THE IMPACT OF INPATIENT COLLABORATIVE CLINICAL PHARMACY RENAL DOSING SERVICE ON DOSAGE ADJUSTMENT IN PATIENTS WITH CHRONIC KIDNEY DISEASE

by

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DEDICATION

To

my parents…

my husband…

my children: Lara, Mumen & Sajed…

for their unconditional love,encouragement, patience and sacrifice during my study

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وَمَا تَوْفِيقِي إِلَّا بِاللَّهِ عَلَيْهِ تَوَكَّلْتُ وَإِلَيْهِ أُنِيبُ (هود – 88)

My guidance depends totally on GOD; I have put my trust in Him. To Him I have totally submitted. (11:88)

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وَآخِرُ دَعْوَانَا أَنِ الْحَمْدُ لِلَّهِ رَبِّ الْعَالَمِينَ

And the last our praise is Alhamdulilah to the Lord of the Worlds

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ACE	Angiotensin Converting Enzyme
ACS	Acute Coronary Syndrome
ADA	American Diabetes Association
ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
ARB	Angiotensin Receptor Blocker
ATC	Anatomical Therapeutic Chemical
bid	Twice Daily
CAPD	Contineous Ambulatory Peritoneal Dialysis
CKD	Chronic Kidney Disease
Cr Cl	Creatinine Clearance
CVD	Cardiovascular Disease
d	Day
DRP	Drug Related Problem
e.g.	For Example
ECF	Extracellular Fluids
ESA	Erythropoiesis Stimulating Agent
ESRD	End Stage Renal Disease
FDA	Food and Drug Administration
g	Gram
GFR	Glomerular Filtration Rate
h	Hour
Hb	Hemoglobin
HD	Hemodialysis
HF	Heart Failure

hs	At Bed Time
HTN	Hypertension
ICU	Intensive Care Unit
IHD	Ischemic Heart Disease
IM	Intramuscular
IV	Intravenous
KDOQI	Kidney Disease Outcomes Quality Initiative
kg	Kilogram
L	Liter
Max	Maximum
mcg	Microgram
MDRD4	The abbreviated 4–Variable Modification of Diet in Renal Disease Study Equation
mEq	Milliequivalent
mg	Milligram
MI	Myocardial Infarction
ml	Milliliter
mm Hg	Millimeter of Mercury
NIDDM	Non Insulin Dependent Diabetes Mellitus
NKF	National Kidney Foundation
od	Once Daily
PD	Peritoneal Dialysis
PGH	Penang General Hospital
PTH	Parathyroid Hormone
q	Every
qd	Every Day
qid	Four Times a Day

SC	Subcutaneous
S_{cr}	Serum Creatinine
TEM	Toxic, Excreted, Metabolized
tid	Three Times a Day
TZD	Thiazolidinedione
USA	United States of America
Vd	Volume of Distribution
WHO	World Health Organization

LIST OF SYMBOLS

Q	Dosage adjustment factor
k	Elimination rate constant
τ_f	Prolonged dosing interval
τ_n	Normal dosing interval
f_e	Fraction of drug eliminated renally unchanged
D_f	Reduced maintenance dose
D_n	Normal dose
Vd	Volume of distribution
f	Fraction of a drug eliminated during dialysis
D	Drug removed from the body during dialysis
D_o	Normally administered single dose
Cl_{cr}	Creatinine clearance
S_{cr}	Serum creatinine
Cp	Desired plasma drug concentration
U	Urine creatinine concentration
V	Urine flow rate
&	And

IMPAK PERKHIDMATAN KERJASAMA FARMASI KLINIKAL UNTUK PENDOSAN RENAL TERHADAP PENGUBAHSUAIAN DOS BAGI PESAKIT GINJAL YANG KRONIK

ABSTRAK

Pesakit ginjal kronik sering mengalami perubahan farmakokinetik dan gerak balas farmakodinamik. Pesakit ginjal kronik merupakan populasi yang berisiko tinggi untuk mendapat kesan mudarat drug dan saling tindak balas drug. Maka dengan itu pendosan drug bagi pesakit-pesakit ini merupakan suatu tanggung jawab yang sangat mencabar. Objektif kajian ini adalah untuk menilai impak suatu perkhidmatan kerjasama pendosan renal melalui penglibatan ahli farmasi semasa rondaan klinikal ke atas pengubahsuaian dos berdasarkan fungsi renal, kejadian kesan mudarat drug dan kos drug. Kajian ini juga memerihalkan pola preskripsi dan menentukan frekuensi dos yang tidak sesuai bagi pesakit ginjal kronik. Penyelidikan ini merupakan suatu kajian perbandingan perspektif intervensi.Sejumlah 600 orang pesakit dipilih secara rawak dan dibahagikan kepada dua kumpulan, iaitu 300 orang bagi setiap kumpulan. Pesakit yang dipilih untuk kajian adalah pesakit yang mempunyai anggaran klearans kreatinin < 50 ml/min. Koleksi rujukan yang dapat dipercayai dan kemas kini, serta diguna secara global telah diguna pakai untuk dijadikan sebuah buku saku. Data yang terkumpul sebelum dan selepas intervensi dibandingkan. Peratus pesakit lelaki bagi kumpulan praintervensi berbanding kumpulan intervensi adalah 56.0% dan 51.0%. Taburan etnik bagi kumpulan praintervensi adalah 51.0% Cina, 32.3% Melayu dan 16.0% India. Min umur bagi mereka ialah 55.56 ± 14.15 tahun. Kebanyakan pesakit 88.7% memupunyai penyakit ginjal tahap hujung (tahap 5). Komobiditi yang sering dihidapi adalah hipertensi 80.0%, diabetes mellitus 62.3% dan penyakit jantung iskemia 25.7%. Taburan etnik

