

A REVIEW ON DOSE ADJUSTMENT IN RENAL FAILURE PATIENTS***Vishwas A.T.L.¹, Dr. Divyashree N.², Nandan H.N.² and Bhanushree D. M.²**

Department of Pharmacy Practice, Bharathi College of Pharmacy, Bharathi Nagara, Mandya.

***Corresponding Author: Vishwas A.T.L.**

Department of Pharmacy Practice, Bharathi College of Pharmacy, Bharathi Nagara, Mandya.

Article Received on 15/03/2017

Article Revised on 05/04/2017

Article Accepted on 26/04/2017

ABSTRACT

Chronic renal failure is an important health care problem throughout the world, with an incidence of 337, 90, 107 and 95 new cases per million inhabitants / year in the United States, Australia, New Zealand and the United Kingdom, respectively. In India it accounts 1 out of 10,000 are affected from chronic kidney disease and one lakh new diagnosis are with end stage renal disease annually. Many medications and their metabolites are eliminated through the kidney. Thus, adequate renal function is important to avoid toxicity. Renal impairment may cause medicines to accumulate or cause toxicity, especially if the medicine has a narrow therapeutic index. Before dose adjustment in renal disease calculation of glomerular filtration rate is needed this reflects the stages of renal disease. Nephrologists and clinical pharmacists can work together to accomplish safe drug prescribing. Clinical pharmacists play an important role in identifying drug related problems, resolving and preventing potential drug therapy problems through careful pharmaceutical practices. This article is an overview of prescribing considerations in the primary care setting for patients with acute and chronic renal impairment.

KEYWORDS: clinical pharmacists, Nephrologists, therapeutic index, glomerular filtration rate, renal impairment.**INTRODUCTION**

Drugs and their metabolites are removed from the body by excretion. Kidneys are the main principle organs in excretion.^[1] Renal excretion of medications is dependent on glomerular filtration rate, renal tubular secretion and reabsorption.^[2] Renal impairment may cause drugs and metabolites to accumulate as a result in toxicity especially drugs having narrow therapeutic index ex: digoxin, lithium.^[3] Pharmacokinetic profile was altered in renal impairment. In renal impairment patients renal clearance and elimination rate are reduced and increased elimination half life of drug.^[1]

Renal injury may occur in various renal compartments: the renal vascular supply, the glomerulus, the tubulointerstitium where extensive tubular-peritubular capillary exchange of solutes takes place, and the collecting ducts.^[4]

Acute renal failure (ARF) is characterized by a sudden and important reduction in glomerular filtration rate (GFR) lasting for hours or days.^[5] Chronic kidney disease (CKD) is a common condition defined by the presence of kidney damage or decreased kidney function for three or more months.^[6]

The number of patients with acute kidney injury and chronic kidney disease has increased dramatically in the past 10 years. Advances in the treatment of disease in general have permitted patients to live longer and many

of them develop decreased kidney function over time. Indeed, kidney function decreases with age, and older patients constitute the most rapidly expanding patient group with chronic kidney disease.^[7]

Nephrotoxic drugs (ND) as therapeutic agents that have the potential to cause adverse effects on renal function as a result of direct toxicity or compromised renal perfusion, and this toxicity may depend on the clinical context involved. The types of kidney dysfunction that are induced by Nephrotoxic drugs include acute tubular necrosis, glomerular and tubulointerstitial injury, haemodynamically mediated damage and obstructive nephropathy.^[8] Potential adverse effects can be prevented by reducing the dose, extending the dose interval, or by prescribing an alternative medicine that is less likely to accumulate.^[3]

Patients with stage III and stage IV CKD have more severe reduction in GFR. These patients are at high risk for developing end stage of renal disease (stage V CKD) and death and should, therefore, be carefully evaluated to determine the etiology and severity of their disease.^[9]

Drug dosing errors are common in patients with renal impairment and can cause adverse effects and poor outcomes. Dosages of drugs cleared renally should be adjusted according to creatinine clearance or glomerular filtration rate and should be calculated using online or electronic calculators.^[10] The Cockcroft and Gault

formula and the Modification of Diet in Renal Disease (MDRD) are the most widely used formulae to estimate renal function.^[4]

Stages of chronic kidney disease

Stage	Description	GFR, mL/min per 1.73m ²
I	Kidney damage with normal or increased GFR	≥90
II	Kidney damage with mildly decreased GFR	60–89
III	Moderately decreased GFR	30–59
IV	Severely decreased GFR	15–29
V	Kidney failure	≤15 (or dialysis)

NOTE:-Adapted from.^[10] Chronic renal failure is defined on the basis of a glomerular filtration rate (GFR) of less than 60 ml/min/1.73 m².

