P)***
		Moderate (N)	***Severe (N)***		***Moderate(N)***	***Severe (N)***		
Enoxaparin	3	3 (100)	0 (0.00)	3 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	
Rosuvastatin	1	1 (100)	0 (0.00)	1 (100)	0 (0.00)	0 (0.00)	0 (0.00)	
Tramadol	1	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (100)	1 (100)	
Codeine +PCM	2	1 (50.0)	1 (50.0)	2 (100)	0 (0.00)	0 (0.00)	0(0.00)	
Ketorolac	2	2 (100)	0 (0.00)	2 (100)	0 (0.00)	0 (0.00)	0 (0.00)	
Gabapentin	2	2 (100)	0 (0.00)	2 (100)	0 (0.00)	0 (0.00)	0 (0.00)	
Diclofenac Sod.	1	1(100)	0 (0.00)	1(0.00)	0 (0.00)	0 (0.00)	0 (0.00)	
Metocloprapamide	2	1(50.00)	1(50.00)	2(100)	0(0.00)	0(0.00)	0(0.00)	

Note, PCM: Paracetamol, Diclofenac sod.: Diclofenac sodium, χ^2: chi square

Table 12 Patterns of appropriate and inappropriate drugs in hospitalized patients (continued)

Drugs	**Drug frequency**	**Appropriateness of drug dose according to the severity of renal dysfunction patients**		**Total (%)**	**Appropriateness of drug dose according to the severity of renal dysfunction patients**		**Total (%)**	χ^2 **(P)**
		Moderate (N)	***Severe (N)***		***Moderate (N)***	***Severe (N)***		
Allopurinol	9	7 (77.78)	0 (0.00)	7 (77.78)	1 (11.11)	1 (11.11)	2 (22.22)	0.05
Colchicine	3	1 (33.33)	1 (33.33)	2 (66.67)	0 (0.00)	1 (33.00)	1 (33.0)	0.39
Levetiracetam	1	1 (100)	0 (0.00)	1 (100)	0 (0.00)	0 (0.00)	0 (0.00)	
Tranexamic acid	1	0 (0.00)	0 (0.00)	0 (0.00)	1 (100)	0 (0.00)	1 (100)	
Ranitidine	5	2 (40.00)	1 (20.00)	3 (60.00)	0 (0.00)	2 (40.00)	2 (40.0)	0.14
Amikacin	17	13 (76.47)	3 (17.65)	16 (94.12)	1 (5.88)	0 (0.00)	1 (5.88)	0.21
Norfloxacin	1	1 (100)	0 (0.00)	1 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	
Ciprofloxacin	3	2 (66.67)	0 (0.00)	2 (66.67)	1 (33.33)	0 (0.00)	1(33.33)	

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Table 12 Patterns of appropriate and inappropriate drugs in hospitalized patients (continued)

Drugs	**Drug frequency**	**Appropriateness of drug dose according to the severity of renal dysfunction patients**		**Total (%)**	**Appropriateness of drug dose according to the severity of renal dysfunction patients**		**Total (%)**	χ^2 **(P)**
		Moderate (N)	***Severe (N)***		***Moderate (N)***	***Severe (N)***		
Levofloxacin	8	4 (50.00)	2 (25.00)	6 (75.00)	0 (0.00)	2 (25.00)	2 (25.00)	0.10
Ofloxacin	2	1 (50.00)	1 (50.00)	2 (100)	0 (0.00)	0 (0.00)	0 (0.000	
Clarithromycin	2	1 (50.00)	1 (50.00)	2 (50.00)	0 (0.00)	0 (0.00)	0(0.00)	
Amoxicillin	3	1 (33.33)	2 (66.67)	3 (100)	0 (0.00)	0 (0.00)	0 (0.00)	
AMX-CLV	7	1 (14.29)	0 (0.00)	1 (14.29)	4 (57.14)	2 (28.57)	6 (85.71)	0.47
Metronidazole	18	12 (66.67)	2 (11.11)	14 (77.78)	1 (5.56)	3 (16.67)	4 (12.22)	0.02
Cefazolin	23	8 (34.78)	15 (65.22)	23 (100)	0 (0.00)	0 (0.00)	0 (0.00)	
Cefixime	7	1 (14.29)	0 (0.00)	1 (14.29)	4 (57.14)	2 (28.57)	6 (85.71)	0.49
Ceftazidime	6	3 (50.00)	3 (50.00)	6 (100)	0 (0.00)	0 (0.00)	0 (0.00)	

Note, AMX_CLV: Amoxicillin- clavulanic acid, χ^2: chi square

Table 12 Patterns of appropriate and inappropriate drugs in hospitalized patients (continued)

Drugs	**Drug frequency**	**Appropriateness of drug dose according to the severity of renal dysfunction patients**		**Total (%)**	**Appropriateness of drug dose according to the severity of renal dysfunction patients**		**Total (%)**	χ^2 ***(P)***
		Moderate (N)	***Severe (N)***		***Moderate (N)***	***Severe (N)***		
Cefadroxil	1	1 (100)	0 (0.00)	1 (100)	0 (0.00)	0 (0.00)	0 (0.00)	
Cefotaxime	3	2 (66.67)	1 (33.33)	3 (100)	0 (0.00)	0 (0.00)	0 (0.00)	
Cefpodoxime	6	3 (50.00)	3 (50.00)	6 (100)	0 (0.00)	0 (0.00)	0 (0.00)	
Cefepime	11	4 (36.36)	2 (18.18)	6 (54.55)	1 (9.09)	4 (36.36)	5(45.45)	0.18
Imipenem	1	1 (100)	0 (0.00)	1 (100)	0 (0.00)	0 (0.00)	0 (0.00)	
Ethambutol	8	5 (62.50)	3 (37.50)	8 (100)	0 (0.00)	0 (0.00)	0 (0.00)	
Pyrazinamide	9	5 (55.56)	3 (33.33)	8 (88.89)	1 (11.11)	0 (0.00)	1 (11.11)	0.45
SMZ/TMP	8	3 (37.50)	0 (0.00)	3 (37.50)	0 (0.00)	5 (62.50)	5 (62.50)	0.04