bagi kumpulan intervensi adalah 40.0% Cina, 44.7% Melayu dan 15.0% India. Min umur bagi mereka ialah 55.30 ± 14.37 tahun. Kebanyakan pesakit 93.7% memupunyai peuyakit ginjal tahap hujung (tahap 5). Komobiditi yang sering dihidapi adalah hipertensi 84.0%, diabetes mellitus 5.6.0% dan penyakit jantung iskemia 20.7%. Bagi kumpulan praintervensi, min ± SP bilangan ubat yang digunakan di wad ialah 9.38 ± 3.63 per pesakit. Dalam kumpulan intervensi pula, min bilangan ubat yang digunakan di wad ialah 9.94 ± 3.78 per pesakit. Kelas drug yang paling sering digunakan ialah suplemen mineral, vitamin, sediaan antianemik, antibakteria, penghalang beta, penghalang saluran kalsium, diuretik, agen pengurangan lipid serum, drug untuk diabetes, drug untuk gangguan asid, agen antitrombotik, analgesik, dan agen yang bertindak terhadap sistem angiotensin. Fasa intervensi dijalankan oleh ahli farmasi klinikal bermula dari Mac 2008 sehingga Julai 2008. Sejumlah 212 (54.6%) cadangan pendosan oleh farmasi daripada 388 cadangan yang diberikan telah diterima oleh doctor yang mempreskripsi. Kebanyakan intervensi yang diterima melibatkan ranitidin, seftazidim, ampisilin / sulbaktam, amoksisilin / klavulanat, metoklopramid, digoksin, atenolol, khlorotiazida, dan amikasin. Bagi kumpulan praintervensi, pengubahsuaian atau penghindaran dos drug berdasarkan fungsi ginjal diperlukan dalam 607 daripada 2814 (21.6%) preskripsi. Daripada jumlah ini, 322 (53.0%) tidak mematuhi garis panduan. Bagi kumpulan intervensi pula, pengubahsuaian atau penghindaran dos drug berdasarkan fungsi ginjal diperlukan dalam 640 daripada 2018 (21.5%) preskripsi. Dengan adanya perkhidmatan kerjsama pendosan ketidakpatuhan dapat dikurangkan kepada 176 (27.5%) (nilai-p < 0.0001). Bagi kumpulan praintervensi, 64 (21.3%) pesakit dijangkakan mengalami kejadian kesan mudarat drug dengan jumlah 73 peristiwa. Jumlah ini berkurangan secara signifikan dalam kumpulan intervensi kepada 49

peristiwa dalam 48 (16.0%) pesakit (nilai-$p < 0.05$). Intervensi mampu menjimatkan kos drug sebanyak RM 7760.Tiada perbezaan yang signifikan bagi tempoh berada di hospital dan hasil pengubatan bagi diantara kumpulan praintervensi dan intervensi. Kami merumuskan bahawa perkhidmatan dos kolaborasi boleh meningkatkan pengubahsuaian drug terhadap fungsi ginjal. Oleh itu, ia mampu menjimatkan kos drug dan berpotensi untuk mengelak kejadian kesan mudarat drug.

THE IMPACT OF INPATIENT COLLABORATIVE CLINICAL PHARMACY RENAL DOSING SERVICE ON DOSAGE ADJUSTMENT IN PATIENTS WITH CHRONIC KIDNEY DISEASE

ABSTRACT

Patients with chronic kidney disease often have alterations in their pharmacokinetic and pharmacodynamic response. They constitute a population at high-risk for adverse drug reactions and drug-drug interactions. Drug dosing in these patients is a very challenging task. The objectives of this study were to evaluate the impact of an inpatient collaborative renal dosing service by pharmacist's participating in clinical rounds on dosage adjustment according to renal function, adverse drug events, and drug costs. It aimed also to describe prescribing patterns for hospitalized chronic kidney disease patients and to assess the frequency of inappropriate dosing. The study was an interventional prospective comparative study. A total of 600 patients were randomly selected with 300 patients in each groups. Patients who had an estimated creatinine clearance of $\leq$ 50 ml/min on admission were included. A collection of reliable and up-to-date references became the basis of applied pocket sized handbook that was used by the clinical pharmacist during medical rounds. Data before and during the intervention were compared. The percentages of male patients in the pre-intervention and intervention groups were 56.0% and 51.0% respectively. In the pre-intervention group 51.0% were Chinese, 32.3% were Malay, and 16.0% were Indian. The mean age was 55.56 ± 14.15 years. Most patients 88.7% had end stage renal disease (stage 5). The most common co-morbidities were hypertension in 80.0% of the patients, diabetes mellitus in 62.3%, and ischemic heart disease 25.7%. In the intervention group, 40.0% were Chinese, 44.7% were Malay, and 15% were Indian. The mean age was 55.30 ± 14.37 years. Most patients 93.7% had end stage

renal disease (stage 5). The most common co-morbidities were hypertension in 84.0% of the patients, diabetes mellitus in 56.0%, and ischemic heart disease 20.7%. In the pre-intervention group, the mean ± SD number of medications used in ward during hospitalization was 9.38 ± 3.63 per patient, whereas in the intervention group, the mean ± SD number of medications used in ward during hospitalization was 9.94 ± 3.78 per patient. The most commonly used medication classes were mineral supplements, vitamins, anti-anemic preparations, anti-bacterials, beta blockers, calcium channel blockers, diuretics, serum lipid reducing agents, drugs used in diabetes, drugs for acid-related disorders, anti-thrombotic agents, analgesics, and agents acting on the renin angiotensin system. The intervention was performed by a clinical pharmacist from March to July 2008. Out of 388 dosing recommendations given by the pharmacist, the prescribers accepted a total of 212 recommendations (54.6%). The most commonly accepted interventions were with ranitidine, ceftazidime, ampicillin/sulbactam, amoxicillin/clavulanate, metoclopramide, digoxin, atenolol, chlorothiazide, and amikacin. In the pre-intervention group, drug dosage adjustments or avoidance based on renal function was necessary in 607 of 2814 (21.6%) of prescriptions. Out of these, 322 (53.0%) did not comply with guidelines. In the intervention group, dosage adjustment or avoidance based on renal function was necessary in 640 of 2981 (21.5%) of prescriptions. During the collaborative dosing service, noncompliance significantly decreased to 176 (27.5%) (p-value < 0.0001). In the pre-intervention group, 64 (21.3%) patients had a suspected adverse drug event with a total of 73 events. The number significantly decreased in the intervention group to 49 events in 48 (16.0%) patients (p-value < 0.05). The intervention caused savings in drug cost of RM 7760. There was no significant difference in length of hospital stay and outcomes of hospitalization

between the pre-intervention and the intervention group. We concluded that the inpatient collaborative clinical pharmacy dosing service can increase the proportion of drugs adjusted to renal function. This can save drug costs and has the potential to prevent adverse drug events.