Etiology of Acute and Chronic Renal Disease

The etiology of ARF can be divided into broad categories based on the anatomic location of the injury associated with the precipitating factors.^[11]

Pre-renal	Intrinsic renal causes	Post-renal
Gastrointestinal losses	Acute tubular necrosis	Bladder obstruction
Excessive perspiration	Severe cortical necrosis	Urethral obstruction.
Bleeding	Severe acute glomerulonephritis	Bilateral ureteral obstruction
Burns with fluid sequestration	Allergic interstitial nephritis	Patients with a single kidney
Renal losses	Malignant hypertension	Bladder rupture ⁵
Cardiovascular failure	Accelerated scleroderma	
Liver failure	Vasculitis	

The working group of Kidney Dialysis Outcomes and Quality Initiative has recommended categorizing CKD risk factors as susceptibility factors, initiation factors, or

progression factors to help clinicians stratify the overall risks of individual patients.^[11]

Susceptibility factors	Initiation factors	Progression factors
Advanced age	Diabetes Mellitus	Proteinuria
Low income or education	Hypertension	Hypertension
Racial/ethnic minority status	Glomerulonephritis	Diabetes Mellitus
Low birth weight		Smoking
Family history of CKD		Obesity ¹¹ .

Assessment of Renal Function

The glomerular filtration rate is the best parameter for assessing renal function.^[1] The measurement of GFR can be accomplished using many exogenous substances. Urinary clearance of inulin, which is the gold standard, is rarely performed except for research purposes because of the limited availability of the substance and the labor intensity of the procedure and the assay.^[7] Clinically, creatinine clearance is widely used to assess renal function.^[1]

Creatinine is produced at a relatively constant rate for each individual, as a result of muscle metabolism, and rate of creatinine clearance is proportional to muscle mass.^[12] Creatinine plays no significant physiological role and is eliminated by renal excretion with no active tubular secretion in the nephron. These unique features mean that the clearance of creatinine may be used as surrogate marker of the glomerular filtration rate.^[13]

Creatinine production varies with age, weight and gender.^[1]

The most practical approach for assessing kidney function in the majority of clinical settings is estimation of creatinine clearance. It seems that there is an underestimation or lack of knowledge of the importance regarding creatinine clearance in determining appropriate medication dose.^[2] The most sensitive methods for determining GFR are those that use radioisotopes. Literature describes methods with radioactive markers Cr-EDTA, Th-DTPA and Iotalamat. There is also a non-radioactive iohexol method of direct GFR determination. These methods, as well as those that use inulin clearance, are more costly and more impractical than indirect GFR determination.^[6]

The determination of GFR utilizing an endogenous substance has therefore been based on the urinary

clearance of creatinine (CrCl) derived from a 24 hour urine collection.^[7]

Blood urea nitrogen (BUN) and serum urea are secondary indicators of renal function. As serum urea and BUN may be affected by the patient hydration status and other factors, these parameters are less sensitive indicators of renal function than serum creatinine.^[13]

Cystatin C has been shown to be a good endogenous marker of glomerular filtration, because it is synthesized by all body cells at a constant rate (even in the presence of inflammatory conditions), removed from circulation by glomerular filtration and completely reabsorbed and broken down in the tubules, but not secreted by the tubules. So it is not that useful for detecting initial changes in glomerular filtration rate.^[6]

Urinary neutrophil gelatinase (NGAL), kidney injury molecule-1 and interleukin-18 are urinary markers that are being evaluated for their potential to separate prerenal from post renal causes of AKI, but their discriminating power has not been high. Notably, these markers will not be useful when marked oliguria is present.^[14]

When evaluating the risk of progression of CRF and of the possible development of end stage renal failure, it is necessary to detect and quantify proteinuria. In addition, in the early stages of CRF, normal or only slightly reduced GFR values may be observed despite an already manifest increase in protein excretion in urine.^[5]

Drugs In Renal Failure

Up to 15% of drug-induced acute renal failure is caused by hypersensitivity reactions that cause renal tubular and interstitial inflammation.^[4] Drug dosing based on actual or relative creatinine clearance has not been compared for efficacy or toxicity outcomes, but basic pharmacokinetic principles explain why it makes sense to leave out the weight variable when assessing renal function for the purposes of drug dosing. Whereas the total daily dose of a medication is based on the overall systemic clearance of the drug, changes to the dosing interval should be made on the basis of relative half-life differences.^[15]