Note, SMZ-TMP: Sulfamethoxazole-trimethoprim, χ^2: chi square

Table 12 Patterns of appropriate and inappropriate drugs in hospitalized patients (continued)

Drugs	Drug frequency	Appropriateness of drug dose according to the severity of renal dysfunction patients		Total (%)	Appropriateness of drug dose according to the severity of renal dysfunction patients		Total (%)	χ^2 (P)
		Moderate (N)	*Severe (N)*		*Moderate (N)*	*Severe (N)*		
Pyrazinamide	9	5 (55.56)	3 (33.33)	8 (88.89)	1 (11.11)	0 (0.00)	1 (11.11)	0.45
SMZ/TMP	8	3 (37.50)	0 (0.00)	3 (37.50)	0 (0.00)	5 (62.50)	5 (62.50)	0.04
Cyclophosphamide	2	2 (100)	0 (0.00)	2 (100)	0 (0.00)	0 (0.00)	0 (0.00)	
Lamivudine	3	3 (100)	0 (0.00)	3 (0.000	0 (0.00)	0 (0.00)	0 (0.00)	
Fluconazole	4	3 (75.00)	1 (25.00)	4 (100)	0 (0.00)	0 (0.00)	0 (0.00)	
PIP-TAZ	5	3(60.00)	1(20.00)	4(80.00)	0(0.00)	1(20.00)	1(20.00)	0.17
Vancomycin	13	8(61.54)	5(38.64)	13(100)	0(0.00)	0(0.000	0(0.00)	
	267	**143**	**70**	**213 (79.8)**	**21 (7.86)**	**33 (12.35)**	**54 (20.22)**	**267**

Note, SMZ_TMP: Sulfamethoxazole-trimethoprim, χ^2: chi square

4.5 Drugs to be Used with Caution in Hospitalized patients

The drugs that were regarded to be used with caution in different stages of kidney disease are presented in table 13. Aspirin was the most frequently ordered drug to be used with caution, constituting a total of 6.82% (20/293). Repaglinide, mycophenolate, thalidomide and escitalopram were also found to be prescribed in the subjects.

Because of the hemorrhagic diathesis in patients with severe renal impairments and variability of the salicylic elimination, it warrants to be used with caution. Use of escitalopram in severe renal impairment may increase bioavailability and half life, necessities to be used with caution. Mycophenolate should be used with cautious as toxicity may be increased (infection, neutropenia) and may warrant dose adjustment at severe renal impairment. Hematuria may occur from thalidomide and warrants to be used with caution in severe renal patients. Repaglinide is advocated to be used with caution in severe renal impairment as it may be more susceptible to glucose lowering effect.

Table 13 Drugs to be used with caution in hospitalized patients

		Renal status	
Drugs	**frequency**	**Moderate, n (%)**	**Severe, n (%)**
Aspirin	20	10 (50.00)	10 (50.00)
Repaglinid	2	1(50.00)	1 (50.00)
Mycophenolate	1	0 (0.00)	(100)
Thalidomide	1	1(100)	0 (0.00)
Escitalopram	2	0(0.000	2 (100)
Total	26	12 (46.16)	14 (53.84)

4.6 Contraindicated Drugs

Nitrofurantoin is considered as a contraindicated drug and was prescribed in one severe renal impairment patient.

4.7 Prescriptions Order Sheet at Hospital Discharged Patients

Details of the prescribed medications according to the degree of renal impairments at the hospital discharge are presented in table 14. Eight hundred and forty eight medications were prescribed in 116 patients, an average of 6.78 medications per patient. Among those, a total of 404 drugs were referred to TEM group, an average of 3.42 ± 1.25 (range: 2-7) items were prescribed per patient. A total of 163 TEM medication were prescribed for 116 patients where 135 medications required dosage adjustment and 28 needed to be used with caution.

Table 14 Prescriptions order sheet at hospital discharged patients

Parameters	Inference
Total no. of drugs, n mean ± SD: (range)	848, 6.78 ± 2.23 (2-11)
Total no. of TEM drugs(n), mean ± (range)	404, 3.42 ± (2-7)
Total no. of TEM drugs that needed dose adjustment or needed to be used with caution (n), mean ± SD (range)	135, 1.65 ± 0.88 (0-4)
Total no. of TEM drugs requiring dose adjustment according to the degree of renal impairment ,	
Moderate renal impairment, *n*	90
Severe renal impairment, *n*	45

Note, Moderate (CrCl < 50 mL/min/1.73 m^2), Severe (CrCl < 10 mL/min/1.73 m^2)

4.8 Prescribing Patterns of Medications at Hospital Discharged Patients

Details of the various classes of drugs that were prescribed in different stages of renal impairment patients and their proportion of dosage appropriateness are summarized in table 15. It showed that 80% of the medication dosage was appropriate. Of the 116 hospital admissions patients enrolled for the study, 96 hospital admissions patients continued receiving at least one TEM medication at hospital discharge. The prescriptions were also evaluated according to the degree of renal dysfunction of each patient. A total 135 TEM medications were required for dosage adjustment. However, according to the severity of renal impairments, there were 90 drugs prescribed in patients with moderate (CrCl 10-50 mL/min) renal impairment and, 45 in severe (CrCl < 10 mL/min) impairment cases at hospital discharge. Data analysis of these medications showed that, 10.37% and 9.63% drugs were inappropriately used in moderate and severe renal impairments cases, respectively.

Noticeably, atenolol was the most frequently prescribed cardiovascular drugs that were regarded for dosage adjustment (19/135) followed by clonidine (6/135), enalapril (6/135), digoxin (1/135), enoxaparin (3/135), bisoprolol (1/135), ramipril (1/135) and tranexamic acid (1/135) respectively. Markedly, 25% prescription for atenolol doses was not ordered properly followed by clonidine (16.67%).

For medications for arthritis and gout, 5.92% (8/135) allopurinol and 2.22% (3/135) colchicine were ordered, and the analysis showed that 66.67% of colchicine was prescribed at too high dose.

Cetrizine was prescribed in one case and was evaluated as overdose. Tramadol and codein were prescribed in total 3 cases.