CHAPTER ONE

INTRODUCTION

1.1 Chronic kidney disease

1.1.1 Background

Chronic kidney disease (CKD) is a worldwide public health problem with an increasing incidence and prevalence, poor outcomes, and high cost (National Kidney Foundation, 2002). It is a progressive and irreversible loss of patient's kidney function occurring over several months to years, and is characterized by the gradual replacement of normal kidney architecture with interstitial fibrosis (Ashley and Morlidge, 2008).

It is a worldwide problem affecting more than 50 million people, and more than 1 million of them are receiving kidney replacement therapy. In the United States of America (USA), it is estimated that CKD affects 11% of the USA population, and those affected are at increased risk of cardiovascular disease (CVD) and kidney failure. Kidney failure represents about 1% of the prevalent cases of CKD in the USA, and the prevalence of kidney failure treated by dialysis or transplantation is projected to increase to 651,000 in 2010 (National Kidney Foundation, 2007a). In Malaysia, the number of prevalent dialysis patients also increased linearly from 4540 in 1998 to almost more than 16000 by the end of 2007. Dialysis prevalence rate continued to increase linearly over the last 10 years, from 205 per million population in 1998 to at least 615 in 2007 (Lim YN and Lim TO, 2008). The incidence and prevalence of the disease have doubled in the past decade, most likely because of

improved treatments for hypertension, diabetes mellitus, and coronary disease have increased longevity in affected patients and, therefore, their likelihood of developing CKD (Snively and Gutierrez, 2004).

The major outcomes of CKD regardless of the specific diagnosis include progression to kidney failure, complications from decreased kidney function, and development of CVD (Johnson *et al.*, 2004). Unfortunately, CKD is "under-diagnosed" and "under-treated", this has led to attempts to improve both the detection and management of patients with impaired renal functions (Macgregor *et al.*, 2006). A growing body of evidence suggests that some of the adverse outcomes of CKD can be prevented or delayed. At each stage patients can benefit from measures that delay or prevent the progressive loss of renal function, modification of medications with renal clearance, avoidance of nephrotoxins, and reduction of cardiovascular risk factors. Early diagnosis, treatment of comorbid conditions, management of complications, education and preparation for kidney replacement therapies have all been associated with better outcomes (Joy *et al.*, 2005; McClellan, 2005; National Kidney Foundation, 2007a).

1.1.2 Definition and stages of chronic kidney disease

Glomerular filtration rate (GFR) is the best measure of overall kidney function in health and disease. The normal level of GFR varies according to age, sex, and body size. Normal GFR in young adults is approximately 120 to 130 ml/min/1.73 m^2 (National Kidney Foundation, 2002). A GFR level of less than 60 ml/min/1.73 m^2 represents loss of half or more of the adult level of normal kidney function. Below this level, the prevalence of complications of CKD increases (Levey *et al.*, 2003).

In 2002, the Kidney Disease Outcomes Quality Initiative (KDOQI) of the National Kidney Foundation (NKF) established a classification system for CKD that had been accepted and used worldwide. This classification defines CKD as a GFR of less than 60 ml/min/1.73 m² for three months or more, with or without kidney damage or kidney damage for three or more months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifested by either: pathologic abnormalities, or markers of kidney damage, including abnormalities in the composition of the blood or urine or abnormalities in imaging tests. Disease stage should be assigned based on the occurrence of kidney damage and the level of kidney function, regardless of the specific diagnosis. Based on this definition, the KDOQI has recommended a classification of CKD into five stages with clinical action plan as shown in the following table (National Kidney Foundation, 2002).

Table 1.1. Chronic kidney disease staging and clinical action plan

Stage	Description	GFR ml/min/1.73m²	Action*
1	Kidney damage with normal or ↑GFR	≥ 90	Diagnosis and treatment. Treatment of comorbidities. Slowing progression. CVD risk reduction.
2	Kidney damage with mild ↓ GFR	60-89	Estimating progression.
3	Moderate ↓ GFR	30-59	Evaluating and treating complications.
4	Severe ↓ GFR	15-29	Preparation for kidney replacement therapy.
5	Kidney failure (ESRD)	<15 (or dialysis)	Replacement (if uremia present).

* Includes actions from preceding stages, GFR: glomerular filtration rate, CVD: cardiovascular disease, ESRD: end-stage renal disease.

Although the age-related decline in GFR has been considered part of normal aging, decreased GFR in the elderly is an independent predictor of adverse outcomes, such as death and CVD. In addition, decreased GFR in the elderly requires adjustment in drug dosages, as in other patients with CKD. Therefore, the definition of CKD is the same, regardless of age (Levey *et al.*, 2003).

1.1.3 Causes and risk factors for chronic kidney disease

Risk factors identified for CKD are classified into three categories:

Susceptibility factors: which are associated with an increased risk of developing CKD, but are not directly proven to cause it. These factors are generally not modifiable by pharmacologic therapy or lifestyle modifications. The factors include advanced age, reduced kidney mass, low birth weight, family history of kidney disease, low income or education, systemic inflammation, and dyslipidemia (Lederer and Ouseph, 2007; Chisholm-Burns *et al.*, 2008).

Initiation factors: are factors or conditions that directly initiate kidney damage, and are modifiable by pharmacologic therapy. These factors include diabetes mellitus, hypertension, autoimmune diseases, polycystic kidney disease, systemic infections, urinary tract infections, urinary stones, lower urinary tract obstructions, and drug toxicity (DiPiro *et al.*, 2005; Chisholm-Burns *et al.*, 2008).