The metabolism and elimination of certain drugs are altered in situations of renal failure. In such cases dose adjustment or modification of the dosing frequency is needed.^[5] Nephrotoxicity can be reduced by taking drug-specific precautions.^[4] The proper dosing of medications for patients with renal impairment can maximize therapeutic efficacy and minimize toxicity. Proper dosing can also have an economic impact on the health system. Dosage adjustment can result in avoidance of costs associated with drug-related toxicity and in cost savings in terms of drug costs.^[2]

Medicines that accumulate in renal impairment

Renal impairment may cause medicines or their metabolites to accumulate. This may result in toxicity, especially if the medicine has a narrow therapeutic index (eg. digoxin, lithium). Potential adverse effects can be prevented by reducing the dose, extending the dose interval, or by prescribing an alternative medicine that is less likely to accumulate.^[3]

Digoxin

Digoxin has a narrow therapeutic index and prolonged elimination half life in older people.^[9] The accepted therapeutic range for serum digoxin has changed in the past few years, and while the trough level of 2.0 mg/L is still useful in helping with the diagnosis of toxicity, at present it seems clear that digoxin should be administered in a dose to reach serum levels between 0.5 and 1.2 mg/L.^[16] For patients with an eliminated GFR of 10–30 mL/min, a daily maintenance dose of 62.5–125 µg is recommended and for patients with a GFR <10 mL/min, a maintenance dose of 62.5 µg once daily or on alternate days is recommended.^[3]

Metformin

Avoid if serum creatinine level is higher than 1.5 mg per dL (130 µmol per L) in men or higher than 1.4 mg per dL (120 µmol per L) in women and in patients older than 80 years or with chronic heart failure; fixed-dose combination with metformin should be used carefully in renal impairment.^[10]

Analgesics

Patients with stage 5 kidney disease are more likely to experience adverse effects from opioid use.^[10] Many opioids (eg. codeine, tramadol, morphine, hydromorphone) (have active metabolites that can accumulate and cause central nervous system or respiratory depression.^[3] These agents are not recommended in patients with stage 4 or 5 disease.^[10]

Medicines that can reduce renal function or cause nephrotoxicity

There are also a number of commonly used medicines that can impair renal function or cause nephrotoxicity. These include ACEIs, ARBs and NSAIDs. Acute interstitial nephritis is a very rare adverse effect of proton pump inhibitors (PPIs); but the high volume of PPI prescribing means that PPIs are a leading cause of acute interstitial nephritis in Australia.^[3]

Non steroidal anti - inflammatory drugs(NSAIDs)

Adverse renal effects of NSAIDs include acute renal failure; nephrotic syndrome with interstitial nephritis; and chronic renal failure with or without glomerulopathy, interstitial nephritis and papillary necrosis.^[10] The rate of acute renal failure (ARF) is up to three times higher in NSAID users compared to non-users.^[3]

Angiotensin converting enzyme inhibitors (ACEIs)

Even without pre-existing risk factors, ACEIs can cause an acute decline in GFR.^[3] ACE inhibitors can be continued safely if the rise in serum creatinine is less

than 30%. Typically, the level will return to baseline in four to six weeks. Dosages should be titrated carefully and followed by weekly monitoring of renal function and potassium levels until values return to baseline.^[10]

Drugs that induces nephrotoxicity	Drugs that Require Dosage Adjustment
Amphotericin B	morphine,
NSAIDs	Aminoglycosides
Mercury	Acyclovir
Pencillamine	Famotidine
Cyclosporine	Carboplatin
Diuretics	clofi brate
Clopidogrel	Sulfonylureas

Note: - only few drugs are mentioned as example.

Formulas For Dose Adjustment In Renal Failure

Formula used to calculate creatinine clearance from the serum creatinine values includes^[1],

For children (between 1to 20 years),

In the neonates, the kidney failure index is higher than 2.5 in renal and less than 2.5 in prerenal azotemia. It should be recognized that GFR are lower in preterm neonates compared with term infants and older children.^[17] The creatinine clearance can be calculated by equation,

$$\text{CrCl} = 0.48\text{H} / \text{SCr} [w / 70]^{0.7}$$

Where, CrCl = creatinine clearance in ml/min

SCr = serum creatinine in mg%

H = height in cms and

W = weighi in kg.