Similarly, the details of the antibiotics are shown in table 15. Antibiotics accounts for 46.66% (59/135) of TEM drugs requiring dose adjustment. Among them, 18.51% (25/135) were cephalosporin, 22.95% (17/135) Antitubercular, 2.96% (4/135) Antifungal, 3.07 % (5/135) SMZ-TMP, 2.96% (4/135) Metronidazole,

2.22% (3/135) quinolone, 0.74% (1/135) Aminoglycoside, and 0.74% (1/135) Macrolide. Data analysis of these prescriptions showed that, 75% (9/12) cefixime, 12.50% (1/8) ethambutol were inappropriately dosed at hospital discharged patients.

Table 15 Pattern of appropriate and inappropriate drugs at hospital discharged patients

Drugs	Drug frequency (f)	Appropriateness of drug dose according to the severity of renal dysfunction patients		Total (%)	Inappropriate drug dose according to the severity of renal dysfunction patients		Total (%)	χ^2 (P)
		Moderate (%)	Severe (%)		Moderate (%)	Severe (%)		
Digoxin	1	1(100)	0 (0.00)	1 (100)	0 (0.00)	0 (0.00)	0 (0.00)	
AML-ATN	6	2 (33.33)	1 (16.67)	3 (50.00)	2 (33.33)	1 (16.67)	3 (50.00)	1.00
Bisoprolol	1	1 (100)	0 (0.00)	1 (100)	0 (0.00)	0 (0.00)	0 (0.00)	
MTP-RMP	1	1 (100)	0 (0.00)	1 (100)	0 (0.00)	0 (0.00)	0 (0.00)	
Atenolol	19	11 (57.89)	5 (26.32)	16 (84.21)	2 (10.53)	1 (5.26)	3 (15.79)	0.94
Enalapril	6	3 (50.00)	3 (50.00)	5 (100)	0 (0.00)	0 (0.00)	0 (0.00)	
Clonidine	6	2 (33.33)	3 (50.00)	5 (83.33)	1 (16.67)	0 (0.00)	1 (16.67)	0.27

Note, AML-ATM: Amlodipine-atenolol, χ^2: chi square

Table 15 Pattern of appropriate and inappropriate drugs at hospital discharged patients

Drugs	Drug frequency (f)	Appropriateness of drug dose according to the severity of renal dysfunction patients		Total (%)	Inappropriate drug dose according to the severity of renal dysfunction patients		Total (%)	χ^2 (P)
		Moderate (%)	*Severe (%)*		*Moderate (%)*	*Severe (%)*		
Enoxaparin	1	1 (100)	0 (0.00)	1 (100)	0 (0.00)	0 (0.00)	0 (0.00)	
Rosuvastatin	1	1 (100)	0 (0.00)	1 (100)	0 (0.00)	0 (0.00)	0 (0.00)	
Tramadol	1	1 (100)	0 (0.00)	1 (100)	0 (0.00)	0 (0.00)	0 (0.00)	
Codein -PCM	2	1 (50.0)	1 (50.0)	2 (100)	0 (0.00)	0 (0.00)	0 (0.00)	
Gabapentin	2	2 (100)	0 (0.00)	2 (100)	0 (0.00)	0 (0.00)	0 (0.00)	
Colchicine	3	1 (33.33)	0 (0.00)	1 (33.33)	1 (33.33)	1 (33.00)	2 (66.67)	0.39
Allopurinol	8	7 (87.50)	1 (12.50)	8 (100)	0 (0.00)	0 (0.00)	0 (0.00)	

Note, PCM: Paracetamol, χ^2: chi square

Table 15 Pattern of appropriate and inappropriate drugs at hospital discharged patients

Drugs	Drug frequency (f)	Appropriateness of drug dose according to the severity of renal dysfunction patients		Total (%)	Inappropriate drug dose according to the severity of renal dysfunction patients		Total (%)	χ^2 (P)
		Moderate (%)	Severe (%)		Moderate (%)	Severe (%)		
Metocloprapamide	2	1 (50.00)	1 (50.00)	2 (100)	0 (0.00)	0 (0.00)	0 (0.00)	
Leviteracetam	1	1 (100)	0 (0.00)	1 (100)	0 (0.00)	0 (0.00)	0 (0.00)	
Tranexamic acid	1	0 (0.00)	0 (0.00)	0 (0.00)	1 (100)	0 (0.00)	1 (100)	
Ranitidine	4	2 (50.00)	0 (50.00)	2 (50.00)	1 (25.00)	1 (25.00)	2 (50.00)	0.25
Cetrizine	1	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (100)	1 (100)	
Amikacin	1	0 (0.00)	1 (100)	1 (1000	0 (0.00)	0 (0.00)	0 (0.00)	
Norfloxacin	1	1 (100)	0 (0.00)	1 (100)	0 (0.00)	0 (0.00)	0 (0.00)	

Note, χ^2 : chi square

Table 15 Pattern of appropriate and inappropriate drugs at hospital discharged patients

Drugs	**Drug frequency (f)**	**Appropriateness of drug dose according to the severity of renal dysfunction patients**		**Total (%)**	**Inappropriate drug dose according to the severity of renal dysfunction patients**		**Total (%)**	χ^2 ***(P)***
		Moderate (%))	***Severe (%)***		***Moderate (%)***	***Severe (%)***		
Ciprofloxacin	1	1(100)	0(0.00)	1(100)	0(0.00)	0(0.00)	0(0.00)	
Levofloxacin	1	1(100)	0	1(100)	0(0.00)	0 (0.00)	0 (0.00)	
Clarithromycin	1	0(0.00)	0(0.00)	0(0.00)	1(100)	0(0.00)	1(100)	
Amoxicillin	1	0(0.00)	0(0.00)	0(0.00)	0(0.00)	1(1000	1(100)	
AMX-CLV	2	0(0.00)	0(0.00)	0(0.00)	0(0.000	2(100)	2(100)	
Metronidazole	4	4(100)	0(0.00)	4(1000	0(0.00)	0(0.00)	0(0.00)	
Cefixime	12	3(25.0)	0(0.00)	3(25.00)	5(41.67)	4(33.33)	9(75.00)	0.16