Progression factors: which result in a faster decline in kidney function and cause worsening of CKD. These factors may also be modified by pharmacologic therapy or lifestyle modifications to slow the progression of CKD. They include proteinuria,

poor blood glucose control in patients with diabetes, elevated blood pressure, and tobacco smoking (Chisholm-Burns *et al.*, 2008).

1.1.4 Clinical presentation of chronic kidney disease

The development of CKD is usually subtle in onset, often with no noticeable symptoms. Stage 1 and 2 CKD are generally asymptomatic. Symptoms usually appear with advanced stages of the disease. Stage 3 and 4 CKD may be associated with minimal symptoms. Typical symptoms and signs associated with stage 5 CKD include fatigue, electrolyte disturbances, hypertension, pruritis, 'restless leg' syndrome, anorexia, nausea, vomiting, and bleeding abnormalities as well as those of anemia and of renal bone disease (Ashley and Morlidge, 2008; Chisholm-Burns *et al.*, 2008).

Laboratory tests abnormalities include increased blood urea nitrogen, serum creatinine, and decreased GFR. With advanced stages patients have increased potassium, phosphorus, and magnesium. Calcium levels are generally low in earlier stages of CKD and may be elevated in stage 5 CKD, secondary to the use of calcium containing phosphate binders. Hematological abnormalities include decreased red blood cells count, hemoglobin, and hematocrit. Other abnormalities include increased parathyroid hormone (PTH) levels and decreased vitamin D levels (stage 4 and 5 CKD) (Chisholm-Burns *et al.*, 2008).

1.2 Pharmacotherapy interventions in chronic kidney disease management

Treatment of CKD should include (National Kidney Foundation, 2002):

- Specific therapy, based on diagnosis.
- Evaluation and management of comorbid conditions.
- Slowing the loss of kidney function.
- Prevention and treatment of CVD.
- Prevention and treatment of complications of decreased kidney function.
- Preparation for kidney failure and renal replacement therapy.
- Replacement of kidney function by dialysis and transplantation, if signs and symptoms of uremia are present.

After the detection of CKD, treatment of comorbid conditions, interventions to slow progression of kidney disease, and measures to reduce the risk for CVD should begin during stage 1 and stage 2. Hypertension is both a cause and a complication of CKD and should be carefully controlled in all patients. Evaluation and treatment of other complications of CKD, such as anemia, malnutrition, bone disease, neuropathy, and decreased quality of life, should be undertaken during stage 3, as the prevalence of these complications begins to rise when GFR declines to less than 60 ml/min/1.73 m^2. Preparation for kidney replacement therapy should begin during stage 4, well before the stage of kidney failure. Initiation of dialysis and transplantation is triggered by the onset of uremic symptoms. Preparations for these treatments should begin when GFR declines to less than 15 ml/min/1.73 m^2 (stage 5). The clinical action plan for each stage should include actions begun in preceding stages. The earlier these measures are implemented, the greater is their success rate (Levey *et al.*, 2003; Macgregor *et al.*, 2006).

Medications prescribed to patients should be reviewed. Dosage adjustments should be based on the level of kidney function. It is important to detect drug interactions, as well as potentially adverse effects of medications on kidney function or complications of CKD. If possible, therapeutic drug monitoring should be performed in patients with CKD (Johnson *et al.*, 2004).

1.2.1 Prevention or slowing the loss of kidney function

The rate of progression for CKD depends on the underlying cause. In general, tubulointerstitial diseases progress more slowly than do glomerular diseases, diabetic and hypertensive nephropathy, and polycystic kidney disease. Rates of progression also vary widely among patients with the same type of kidney disease. In rapidly progressing kidney disease, the GFR may decrease by as much as 10 to 20 ml/min/1.73 m^2 per year. In more slowly progressing disease, the GFR may decrease by as little as 2 ml/min/1.73 m^2 per year. Plotting the GFR against time is helpful in estimating the rate of disease progression and the time to kidney failure, and it helps predict the need for kidney replacement therapy (Snyder and Pendergraph, 2005).

Three interventions have been proved to slow the progression of kidney disease: blood pressure control, glycemic control in patients with diabetes, and reduction of proteinuria with an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). Other interventions that may be beneficial include lipid-lowering measures, partial correction of anemia, limiting dietary protein intake, weight loss, and smoking cessation (McClellan, 2005; Snyder and Pendergraph, 2005).

Attempts should be made to prevent and correct acute decline in GFR. Frequent causes of acute decline in GFR include; volume depletion, IV radiographic contrast, selected antimicrobial agents (e.g., aminoglycosides, amphotericin B), nonsteroidal anti-inflammatory drugs, including cyclo-oxygenase 2 inhibitors, ACE inhibition, angiotensin-2 receptor blockers, cyclosporine, tacrolimus, and obstruction of the urinary tract (National Kidney Foundation, 2002).

Proteinuria is associated with more rapid progression of CKD and a greater likelihood of developing ESRD. Consequently, detection and quantitation of proteinuria are essential for the diagnosis and treatment of CKD. Microalbuminuria is defined as an albumin-creatinine ratio of 30–300 mg/g from a spot urine collection, 30–300 mg/24 hours in a 24-hour urine collection, or 20–200 mg/min in a timed urine collection. Macroalbuminuria is defined as > 300 mg/g, > 300 mg/24 hours, and > 200 mg/min in the same tests, respectively (Snyder *et al.*, 2005; Cavanaugh, 2007).

The role of dietary protein restriction in chronic renal disease remains controversial. The largest controlled study initially failed to find an effect of protein restriction, but secondary analysis based on achieved protein intake suggested that a low protein diet slowed the progression (Parmar, 2002). It is recommended to restrict protein intake 0.60 to 0.75 g/kg of body weight per day in patients with a GFR below 25 ml/min/1.73 m^2. Malnutrition is common in patients with end stage renal disease (ESRD) for various reasons, including decreased appetite, hypercatabolism, and nutrition losses through dialysis. For this reason, patients receiving dialysis should

maintain protein intake of 1.2-1.3 g/kg per day (McClellan, 2005; Chisholm-Burns *et al.*, 2008).