Cockcroft–Gault (CG) equation

Cockcroft - Gault equation for estimation of GFR contains data for age, weight and serum creatinine concentration and this is determined by a more specific enzymatic method. While some studies show that Cockcroft-Gault equation is the best for estimation of glomerular filtration rate in obese patients.^[6]

For adults (above 20 years),

$$\text{CrCl (mL/min)} = [(140 - \text{age}) \times \text{weight (kg)}] / [72 \times \text{SCr (mg/dL)}]$$

For women, multiply the result by 0.85

Where, CrCl = creatinine clearance in ml/min

SCr = serum creatinine in mg%

Renal function (RF) can be calculated by equation^[1]

$$\text{RF} = \text{CrCl of patient} / \text{CrCl of normal person}$$

Modification of Diet in Renal Disease Study equation^[15]

Modification of Diet in Renal Disease study (MDRD equation) uses data for serum creatinine concentration and the age of patient.^[6] The full MDRD equation also adjusts for serum albumin level. A simplified MDRD equation that does not rely on albumin levels or weight is also highly accurate.^[9]

$$\text{GFR (mL min}^{-1} \text{ 1.73 m}^{-2}) = 170 \times [\text{SCr (mg/dL)}]^{-0.999} \times \text{age}^{-0.176}$$

$$\times [\text{BUN (mg/dL)}]^{-0.170} \times [\text{Alb (g/dL)}]^{0.318}$$

For women, multiply the result by 0.762

For blacks, multiply the result by 1.18

Where,

Alb = albumin

BUN = blood urea nitrogen

GFR = glomerular filtration rate

SCr = serum creatinine

The required **Dose in patient with renal impairment** can be calculated by simple formula,

$$\text{Drug dose in renal impairment} = \text{normal dose} \times \text{renal function}$$

Dosing interval in hours can be computed from folloeing equation^[1],

$$\text{Dosing interval} = \text{normal interval in hours} / \text{renal function}$$

Calvert equation^[15]

The discrepancy between the doses calculated with measured and estimated GFR is not surprising, as the Calvert equation causes the dose of carboplatin to change in direct proportion to renal function, whereas most drug dosing tables have broad categories. Although de Lemos and others used the Calvert equation as the reference equation.^[15]

$$\text{Dose (mg)} = \text{AUC (mg mL}^{-1} \text{ min}^{-1}) \times [\text{GFR (mL/min)} + 25]$$

Where,

GFR = glomerular filtration rate

AUC = area under curve

Relation between clearance (Cl), volume of distribution (V_d), and half-life (t_{1/2})^[5]

The total daily dose of a medication is based on the overall systemic clearance of the drug, Changes to the dosing interval should be made on the basis of relative half-life differences. The half-life is in turn based on the ratio of volume of distribution and systemic clearance.^[15]

$$t_{1/2}/0.693 = V_d/Cl$$

Factors Affecting Drug Dosing in Patients with Acute Kidney Injury

Mainly two important factor will affect the dosing in patient with acute kidney injury are Patient related and drug-related variables.

A) Patient related factors

- Differences in baseline characteristics: Age, sex, body mass and surface, fat tissue and muscle tissue content
- Altered drug pharmacokinetics (individual variations)
- Changes in volume of distribution
- Hypoalbuminemia
- Changes in renal clearance
- Commonly observed disturbances in drug metabolism in the liver (individual variations)
- Dynamic changes in patient's clinical state and organ function.

B) Drug-related variables

- The molecular weight of the drug
- Protein binding
- The degree of renal clearance.^[18]

Role of clinical pharmacist

The pharmacist has a role to play in methodical prescription assessment and appropriate medicine dose review for all patients in chronic kidney disease.^[12] Pharmacists should be mindful of medications with well-known dose-related side effects, such as aminoglycosides. In patients with renal dysfunction, potentially nephrotoxic medications such as aminoglycosides should be avoided wherever possible, and safer alternatives should be used instead.^[15]

Evaluate the degree of renal impairment. The evaluation of GFR is the most reliable index and surrogate marker of overall kidney function.^[2] The pharmacist should make an informed dosage recommendation but should be meticulous in monitoring for adverse events.^[15]

The large number and the continuously increasing medications list makes it difficult for medical staff to remain updated on dosage adjustment issues. Since clinical pharmacists are well trained in pharmacokinetics, mechanisms of drug interactions and pharmacodynamics, they can assist physicians to adjust drug dosages in patients with chronic kidney disease.^[2] One of the hospital pharmacist's many clinical roles is to estimate renal function, refer to literature references and adjust medication doses for renal dysfunction.^[15]

Pharmacists have shown an impact in improving medical management in other areas. Clinical pharmacy interventions and involvement in disease management by Community pharmacists have the potential to provide a valuable contribution to healthcare and decrease the overall healthcare cost.^[2]

CONCLUSION

Clinical pharmacists and physician play an important role for improving health status in patients. Improper drugs or improper dosage regimen of a drugs leads to serious complications which includes acute or chronic kidney damage. In this conditions dose adjustment required to provide safe, effective and good therapeutic effect. Clinical pharmacists must review the medication chart to prevent adverse effects and drugs related problems especially in renal diseases.