Note, AMX-CLV: Amoxicillin- clavulannic acid, χ^2 : chi square

Table 15 Pattern of appropriate and inappropriate drugs at hospital discharged patients

Drugs	Drug frequency	Appropriateness of drug dose according to the severity of renal dysfunction patients		Total (%)	Inappropriate drug dose according to the severity of renal dysfunction patients		Total (%)	χ^2 (P)
		Moderate (%)	Severe (%)		Moderate (%)	Severe (%)		
Cefadroxil	1	0(0.00)	1(100)	1(100)	0(0.00)	0(0.00)	0(0.00)	
Cefpodoxime	12	7(53.9)	6(46.15)	13(100)	0(0.00)	0(0.00)	0(0.00)	
Ethambutol	8	5(62.5)	2(25.00)	7(87.50)	0(0.00)	1(12.50)	1(12.50)	0.17
Pyrazinamide	9	6(66.67)	3(33.33)	9(100)	0(0.00)	0(0.00)	0(0.00)	
SMZ-TMP	5	2(40.00)	3(60.00)	5(100)	0(0.00)	0(0.00)	0(0.00)	
Fluconazole	4	3(75.00)	1(25.00)	4(100)	0 (0.00)	0 (0.00)	0 (0.00)	
Cyclophosphamide	2	2(100)	0(0.00)	2(100)	0(0.00)	0(0.00)	0(0.00)	

Note, SMZ-TMP: Sulfamethoxazole-trimethoprim, χ^2: chi square

Table 15 Pattern of appropriate and inappropriate drugs at hospital discharged patients

Drugs	Drug frequency	Appropriateness of drug dose according to the severity of renal dysfunction patients		Total (%)	Inappropriate drug dose according to the severity of renal dysfunction patients		Total (%)	χ^2 (P)
		Moderate (N)	Severe (N)		Moderate (N)	Severe (N)		
Lamivudine	3	3(100)	0(0.00)	3(100)	0(0.00)	0(0.00)	0(0.00)	
Total	**135**	**76(56.29)**	**32(23.70)**	**108(80)**	**14(10.37)**	**13(9.62)**	**27(20)**	

Note, SMZ-TMP: Sulfamethoxazole-trimethoprim, χ^2: chi square

4.9 Drugs to be Used with Caution at Hospital Discharged Patients

Details of the drugs that were considered to be used with caution according to the severity of renal impairments are depicted in table 16. The table showed that a total of 26 TEM medications to be used with caution were prescribed, comprising 50% in moderate renal impaired cases while 50 % in severe renal impaired cases. Markedly, aspirin was the most ordered drug in a total 20 renal impaired cases followed by repaglinide, mycophenolate thalidomide and escitaloparam in 2, 1, 1, 2 cases, respectively.

Table 16 Drugs to be use with cautions at hospital discharged patients

Drugs	**frequency**	**Renal status**	
		Moderate	**severe**
Aspirin	20	10 (50.00)	10 (50.00)
Repaglimide	2	1(50.00)	1(50.00)
mycophenolate	1	0(0.00)	1(100)
Thalidomide	1	1(100)	0(0.00)
Escitalopram	2	1(50.00)	1(50.00)
Total	26	13 (50.00)	13 (50.00)

4.10 Prescribing Pattern and Adverse Drug Reaction in Study Population

A causality assessment of adverse drug reactions of the patients receiving TEM drugs was made, and details of adverse drug reactions are presented in table 17.

An extrapyramidal symptom was manifested in one severe renal impaired patient receiving cefixime. Additionally, causality assessment of Naranjo's

algorithm showed that ethambutol was regarded for causing optic neuritis which was manifested in one severe renal impaired patient.

Table 17 Prescribing patterns and adverse drug reaction

Drugs	Characteristics of ADR	Renal status	Appropriate dose	Inappropriate dose
			Rating	Rating
Ethambutol	Optic neuritis	moderate	Probable	
Cefixime	Sign of extrapyramidal	severe	-	possible

4.11 Drugs Prescribed at High Dose (in percentage) in Hospitalized Patients

Percentage of excessive dose prescribed in moderate as well as in severe renal impaired patients during hospital admissions are shown in table 18. This table depicts that overdosing rates of TEM drugs were considerably high, varying 9% to 376% in moderate renal impaired cases, while 28% to 300% in severe renal impaired patients. The pattern of extensive overdoses rate reflects that the dosage adjustments were overlooked in both moderate as well as in severe renal impairment cases. However, the percentage overdoses rate were remarkably high in severe renal impaired cases. Antibiotics were prescribed substantially at high percentage overdose rate. Among these drugs, Cefepime was the most overdosed TEM drugs exhibiting 300% overdose rate, followed by amoxicillin-clavulanic acid 200%, amikacin 117% cefixime 100% SMZ-TMP 60%, and pipercillin-tazobactam 28% in severe renal impairment patients.

Cardiovascular drugs, encompassing both digoxin and atenolol were prescribed by 100% overdose rate in each severe renal impairment patients. Tranexamic acid was the highest percentage overdosed TEM drug showing 376% in moderate renal impaired patient followed by atenolol-amlodipine and clonidine, each showing by 100% overdose.

Ranitidine was prescribed by 100% overdose in severe renal impaired patients. Similarly, colchicine was overdosed by 33% in each moderate in severe cases.

Table 18 Rate of excessive dose (%) of the prescribed TEM drugs in hospitalized patients

Frequency of medications at high dose (N)	**Adjustment dose for renal impairment**		**prescribed dose (mean)**		**Excessive dose at MRI**	**Excessive dose at SRI**
	Moderate (N)	***Severe (N)***	***Moderate (N)***	***Severe (N)***		
Atenolol (7)	50 mg/day	25 mg/day	100 mg/day (4)	50 mg/day (3)	100%	100%
Atenolol-amlodipine (2)	50 mg/day	-	75 mg/day	-	50%	-
Clonidine (1)	300 mcg/day		600 mcg/day		100%	
Digoxin (2)		0.125 mg/day	-	0.25 mg/day (2)	-	100%
Allopurinol (2)	150 mg/day	75 mg/day	200 mg/day (1)	100 mg/day (1)	33.33%	33.33%
Colchicine (1)		250 mg/day		500 mg/day (1)	-	100%
Ranitidine (2)		150 mg/day	-	300 mg/day	-	100%
Tramadol (1)	-	100 mg/day	-	150 mg/day	-	50%
Tranexamic acid (1)	315 mg/day		1500 mg/day	-	376%	
Amikacin (1)		345 mg q 48-72 hr	-	250 mg/day	-	117%