Smoking, besides increasing the risk of cardiovascular events, is an independent risk factor for development of ESRD in patients with kidney disease. Recently, several small observational studies have reported that smoking cessation is associated with reduced risk of progressive renal injury, suggesting that smoking should be considered a risk factor for progressive renal insufficiency and cessation may be renoprotective and beneficial to general and cardiovascular health (Parmar, 2002; McClellan, 2005).

There is growing evidence that obesity may be a risk factor for progressive renal injury (McClellan, 2005). Exercise even without change in body mass index may decrease proteinuria (Lederer and Ouseph, 2007).

1.2.2 Prevention and treatment of cardiovascular disease

Cardiovascular disease is the most common cause of death in patients with CKD. The risk of CVD and associated mortality increases in proportion to the decrease in the GFR. Patients with albuminuria and normal GFR also are at increased risk. Indeed, recent studies show that patients with CKD are 100 times more likely to die, principally of CVD, than to develop kidney failure (Keith *et al.*, 2004).

Evaluation for traditional cardiovascular risk factors, including smoking, high lipid levels, hypertension, and sedentary lifestyle, is essential. The KDOQI guidelines recommend a blood pressure goal of 130/80 mm Hg in patients with normal urinary

albumin concentrations, and a blood pressure goal of 125/75 mm Hg in patients with excretion of more than 1 g of protein per 24 hours.

The KDOQI guidelines on managing dyslipidemias in CKD recommend a low-density lipoprotein (LDL) cholesterol goal of less than 100 mg/ dL (2.60 mmol/L) for patients with CKD, because they are statistically at highest risk for CVD (National Kidney Foundation, 2003a).

Additional cardiac risk factors specific to CKD include volume overload, hyperparathyroidism, and uremia. Anemia caused by decreased erythropoietin production also may contribute to cardiovascular mortality. Treatment with exogenous erythropoietin has been shown to improve the prognosis (Snyder and Pendergraph, 2005).

The medical management of chronic CAD in CKD and dialysis patients should follow that of the general population. Patients should receive acetylsalicylic acid, beta-blockers, nitroglycerin, ACE inhibitors or ARBs, statins, and/or calcium channel blockers (CCB) as indicated. Dose adjustments are required for medications that are renally excreted or dialyzed (National Kidney Foundation, 2005).

1.2.3 Treatment of Comorbidities

1.2.3.1 Hypertension

Hypertension is the second most common cause of ESRD. Elevated blood pressure is also an important modifiable risk factor for progressive CKD regardless of the initial cause of kidney injury. Evidence from clinical trials shows that blood pressure

reduction reduces the rate of loss of renal function and progression to renal failure (Parmar, 2002; McClellan, 2005).

Systemic hypertension causes direct damage to small blood vessels in the nephron. The kidneys lose their ability to autoregulate glomerular filtration flow and pressure, with resultant hyperfiltration manifesting as albuminuria and proteinuria. When the proximal convoluted tubule reabsorbs the excess protein, secretion of vasoactive substances further damages the glomerular-tubular apparatus. Nephron damage activates the renin-angiotensin-aldosterone system, resulting in increased sympathetic tone and fluid overload, which compound the progression of hypertension and nephron loss (Snively and Gutierrez, 2004).

The seventh report of the Joint National Committee (JNC7) recommends a target blood pressure of less than 130/80 mm Hg in patients with CKD (Snively and Gutierrez, 2004). The NKF-KDOQI guidelines recommend a target blood pressure of less than 130/80 mm Hg in patients with stage 1 through 4 CKD (National Kidney Foundation, 2004). Stage 5 CKD patients who are receiving hemodialysis (HD) should achieve a goal blood pressure of less than 140/90 mm Hg before hemodialysis and less than 130/80 mm Hg after hemodialysis (Chisholm-Burns *et al.*, 2008).

Dietary sodium intake of < 2.4 g/d (<100 mmol/d) should be recommended in most adults with CKD and hypertension. ACE inhibitors and ARBs preferentially lower intraglomerular pressure and reduce proteinuria. Evidence from both animal models of renal injury and clinical trials shows that blockade of the renin-angiotensin system with ACE inhibitors and ARBs reduces the risk of progressive renal injury

(McClellan, 2005; National Kidney Foundation, 2007a). Efficacy may be increased when these agents are given in combination. Agents that block the renin-angiotensin system should be first-line drugs for the management of hypertension. When ACE inhibitor therapy is started, some patients with CKD may have an initial decrease in GFR (usually less than 10 ml/min/1.73 m^2), a mild increase in the serum creatinine concentration (less than 20% of the baseline value), and a mild increase in the potassium level (usually less than 0.5 mmol/L). Therefore, serum creatinine and potassium levels should be monitored one to two weeks after an ACE inhibitor was initiated. It is recommended to reduce or discontinue ACE inhibitoe if serum potassium consistently exceeds 5.5 mg/dL or if renal function reduces more than 30% of baseline within 4 months (Snively and Gutierrez, 2004; McClellan, 2005; Lederer and Ouseph, 2007).

Non-dihydropyridine calcium channel blockers have also been shown to retard progression of renal insufficiency in patients with type 2 diabetes (Parmar, 2002). As decline in kidney function progresses, the effect of thiazide diuretics for blood pressure control may lessen and the potential for electrolyte disturbances may increase. Therefore, it is generally recommended that, for patients with a GFR < 30 ml/min/1.73 m^2, thiazide diuretics should be replaced with loop diuretics. Potassium-sparing diuretics should be used with caution with GFR <30 ml/min/1.73m^2 (CKD stages 4–5), in people receiving concomitant therapy with ACE inhibitors or ARBs, and in people with additional risk factors for hyperkalemia (Cavanaugh, 2007; National Kidney Foundation, 2004).