REFERENCE

1. D. M Brahmkar and sunil B. Jaiswal. Biopharmaceutics and pharmacokinetics – A treatise, 2014; 196-221.
2. Yahaya Hassan, Rowa'J Al-Ramahi, Noorizan Abd Aziz and Rozina Ghazali. Drug Use and Dosing in Chronic Kidney Disease. *Ann Acad Med Singapore*, 2009; 38: 1095-103.
3. J Simon Bell, Natalie Blacker, V Tammy LeBlanc, Christopher P Alderman, Adam Phillips et al. Prescribing for older people with chronic renal impairment. *Australian Family Physician*, 2013; 42(1): 24-28.
4. Eric Decloedt and Gary Maartens. Drug-induced renal injury. *CME*, JUNE 2011; 29(6): 252-255.
5. Alba Jover Cervero, José V. Bagan, Yolanda Jimenez Soriano, Rafael Poveda Roda. Dental management in renal failure: Patients on dialysis. *Med Oral Patol Oral Cir Bucal*, 2008; 13(7): 19-26.
6. Lucija simetic, Lada Zibar, Sandra Drmic, Ivana Begic and Vatroslav seric. Creatinine Clearance and Estimated Glomerular Filtration Rate – When are they Interchangeable. *Coll. Antropol*, 2015; 39(3): 735–743.
7. Gary R. Matzke, George R. Aronoff, Arthur J. Atkinson Jr, William M. Bennett, Brian S. Decker et al. Drug dosing consideration in patients with acute and chronic kidney disease—a clinical update from Kidney Disease: Improving Global Outcomes. *Kidney International*, 2011; 80: 1122–1137.
8. Millena Drumond Bicalho, Danielly Botelho Soares, Fernando Antonio Botoni, Adriano Max Moreira Reis and Maria Auxiliadora Parreiras Martins. Drug-Induced Nephrotoxicity and Dose Adjustment Recommendations: Agreement among Four Drug Information Sources. *Int. J. Environ. Res. Public Health*, 2015; 12: 11228-11240.
9. Samir K. Gupta, Joseph A. Eustace, Jonathan A. Winston, Ivy I. Boydston et al. Guidelines for the Management of Chronic Kidney Disease in HIV-Infected Patients: Recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. *CID*, 2005; 40(1): 1559-1585.
10. Myrna Y. Munar and Harleen Singh. Drug Dosing Adjustments in Patients with Chronic Kidney Disease. *American Family Physician*, 2007; 75(10): 1488-1496.

11. Joseph T. Dipiro, Robert L. Talbert, Gary C. Yee, Gary R. Matze, Barbara G. Wells and L. Michel Porey. *Pharmacotherapy*. 7th edition. 2008; 723-764.
12. Andera Devaney and Charlie Tomson. Chronic kidney disease – new approaches to classification. *Hospital pharmacist*, 2006; 13: 406-410.
13. G. Parthasarathi, Karin Nyfort – Hanses and Milap C Nahata. *A textbook of clinical pharmacy practice*. 2012; 141-144.
14. Laurent Brochard, Fekri Abroug, Matthew Brenner, Alain F. Broccard, Robert L. Danner, et al. Prevention and Management of Acute Renal Failure in the ICU Patient. *American Thoracic Society Documents*, 2010; 181: 1128–1155.
15. Deonne Dersch and James McCormack. Estimating Renal Function for Drug Dosing: Rewriting the Gospel. *CJHP*, 2008; 61(2): 138-143.
16. Marta Vazquez-Hernandez, Lorena Bouzas and J.Carlos Tutor. Glomerular filtration rate estimation using the Cockcroft-Gault and Modification of Diet in Renal Disease formulas for digoxin dose adjustment in patients with heart failure. *Upsala Journal of Medical Sciences*, 2009; 114: 154-159.
17. James C.M. Chan, Debra M. Williams and Karl S. Roth. Kidney failure in infants and children. *Pediatrics in review*, 2002; 23(2): 42-59.
18. Anish Kumar and Narinder Pal Singh. Antimicrobial dosing in critically ill patients with sepsis-induced acute kidney injury. *Indian Journal of Critical Care Medicine*, 2015; 19(2): 99-108.