Table 18 Rate of excessive dose (%) of the prescribed TEM drugs in hospitalized patients (continued)

Frequency of medications at high dose (N)	**Adjustment dose for renal impairment**		**prescribed dose (mean)**		**Excessive dose at MRI**	**Excessive dose at SRI**
	Moderate (N)	***Severe (N)***	***Moderate (N)***	***Severe (N)***		
Levofloxacin (2)	-	250 mg q 48 hr	-	500 mg iv/day (2)		100%
AMX-CLV (6)	1 g/day	500 mg/day	1500/375 mg/day (4)	1500/375 mg/day	50%	200%
Metronidazole (4)	920 mg/day	712 mg/day	1500 mg/day (1)	1g/day (3)	63%	40%
Cefixime (6)	300 mg/day	200 mg/day	400 mg/day (4)	400 mg/day (2)	33%	100%
Cefipime (5)	2 g/day	1 g/day	400 mg/day (1)	400 mg/day (4)	100%	300%
Meropenem (3)	-	500 mg/day	-	2 g/day (3)		300%
SMZ-TMP (5)	SMZ: 1g/day TMP: 200 mg/day			SMZ: 1600 mg/day TMP: 320 mg/day		60% 60%
Pyrazinamide (1)	1100 mg/day	-	1200 mg/day (1)	-	9%	-
Pip-TAZ (1)	-	6.84 g/day	-	13.5 g/day		28%

Note, MRI: moderate renal impairment (CrCl: 10-50 mL/min/1.73 m^2). SRI: severe renal impairment (CrCl < 10ml/min/1.73m^2). AMX-CLV: amoxicillin-clavulanic acid, SMZ-TMP: sulfamethoxazole-trimethoprim

4.12 Over Dose Rate (in percentage) Prescribed at Hospital Discharged Patients.

Rate of excessive dose prescribed in moderate as well as in severe renal impaired patients at hospital discharged are shown in table 19. The current table demonstrates that the overdoses rate of TEM drugs were extremely high, varying 33% to 100% in moderate cases, while 100% to 600% in severe renal impaired patients. The considerable varying overdoses rate in severe cases indicates that dosage adjustments were highly ignored while prescribing. As concern the antibiotics, amoxicillin (600%) was the highest percentage of overdosed TEM drug prescribed in severe renal impairment patients followed by cefixime (100%). Similarly, amoxiicillin-clavulanic acid were prescribed by 50% overdose rate in moderate case.

Cardiovascular drugs, constituting both atenolol, atenolol-amlodipine, were prescribed at 100% overdose rate in moderate renal dysfunction patients and 100% overdose rate in moderate cases.

Colchicine, ranitidine and cetrizine were prescribed by 100% overdose rate in each severe cases.

Table 19 Rate of excessive dose (%) of prescribed TEM drugs at hospital discharged patients

Frequency of medications at high dose	**Adjustment dose for renal impairment**		**prescribed dose (Mean)**		**Over-Dose rate at MRI**	**Over-dose rate at SRI**
	Moderate	***Severe***	***Moderate (N)***	***Severe (N)***		
Atenolol (7)	50 mg/day	25 mg/day	100 mg/day (4)	75 mg/day (3)	100%	200%
Atenolol-amlodipine (3)	50 mg/day	25 mg/day	100 mg/day (2)	75 mg/day (1)	100%	200%

Note, MRI: moderate renal impairment (CrCl: 10-50 mL/min/1.73 m^2 SRI: severe renal impairment (CrCl < 10ml/min/1.73m^2), AMX-CLV: amoxicillin-clavulanic acid

Table 19 Rate of excessive dose (%) of prescribed TEM drugs at hospital discharged patients

Frequency of medications at high dose	**Adjustment dose for renal impairment**		**prescribed dose (Mean)**		**Over-Dose rate at MRI**	**Over-dose rate at SRI**
	Moderate	***Severe***	***Moderate (N)***	***Severe (N)***		
Clonidine (1)	300 mcg/day	-	600 mcg/day	-	100%	-
Colchicine (2)		250 mg/day	250 mg/day	500 mg/day (2)	-	100%
Ranitidine (2)	150 mg/day	150 mg/day	300 mg/day	300 mg/day	100%	100%
Cetrizine (1)	-	5 mg/day	-	10 mg/day	-	100%
Amoxycillin (1)		500 mg/day		2 g/day	-	600%
AMX-CLV (2)	1g/day	-	1500 mg/day	-	50%	-
Cefixime (6)	300 mg/day	200 mg/day	400 mg/day (4)	400 mg/day (2)	33%	100%

Note, MRI: moderate renal impairment (CrCl: 10-50 mL/min/1.73 m^2 SRI: severe renal impairment (CrCl < 10ml/min/1.73m^2), AMX-CLV: amoxicillin-clavulanic acid

4.13 Drugs Continued at Excessive Dose in Hospitalized as well as at Hospital Discharged Patients

TEM drugs that were prescribed at high dose in hospitalized patients as well as hospital discharged patients according to the severity of renal dysfunction are shown in table 20. The table illustrates that atenolol was the most frequently prescribed drug at high dose in hospitalized patients and were still continued at the

same dose at hospital discharge. Similarly, allopurinol, ranitidine, amoxicillin-clavulanic acid and pyrazinamide were discovered to be prescribed at high dose in hospitalized patients and were continued further at excessive dose at hospital discharge which are shown in table 20, accordingly.