1.2.3.2 Diabetes mellitus

Diabetes is the most common cause of kidney disease. From 40 to 60 % of patients who progress to ESRD have diabetes (Snyder and Pendergraph, 2005). Hyperglycemia is an independent risk factor for nephropathy. The pathophysiology of diabetic nephropathy is complex and most likely involves both hemodynamic and glucose-dependent factors, including the accumulation of advanced glycated products, endothelial dysfunction, and loss of intraglomerular blood pressure regulation (Snively and Gutierrez, 2004). Studies have shown that glycemic control reduces the progression of kidney disease. The target Hb A1c concentration should be below 7%, irrespective of the presence or absence of CKD (National Kidney Foundation, 2007a). Yearly screening for microalbuminuria and blood pressure control with an ACE inhibitor or ARB is recommended (Snively and Gutierrez, 2004).

Patients with decreased kidney function (stage 3 to 5) have increased risk of hypoglycemia for two reasons: (1) decreased clearance of insulin and some of the oral agents used to treat diabetes, and (2) impaired kidney glucogenesis that may decrease the ability of the patient to defend against hypoglycemia. About one third of insulin degradation is carried out by the kidney. However, when there is impairment of kidney function, the half-life of insulin is prolonged because of lower levels of degradation. Therefore, in patients with moderate to severe kidney dysfunction, the frequency of hypoglycemic episodes may be as much as five times that of patients without kidney disease. Caution must be exercised when administering therapy to patients with kidney disease, and frequent blood glucose monitoring may be used to

adjust dosing and prevent hypoglycemia (National Kidney Foundation, 2007a; Cavanaugh, 2007).

The NKF-KDOQI guidelines have mentioned special considerations in drug therapy. For oral hypoglycemic agents, the clearance of both sulfonylureas and their metabolites is highly dependent on kidney function, and severe prolonged episodes of hypoglycemia as a result of sulfonylurea use have been described in dialysis patients. In patients with stage 3–5 CKD, first-generation sulfonylureas should be avoided. Of the second-generation sulfonylureas, glipizide and gliclazide are recommended because their metabolites are not active, and there is a lower potential for development of hypoglycemia. In the meglitinide class, nateglinide has increased active metabolites with decreased kidney function, but these don't occur with repaglinide. Although the mechanisms are not clear, alpha-glucosidase inhibitors and metabolites may result in damage from cumulative dose effects and result in possible hepatic damage. Therefore, this class of medications is not recommended for patients with a serum creatinine > 2 mg/dl. Metformin is in the biguanides class of oral hyperglycemic drugs, which does not exhibit the high risk of hypoglycemia associated with other drug classes used to treat diabetes. However, there is a risk of development of lactic acidosis, even in patients with mild impairment of kidney function, again likely resulting from the accumulation of the drug and its metabolites. Metformin is contraindicated in male patients with a serum creatinine > 1.5 mg/dl and in female patients with serum creatinine > 1.4 mg/dl. Recently, it has been suggested that thiazolidinediones (TZDs) may have a protective effect to either prevent or slow the progression of CKD independent from glycemic control. Several small studies have reported a greater reduction in albuminuria in patients

administered TZDs; however, there has been no evidence to support an independent association between TZD use and actual prevention of CKD. This class of drugs undergoes hepatic metabolism. It has been demonstrated to be effective without increasing the risk of hypoglycemic episodes in patients with CKD, including those receiving dialysis. No adjustment in dosing of TZDs is required for these patient groups (National Kidney Foundation, 2007a; Cavanaugh, 2007).

1.2.3.3 Dyslipidemia

Dyslipidemia is a primary risk factor for cardiovascular disease and a common complication of progressive kidney disease. Most patients with CKD have an abnormal lipid panel that increases their risk for atherogenesis. Dyslipidemia contributes to cardiovascular mortality, which is 10 to 20 times higher in dialysis patients than in the normal population even after adjustments are made for age, sex, and diabetes mellitus.

The most noticeable lipid abnormality in CKD is an elevated triglyceride level, possibly because of defective clearance. Patients with CKD also have an elevated ratio of low-density lipoprotein (LDL) cholesterol to high-density lipoprotein (HDL) cholesterol. LDL cholesterols, including lipoprotein(a), are pro-atherogenic, and levels are slightly elevated in patients with CKD. Levels of oxidized LDL cholesterol are also elevated; these cholesterols activate pro-inflammatory pathways, thereby promoting atherogenesis and endothelial dysfunction. HDL cholesterol levels are decreased, indicating loss of anti-atherogenic effect (Snively and Gutierrez, 2004).

The most recent guidelines from the NKF-KDOQI recommend treating dyslipidemia aggressively in patients with CKD. The goals are a LDL cholesterol level below 100 mg/dL (2.60 mmol/L) and a triglyceride level below 200 mg/dL (2.26 mmol/L). Fibrates are known to decrease triglyceride levels, but they may increase the risk for rhabdomyolysis in patients with CKD. Statins can lower cholesterol levels safely and effectively in these patients (National Kidney Foundation, 2003a, Snively and Gutierrez, 2004).

1.2.4 Treatment of complications of chronic and end stage renal disease

1.2.4.1 Anemia

Anemia develops early in the course of CKD and is nearly universal in patients with CKD stage 5. The prevalence of anemia is correlated with the degree of renal dysfunction. More than 26% of patients with a GFR greater than 60 ml/min/1.73 m^2 are estimated to have anemia, and the number increases with a GFR of less than 15 ml/min/1.73 m^2 (Chisholm-Burns *et al.*, 2008).

In the opinion of the work group of the NKF, hemoglobin (Hb) testing should be carried out in all patients with CKD, regardless of stage or cause. Hb levels should be measured at least annually. Diagnosis of anemia should be made and further evaluation should be undertaken at Hb concentrations less than 13.5 g/dL in adult males and less than 12.0 g/dL in adult females (National Kidney Foundation, 2006). In dialysis and nondialysis patients with CKD receiving erythropoiesis stimulating agent (ESA) therapy, the selected Hb target should generally be in the range of 11.0 to 12.0 g/dL. The Hb target should not be greater than 13.0 g/dL. Patients with

plasma ferritin concentrations below 100 ng/mL should be given iron supplements (National Kidney Foundation, 2007b).

Anemia of chronic renal disease begins when the GFR falls below 30-35% of normal and it is normochromic and normocytic. This is primarily caused by decreased production of erythropoietin by the failing kidney as the progenitor cells of the kidney produce 90% of the hormone erythropoietin, but other potential causes include blood loss through frequent blood draw and increased tendency toward gastrointestinal bleeding due to diminished platelet function and decreased red blood cell lifespan from a normal of 120 days to as low as 60 days in patients with stage 5 CKD. Whether anemia accelerates the progression of renal disease is controversial. However, it is independently associated with the development of left ventricular hypertrophy and other cardiovascular complications. Treatment of anemia results in partial regression of left ventricular hypertrophy in both patients with pre-end stage renal disease and patients receiving dialysis and has reduced the frequency of heart failure, hospitalization and mortality among patients receiving dialysis (Parmar, 2002; Lederer and Ouseph, 2007; Chisholm-Burns *et al.*, 2008).

Generally, treatment requires a combination of ESA and iron supplementation. Erythropoietin should be administered to predialysis patients who have anemia-dependent angina or severe anemia with a hemoglobin concentration below 10 g/dL. Hypertension and an increased risk for thrombotic events are potential adverse effects of treatment. Therefore, patients receiving erythropoietin must be monitored closely (Snively and Gutierrez, 2004). Subcutaneous (SC) administration is

recommended for patients not on HD and IV route can be used in HD patients (National Kidney Foundation, 2006).

Oral iron supplements are less costly than IV supplements and are generally the first line treatment. Oral iron supplementation is generally not effective in maintaining adequate iron stores in patients receiving ESAs because of poor absorption and increased iron need, making the IV route necessary. The IV route is recommended by the NKF for HD patients while either oral or IV route can be used for non dialysis or peritoneal dialysis (PD) patients. The goal of treatment for anemia of CKD is to increase Hb levels to greater than 11 g/dL. The goal of iron supplementation is to maintain serum ferritin levels between 100-500 ng/mL in patients not receiving HD and between 200-500 ng/mL in patients receiving HD and total saturation greater than 20% (Chisholm-Burns *et al.*, 2008).

1.2.4.2 Renal osteodystrophy

Changes in mineral metabolism and bone structure begin early in CKD. These changes include osteitis fibrosa cystica (because of secondary hyperparathyroidism); less commonly, osteomalacia (defective mineralization); and adynamic bone disease (absence of cellular activity). Osteitis fibrosa cystica, the predominant bone defect, is characterized by an increase in bone turnover that leads to decreased cortical bone and impaired bone strength. Bone disease can result in pain and an increased risk of fracture.

In patients wih CKD (stages 3 and 4), the serum level of phosphorus should be maintained at or above 2.7 mg/dL (0.87 mmol/L) and no higher than 4.6 mg/dL (1.49

mmol/L). In patients with CKD with kidney failure (stage 5) and those treated with HD or PD, the serum levels of phosphorus should be maintained between 3.5 and 5.5 mg/dL (1.13–1.78 mmol/L). The preferred phosphate binder are calcium-based phosphate binders. The total dose of elemental calcium provided by the calcium-based phosphate binders should not exceed 1500 mg/day, and the total intake of elemental calcium (including dietary calcium) should not exceed 2000 mg/day. Calcium-based phosphate binders should not be used in people on dialysis who are hypercalcemic (corrected serum calcium of 10.2 mg/dL [2.54 mmol/L]), or whose plasma parathyroid hormone levels are <150 pg/mL (16.5 pmol/L) on two consecutive measurements (National Kidney Foundation, 2003b).

Parathyroid hormone levels begin to rise when creatinine clearance falls below 60 ml/min. The development of hyperparathyroidism may be prevented by restricting dietary phosphate intake (e.g., colas, nuts, peas, beans, dairy products), using a calcium-based phosphate binder with meals, and administering vitamin D to suppress parathyroid hormone secretion (Parmar 2002). In people with CKD (stages 3 and 4) who have plasma levels of intact PTH >70 pg/mL (7.7 pmol/L; stage 3) or >110 pg/mL (12.1 pmol/L; stage 4) on more than two consecutive measurements, dietary phosphate intake should be restricted. If this is ineffective in lowering plasma PTH levels, calcitriol or one of its analogs (alfacalcidol or doxercalciferol) should be given to prevent or ameliorate bone disease. In people with CKD (stage 5) who have elevated plasma levels of intact PTH (>300 pg/mL [33.0 pmol/L]), calcitriol or one of its analogs (doxercalciferol, alfacalcidol or paricalcitol) should be used to reverse the bone features of PTH overactivity (i.e., high-turnover bone disease) and to treat defective mineralization (National Kidney Foundation, 2003b).

Even with appropriate medical therapy, some patients continue to have refractory hyperparathyroidism. Parathyroidectomy should be recommended in people with severe hyperparathyroidism (persistent serum levels of intact PTH >800 pg/mL [88.0 pmol/L), associated with hypercalcemia and/or hyperphosphatemia that are refractory to medical therapy (National Kidney Foundation, 2003b).

1.2.4.3 Malnutrition

The prevalence of hypoalbuminemia is high among patients beginning dialysis, is of multifactorial origin, and is associated with poor outcome. Hypoalbuminemia may be a reflection of chronic inflammation rather than of nutrition in itself. Spontaneous intake of protein begins to decrease when the glomerular filtration rate falls below 50 ml/min. Progressive decline in renal function causes decreased appetite, thereby increasing the risk of malnutrition. Hence early dietary review is important to avoid malnutrition. Adequate dialysis is also important in maintaining optimal nutrition (Parmar, 2002).

The recommended daily protein intake for patients on HD is 1.2g/kg and for those on PD is 1.2-1.3 g/kg. The recommended daily energy intake for people on HD or PD is 35 kcal/kg for those who are less than 60 years of age and 30 to 35 kcal/kg for individuals 60 years or older. For individuals with chronic renal failure (GFR < 25 mL/min) who are not undergoing maintenance dialysis, the institution of a planned low-protein diet providing 0.60 g protein/kg/d should be considered. For individuals who will not accept such a diet or who are unable to maintain adequate dietary energy intake with such a diet, an intake of up to 0.75 g protein/kg/d may be prescribed (National Kidney Foundation, 2000).