Table 20 Drugs continued at high dose in hospitalized patients as well as at hospital discharged patients

Drugs	**Adjustment dose for renal impairment**		**Renal status**	**Dose at hospitalized patient**	**Dose at hospital discharge**	**Excessive dose (%)**
	moderate	**Severe**				
Atenolol (4)	50 mg/day		Moderate	100 mg/day	100 mg/day	100%
Atenolol		25 mg/day	Severe	50 mg/day	50mg/day	100%
Allopurinol	150 mg/day		Moderate	300 mg/day	300 mg/day	100%
Ranitidine (1)	150 mg/day		Moderate	300 mg/day	300 mg/day	100%
Ranitidine (1)		150 mg/day	Severe	300 mg/day	300 mg/day	100%
AMX_CLV	1g/day		Moderate	3.6 g/day	1.5 g/day	260% & 50%
Pyarazinamide		575 mg/day	Severe	1000 mg/day	1000 mg/day	74%

Note, AMX-CLV: amoxicilin-clavulanic acid

CHAPTER V

DISCUSSION

The various studies have revealed that there are widespread overdosing rates, where, the studies conducted by Sheen et al.,[18], Salomon et al., [17], and Pillans et al., [16], found that 5.3%, 20%, 42.2% of drugs, respectively, were used at inappropriate dose. In our study, we found that the doses of 20.22 % drugs requiring dosage adjustments were not properly adjusted which is consistent with the study shown by Salomon et al. However, our finding was lower than that in the previous study by Pillans et al., but higher than that in the study by Sheen et al., (5.3%) [18].

In our study, the overdose rate of patients with severe renal impairment was higher than that with moderate renal impairment cases (12.40% vs 7.89%).

Our study showed that ranitidine, allopurinol, colchicine, atenolol, enalapril, digoxin, amoxicillin-clavulunic acid, cefixime, meropenem, cefepime, ciprofloxacin, levofloxacin, piperacillin, metronidazole, pyrazinamide, ethambutol and sulfamethoxazole-trimethoprim were TEM drugs with highest proportion of inappropriate dose during hospital stay whereas, atenolol, clonidine, colchicine, ranitidine, cetrizine, clarithromycin, amoxicillin-clavulanic acid, cefixime, ethambutol were marked with inappropriate dose at hospital discharge.

Our study indicated that atenolol was the most frequently prescribed cardiovascular drugs with high frequency of overdose. Limited information is available on atenolol overdose. In general, overdosage of atenolol may be expected to produce effects that are mainly extensions of pharmacologic effects, including symptomatic bradycardia, hypotension, bronchospasm, and acute cardiac failure, hypoglycemia, impaired conduction, decreased cardiac contractility, heart block,

shock, and cardiac arrest may also occur [52, 53]. The reason behind the overdose may be due to the combination dosage form of the drug (atenolol plus amlopdipine) that might create problem to the prescriber to adjust the individual drug. Thus, it would be wise to avoid such a combination drugs in renal impaired patients. Assessment of arthritis and gout agent revealed that two-third of the colchicine prescription and one- thirds of the total allopurinol prescriptions were at overdose. A life-threatening toxicity syndrome consisting of an erythematous, desquamative skin rash, fever, hepatitis, eosinophilia, and worsening renal function has been reported with the use of standard (200 to 400 mg per day) doses of allopurinol in patients with renal insufficiency. In pharmacologic studies, it has been demonstrated that the renal clearance of the major metabolite of allopurinol, oxipurinol, is directly proportional to the renal clearance of creatinine. Long-term use of 300 mg per day of allopurinol is associated with elevated steady-state serum oxipurinol concentrations in patients with renal insufficiency [54]. Hence, to reduce the incidence of life- threatening allopurinol toxicity, use of reduced doses in patients with renal insufficiency adhering the proposed guidelines might be adequate to inhibit uric acid production in most patients. Similarly, patients may experience toxicity like myopathy and neuropathy on administration of colchicine [55]. Cardinally, colchicine induced myotoxicity appears to occur at the usual dose in patients with impaired renal function in those receiving long term therapy [56]. Therefore, assessment of renal function should be performed in any patients for whom colchicine therapy is contemplated and appropriate precautions should be adopted accordingly.

As regard to antibiotics, a total of 12 different class of antibiotic constituting 35.20% of total TEM medications were prescribed to the 70 patients. Among them, 25.46 % was prescribed at high dose. Amoxicillin-clavulunic acid was the most frequently ordered antibiotic. However, it is crucial to take into account of such drugs which is prone to toxicity like diarrhea, pseudomembranous colitis [57] at therapeutic dose and this could be more serious in case of impaired renal function.

Pipercillin and tazobactam were the second most prescribed penicillin in TEM group including four in mild cases and one in severe renal impaired case. However, this drug was overdosed in severe impaired renal function patient. This is

crucial to emphasize that excessive dose of piperacillin can evoke encephalopathy in renal impairment patients [58]. Furthermore, the patients with advanced renal failure may experience piperacillin associated neurotoxicity, even at standard dose and accumulated dose in a such case could precipitate toxic effect though. Thus, patients receiving this drug should be guided and monitored thoroughly.

Cefixime and cefepime were the most frequently prescribed drug among cephalosporins and among them, two third of prescriptions were not ordered properly followed by cafazolin, cefpodoxime, cefotaxime ,ceftazidime, and cefadroxil. Acute renal failure has been reported with cefazolin and cefixime [59, 60]. Renal toxicity is most likely to occur in patients older than 50 years of age, patients with prior renal impairment, or patients who are receiving other nephrotoxic drugs. Additionally, neurological disorder (temporospatial disorientation, myoclonus, and seizures), was encountered with most of the cephalosporoin (cefepime and ceftazidime), particularly in elderly and uremic patient [61]. These unwanted hazardous consequences implies that cephalosporins should be administered with caution with dose reduction and careful clinical observation as well.

One third of the total ciprofloxacin and two third of the total levofloxacin medication were prescribed high dose. The incidence of tendon injury associated with fluoroquinolone [62] use is low in a healthy population however, it increases in patients who have renal dysfunction, especially hemodialysis and transplant patients. Additionally, it can cause severe hypoglycemia in older individuals taking oral hypoglycemic agent and without diabetes as well. The condition may manifest profound neurologic disturbance [63]. Therefore, clinicians should be aware of the occurrence of potentially serious or even fatal hypoglycemic effect with its use and in such a circumstances, practice of dose adjustment seems obligatory.

Amikacin was the sole drug of aminoglycoside prescription where in one case it was discovered to use inappropriately. Several studies have indicated that this drug could lead to nephrotoxicity in the form of interstitial nephritis

or proximal tubular damage [64, 65]. Furthermore, in case with renal failure, especially in our study population, this drug may accumulate and increased concentration in the plasma which may worsen the condition eventually.

Digoxin, a well known medication to have narrow therapeutic index and high risk toxicity at overdose, was ordered inappropriately in our study. This may cause several problems such as high premature ventricular beats, bradydysrhythmias, paroxysmal atrial tachycardia with block, functional tachycardia, and bidirectional ventricular tachycardia and hyperkalemia [66]. More importantly, inappropriate dosing of this drug may add noxious effect for the patients in our study who already bear cardiac problem. Acute interstitial nephritis, bradycardia, atrioventricular blockade and hematological toxicity have been reported on the administration of ranitidine. Similarly, CNS-ADRs, particularly lethargy, confusion, somnolence, and disorientation, have been reported and occurred more frequently in patients with renal function impairment. Such toxicity could be hazardous among the patients in the study provided that all of them having impaired renal function and most of them have cardiac problem. Furthermore, renal impairment negatively affects the bone marrow and hematopoeisis which could eventually lead to deteriorating the blood profile of the patient [67-70].

In our study one third line of total metronidazole prescription was found to be inappropriately dosed during the hospital stay. Neurologic side effects with high-dose attributed to metronidazole therapy including convulsion-sensory polyneuropathy, encephalopathy, cerebellar dysfunction with ataxia [71, 72]. In chronic kidney patient, generally, uricemia is one of the common manifestation and uremic patients have more prone to develop CNS related adverse effect which could potentiate negative effect profoundly, associated with high-dose of metronidazole therapy. This detrimental effect indicates that clinician should be alert to modify the drug dose in response to the degree of renal impairment to avert the negative consequences.

A total of 62.5 % of total sulfamethoxazole-trimethoprime was ordered with markedly high dose. Rashes have been reported to occur in up to 24% of

patients receiving 400 mg or more of trimethoprim [73]. Acute kidney injury associated with trimethoprim-sulfamethxazole has also been reported [74]. An increasing number of cases both SMZ-TMP induced hyperkalemia at high dose have been reported in patients occurring with existing renal impairment [75, 76]. Similarly, hematological toxicity (thrombocytopenia, neutropenia, megaloblastic anemia may occur with increased frequency in folate–depleted patient including geriatric and impaired renal function [77, 78]. Hyperkalemia and change in the hematopoesis blood profile are also the secondary complication of chronic kidney disease. The dosing guideline suggests that one should avoid the use of this drug in severe renal impaired patients, where 62.5 % of SMZ-TMP inappropriate dose was prescribed in such population. This is critical to figure that dosage adjustment should be acknowledged

Antitubercular drugs encompassing pyrazinamide and ethambutol were subjected to assess the appropriateness of prescribed dose. Investigation of our study revealed that one case of pyrazinamide and one case of ethambutol during hospital stay and at hospital discharge were marked with overdose respectively. Optic neuritis, a serious and well known adverse effect of ethambutol, is related to dose and duration of the therapy. Renal failure prolongs the half-life of ethambutol and increases the risk of ethambutol-induced optic neuritis [79]. On the other hand, serum uric acid becomes elevated with the administration of pyrazinamide [80] and the anticipated mechanism is likely to decrease in the urinary output. This becomes more important to our study population owing that all were renal impairment where the renal output is more likely to be affected. Also, dosing guideline recommends that the patients with renal impairment with CrCl < 50 ml/min should be avoided or targeted on reduced dose by 12-20 mg/kg/day. In our study each patient with renal impairment received an average of 2.59 TEM drugs. Nevertheless, in our study the dosage of 20.22 % TEM drugs was not adjusted properly which is regarded as too high for the renal impaired patients. Such a failure to adjust drug dose bear several possible illustrations.

−References exists to guide the dose adjustment in renal impairment might not freely be available in the hospital ward and the large number and continuously

increasing TEM medication list makes it difficult for prescriber to remain update on the adjustment issue.

−Adjustments made by clinicians may be different due to the variability of dosing reference sources available at the hospital.

−It is important that CrCl should be calculated and documented for all the patient for dose calculation. The assessment of cretinine clearance with the Cockroft-Gault formula taking in to account patient's weight , age and serum creatinine provide an accurate assessment of renal function. Prescriber might have used different method to calculate and define renal impairment, such as using only serum creatinine as an indicator of renal impairment rather than calculating creatinine clearance. The patients with serum creatinine on the border line or just having it mild elevation could have the low creatinine clearance especially in elder patient, suggests that only the marker of serum creatinine cannot exclude the severity of renal impairment. Moreover, in our study the failure of dosage adjustment was found higher in severe impaired renal function than moderate (12% vs 8%).

However, in most of the circumstances, it deemed critical to initiate further studies in renal patients at this hospital to investigate the cause of dosing errors and to investigate why clinicians have chosen certain dosages despite the patient's renal impairment

The problems identified in this study may be resolved by the general education and awareness promotion of the adjustment among the health care team. Most of the drugs prescribed in the study was belong to TEM drug and it could brings into more difficult task to memorize all individual drugs at each stage of renal impairment for dosage adjustment. It would be also time consuming to consult the guideline or dosing references for each drug. However, study have shown that adaptation of computerized subsystem bears promising effect in a substantial reduction in inappropriate drugs dosing and thereby, reducing the risk adverse effect [81, 82]. Therefore,, implementing the computing would be the strategy to minimize the dosing error at this hospital setting. Besides this, the participation of clinical pharmacist in health care would be the another approach to reducing medication dosing errors.

Limitations of the study

We acknowledged that this study was accomplished with few limitations with respect to our study design.

i. Since, the study design was retrospective, we could not able to determine the methods that the prescribers adopted to measure the renal impairment and assess the severity of renal dysfunction.

ii. Prescriber might have used different references sources for dosage adjustment. Thus our dosage assessments may have differ from them owing to the variability of the references.

iii. Lack of real indication of few antimicrobials in the prescriptions chart made us difficult to determine the appropriate dose. However, to minimize overestimation, we adopted the daily maximal dose that patient can receive.

iv. Since, the study being retrospective, we recognized adverse drug reaction only in limited renal impaired cases, necessitating that a comprehensive study at bed site is mandatory for the renal patients experiencing adverse drug reaction due to over-dose.

v. The rating of adverse drug reaction in this study was evaluated by only one investigator. However, values obtained from this algorithm may need many assessors to verify the validity of author's conclusions regarding adverse drug reactions.