1.3 Pharmacokinetic and pharmacodynamic in patients with renal impairment

Patients with CKD constitute a population at high-risk for adverse drug reactions (ADRs) and drug-drug interactions. Drug dosing in these patients often proves to be a difficult task. Patients with CKD almost always require a large number of medications to treat comorbid conditions and complications. Patients with renal impairment often have alterations in their pharmacokinetic parameters, including drug absorption, distribution, protein-binding, biotransformation, and renal excretion (Swan and Bennett, 1992; Kappel and Calissi, 2002). Elimination of many drugs is dependent on renal filtration, secretion and reabsorption. Glomerular filtration is impaired by renal disease or aging. The clearance of drugs eliminated primarily by this mechanism is decreased by renal disease. Therefore, special consideration should be taken when these drugs are prescribed to patients with impaired renal function. Patients with severe renal insufficiency can experience accumulation of drug metabolites also, which can contribute to pharmacologic activity or toxicity. Patients can also have an altered pharmacodynamic response to a given drug because of the physiologic and biochemical changes associated with progressive renal insufficiency (Gabardi and Abramson, 2005; Perazella and Parikh, 2005). For ESRD patients on dialysis, some medications are removed during dialysis. All these changes should be considered when drugs are prescribed to patients with impaired renal functions.

1.3.1 The effect of renal disease on drugs pharmacokinetics

Clinical pharmacokinetics is the discipline that describes the absorption, distribution, metabolism, and elimination of drugs in patients requiring drug therapy. Pharmacokinetic concepts are important to individualize patient drug therapy.

Combined with a knowledge of the disease states and conditions that influence the disposition of a particular drug, kinetic concepts can be used to modify doses to produce serum drug concentrations that result in desirable pharmacologic effects without unwanted side effects. Many factors must be taken into consideration when deciding on the best drug dose for a patient including age, gender, weight, other drug therapy, disease states and conditions (DiPiro *et al*., 2005). The followings need to considered in patients with CKD:

1.3.1.1 Effects on absorption

A medication's oral bioavailability is defined as the fraction of an administered dose that reaches the systemic circulation. This pharmacokinetic parameter may be influenced by numerous physiologic changes in the gastrointestinal tract, several of which are commonly seen in the CKD population (Gabardi and Abramson, 2005). These changes include changes in gastric pH, gastroparesis, bowel wall edema, vomiting, diarrhea, and reduced intestinal metabolism and transport.

Increased gastric pH is a common manifestation of CKD. The etiology of this finding is multifactorial. One explanation for increased pH is ammonia formation in the gut secondary to the conversion of salivary urea by urease enzymes. The administration of phosphate binders, antacids, H2-receptor antagonists, and proton-pump inhibitors in this patient population is common. For medications that are best absorbed in an acidic environment, increased gastric pH often reduces drug dissolution, ionization, and bioavailability. Examples include furosemide, ketoconazole and ferrous sulphate (Kappel and Calissi, 2002; Gabardi and Abramson, 2005; Perazella and Parikh, 2005).

It has been shown that the administration of magnesium hydroxide and sodium bicarbonate can enhance the absorption of some weakly acidic molecules (e.g., ibuprofen, glipizide, glyburide, and tolbutamide) by increasing their water solubility and subsequent absorption. The ingestion of cation-containing antacids (e.g., calcium and magnesium), aluminium hydroxide, sodium polystyrene sulfonate, and iron may reduce drug absorption because of chelation of other medications and the formation of insoluble compounds. Fluoroquinolones and tetracyclines are two medication classes that are highly susceptible to chelate formation in patients with renal insufficiency (Kappel and Calissi, 2002; Nolin *et al.*, 2003; Gabardi and Abramson, 2005; Perazella and Parikh, 2005).

Many patients with renal insufficiency suffer from gastroparesis, which can result in delayed gastric emptying. Though delayed emptying may prolong the time to maximum drug concentration, these delays generally do not affect the overall extent of absorption (Nolin *et al.*, 2003; Gabardi and Abramson, 2005; Perazella and Parikh, 2005). However, these delays might be important for drugs such as short-acting sulfonylureas (Kappel and Calissi, 2002).

Bowel wall edema has also been reported as a potential cause of diminished oral absorption in CKD patients (Swan *et al.*, 1992; Kappel and Calissi, 2002; Nolin *et al.*, 2003; and Abramson, 2005)

Vomiting and diarrhoea are also common in CKD patients and can reduce the amount of drug absorbed (Swan and Bennett, 992; Kappel and Calissi, 2002; DiPiro *et al*., 2005).

CKD-induced reductions in intestinal metabolism and P-glycoprotein–mediated drug transport may result in increased oral bioavailability of certain medications. Several medications undergo significant metabolism in the gastrointestinal tract, including cyclosporine and tacrolimus. Renal insufficiency is associated with decreased intestinal cytochrome P 450 (CYP450) enzymes 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 absorption. P-glycoprotein is a transport protein that plays a vital role in drug-disposition. This protein is found in several areas of the body, including the intestines, liver, and kidneys. P-glycoprotein functions to protect the body against the accumulation of toxic compounds by transporting these compounds out of the systemic circulation and into the intestinal lumen, bile, or urine. Several animal models of CKD have demonstrated decreased activity of intestinal P-glycoprotein. Decreased P-glycoprotein activity results in a greater concentration of medications remaining in the systemic circulation (Nolin *et al.*, 2003; Gabardi and Abramson, 2005).

Unfortunately, there is little quantitative information regarding the influence of impaired renal function on drug absorption and bioavailability (DiPiro *et al.*, 2005). Physicians and pharmacists need to modify the regimens according to the patient's response.

1.3.1.2 Effects on distribution

CKD-induced alterations in protein binding can have clinical implications. Medications that are acidic (e.g., barbiturates, cephalosporins, furosemide,