CHAPTER VI

CONCLUSION

The present study, conducted retrospectively in the hospitalized patients over one year period of the renal dysfunction patients at tertiary care teaching hospital, resulted that 20.22% drugs were used at high dosage. According to the severity of renal dysfunction, 7.89% and 12.40% drugs were inappropriately charged in moderate and severe renal impairments cases, respectively. Appropriateness of dosage adjustments were significantly different in metronidazole ($P < 0.02$), SMZ-TMP ($P < 0.04$) and meropenem ($P < 0.03$) in patients with moderate renal impairment cases compared with those of the severe impaired renal cases..

Similarly, at hospital discharge, data analysis showed that 20% drugs were prescribed at high dose. Further assessment according to the severity of renal dysfunctions, it showed that 10.37% and 9.63% drugs were prescribed with higher dose in moderate and severe impaired renal cases, respectively. However, comparing the appropriateness of prescriptions order between the patient with moderate and with severe renal impairment, the frequency of inappropriate drugs were not significantly influenced ($p > 0.05$).

Antibiotics were the major prescribed drugs, constituting 35.20% of total TEM drugs, filled in the hospitalized patients. However, 25.46 % of them were rated at inappropriate dose. Similarly, at hospital discharge, 43.70 % antibiotic were determined as TEM drugs, yet, 10.37 % of them were prescribed inappropriately.

Apparently, the result showed that, dosing errors remained the unresolved problem among the hospitalized patients at teaching hospital, reflecting that there is a clear clinical need to improve the prescription process for patients with impaired renal function. Moreover, considering the iatrogenic risk and irreversible

renal impairment associated with the inappropriate dosing, it deemed critical to initiate further studies to reveal the cause of dosing errors and to investigate why clinicians have chosen certain dosages despite the patient's renal impairment.

In light of the study findings, we strongly recommend the uniformity in guidelines to be used at this hospital. Importantly, we urge a guideline, solely based on the drugs that are frequently prescribed at this hospital. Moreover, implementation of these guidelines in a dynamic alert system could support dosage adjustment in renal impaired patients abruptly and appropriately. Moreover, adaptation of computing sub-system at this hospital setting could be useful means to get easy and regular access of laboratory data, and would further help to recognize the patients at risk. This would facilitate to continuous and comprehensive screening of all renal risk drugs, the severity of renal impairment and appropriate dosing accordingly, which ultimately, would serves to optimize pharmaceutical care in patients with impaired renal function

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APPENDIX-A

Data Collection Form

S.N. [ ] H.N……..

Age: Sex: Weight:

Date of Admission: Date of discharge:

Total days stay:

Chief compliant:

Diagnosis:.

PMH:

Social history: i. Smoking ii. Alcoholism

Laboratory data

	Date								
BUN									
SCr									

CrCl(mL/min):

Renal status : Moderate [ ] Severe [ ]

Data Collection Form (continued)

Medication Chart (TEM drugs)

S.N.	Medication	indication	Appropriate dose	Dose at CrCl ……	Prescribed dose	
					Date	

Total No. of drugs:

Total no. of TEM drugs:

Contraindicated drug

i …… Total:

ii……

Dose adjustment

S.N.	Drugs	Dose adjustment	

Data Collection Form (continued)

Adverse Drug Reaction Form

Type of ADR:……

ADR manifestation date :…….

The Naranjo's Algorithm:

Drugs:……

	Question	Yes	No	Do not score know
1	*Are there previous conclusive reports on this reaction*	*+1*	*0*	*0*
2	*Did the ADR appear after the suspected drug was administered?*	*+2*	*-1*	*0*
3	*Did the ADR improved when the drug was removed or a specific antagonist was administered?*	*+1*	*0*	*0*
4	*Did the ADR reappear when the drug was readministered?*	*+2*	*-1*	
5	*Are there alternative cause that could on their own have the reaction?*	*-1*	*+2*	*0*
6	*Did the reaction reappear when the placebo was given?*	*-1*	*+1*	*0*
7	*Was the drug detected in the blood (or other fluids) in concentration known to be toxic?*	*+1*	*0*	*0*
8	*Was the reaction more severe when the dose was increased or less severe when the dose was decreased?*	*+1*	*0*	*0*
9	*Did the patient have similar reaction to the same or similar drug in any previous exposure?*	*+1*	*0*	*0*
10	*Was the adverse event confirmed by the objective evidence?*	*+1*	*0*	*0*

Data Collection Form (continued)

Total score:……

i. Definite [ ] ii. Probable [ ]

iii. Possible [ ] iv. Doubtful [ ]

Drugs:…….

	Question	Yes	No	Do not score know
1	*Are there previous conclusive reports on this reaction?*	*+1*	*0*	*0*
2	*Did the ADR appear after the suspected drug was administered?*	*+2*	*-1*	*0*
3	*Did the ADR improved when the drug was removed or a specific antagonist was administered?*	*+1*	*0*	*0*
4	*Did the ADR reappear when the drug was readministered?*	*+2*	*-1*	
5	*Are there alternative cause that could on their own have the reaction?*	*-1*	*+2*	*0*
6	*Did the reaction reappear when the placebo was given?*	*-1*	*+1*	*0*
7	*Was the drug detected in the blood (or other fluids) in concentration known to be toxic?*	*+1*	*0*	*0*
8	*Was the reaction more severe when the dose was increased or less severe when the dose was decreased?*	*+1*	*0*	*0*
9	*Did the patient have similar reaction to the same or similar drug in any previous exposure?*	*+1*	*0*	*0*
10	*Was the adverse event confirmed by the objective evidence?*	*+1*	*0*	*0*

Total score:……

i. Definite [ ] ii. Probable [ ]

iii. Possible [ ] iv. Doubtful [ ]

VITAE

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