



Received on 04 May, 2015; received in revised form, 21 July, 2015; accepted, 10 September, 2015; published 01 November, 2015

A STUDY ON DRUG DOSE ADMINISTRATION IN GERIATRICS WITH RESPECT TO CREATININE CLEARANCE RATE

S. K. Shama¹, P. Chandra Sai^{*1}, A. Ramya¹, V. Raghuram³ and T. V. A. Seshu Babu²

Department of Pharmacy Practice¹, Chalapathi Institute of Pharmaceutical Sciences, Guntur, Andhra Pradesh, India

Department of General Medicine², Government General Hospital, Guntur, Andhra Pradesh, India.

Department of Pharmacy Practice³, Chalapathi Institute of Pharmaceutical, Sciences, Acharya Nagarjuna University, Guntur, Andhra Pradesh, India.

Keywords:

Geriatrics, Creatinine clearance, Pharmacist, Dose modification, adverse drug reactions

Correspondence to Author:

P. Chandra Sai

Intern at Department of Pharmacy Practice, Chalapathi Institute of Pharmaceutical Sciences, Guntur, Andhra Pradesh, India

E-mail: chandrasai4304@gmail.com

ABSTRACT: Objective: The objectives are to assess the drug dose administration and reduce the dose toxicity in geriatric patients. **Method:** A Prospective interventional study has been carried out on drug dose administration in geriatric patients with respect to creatinine clearance rate at a tertiary care hospital for about 6 months. A total number of 204(47 baseline+157study) geriatric patients are included who has attended the general medicine ward. **Results:** In our study, we observed that Creatinine clearance was decreased as age increases. In study population 60-65yrs (48.6ml/min) was more, in 80-85yrs (29.2ml/min) was less and also similar in baseline study. So we can understand that geriatrics has a moderate renal failure. In a baseline among 47 subjects, 53% require dose modifications. In baseline 11 (44%) subjects experienced adverse drug reactions. Mostly Augmented types of adverse effects were observed. Among 157 study population, 28% were undergone dose modification by the suggestion of a pharmacist. It was observed that in 31 (70.4%) dose of the drug was reduced, in 6(13.6%) dose interval was increased, in 7(16%) both dose and dose interval was changed. Among the study population, 8(18%) were experienced adverse drug reactions. As compared to baseline, in study population the adverse drug reactions and dose burden on the renal system is reduced. **Conclusion:** The geriatric patient's creatinine clearance was decreased with respect to the age. It was observed that dose modifications were needed based on Creatinine clearance in geriatrics. The clinical outcome of the patient was improved, and adverse effects were reduced after dose modification. Pharmacist intervention plays a pivot role in avoiding drug-related problems and improves the quality of life.

INTRODUCTION: Aging is associated with deleterious effects at the cellular level and altered homeostatic mechanisms that are liable to diseases and death^{1, 2, 3, 4}. As the man gets older the physiological changes are inevitable. These physiological changes alter the pharmacokinetics and pharmacodynamics of the drug⁵.

Pharmacodynamic changes alter the effectiveness of the drug due to alteration of sensitivity and number of receptors. The amount of drug reaches the systemic circulation is determined by the pharmacokinetics of a drug. Elimination is more influenced in pharmacokinetic parameters due to loss of kidney function⁶. Physiological changes related to excretion in elderly are decreased renal blood flow, kidney mass, reduction in the number of functioning nephrons and glomerular filtration rate are decreased⁷.

The creatinine clearance is most extensively used method to measure glomerular filtration rate Creatinine clearance decreases 1% every year after

<p>QUICK RESPONSE CODE</p> 	<p>DOI: 10.13040/IJPSR.0975-8232.6(11).4721-27</p> <hr/> <p>Article can be accessed online on: www.ijpsr.com</p> <hr/> <p>DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.6(11).4721-27</p>
---	---

40 years of age^{1, 8}. Generally serum creatinine is one of the parameters to measure the kidney function. However, this is inaccurate in geriatrics due to muscle breakdown, and they have a moderate decrease in renal function^{9, 10}. Creatinine clearance is a valid predictor of nephritic function. The drug clearance is similar to that of creatinine clearance. As the drug clearance is decreased it accumulates in the body lead to adverse effects. Almost 3.4% of the population admitting in hospitals and hospital stay also increased due to adverse drug reactions¹⁰. The practitioners should refer the several monographs and literature to modify the dose based on creatinine clearance there by the drug toxicity, and adverse effects will be minimized¹¹. The clinical pharmacist helps in drug dosage modification and provides the pharmaceutical care in geriatrics¹².

Aims of our study are.

1. To assess the drug dose administration in geriatrics with respect to creatinine clearance rate.
2. To reduce the dose burden on geriatric patients
3. To minimize the drug toxicity and undesired events.

MATERIALS AND METHODS:

The study was conducted in a government tertiary care teaching hospital in a period of six months. The subjects were selected based upon inclusion and exclusion criteria. The study material consists of a data collection form approved by an ethical committee of the institution, and confidentiality was assured for data.

Inclusion criteria:

Geriatric patients (≥ 60) who were attending the general medicine wards of government general hospital.

Exclusion criteria:

- Patients with less than (< 60) years of age.
- Patients with acute kidney diseases.

It was a prospective interventional study to assess the drug dose administration in geriatric patients with respect to Creatinine clearance rate. Patients of either gender greater than or equal to 60 years of

age were included into the study. The patient demographic details like age, sex, weight, height, diagnosis, laboratory tests which include renal function tests and other laboratory data were recorded. Creatinine clearance was calculated by using the Cockcroft gault equation^{13, 14}.

For Obese patient's Ideal Body Weight was calculated & for the patients who are critically ill/immobilized an equation is used for the prediction of weight¹⁵.

Weight (kg) = 0.5759 x (arm circumference, cm) + 0.5263 x (abdominal circumference, cm) + 1.2452 x (calf circumference, cm) - 4.8689 x (Sex, male = 1 and female = 2) - 32.9241 (r = 0.94).

Upon calculating the creatinine clearance, the dose was estimated and modified by using various literature and standard references like.

- Databases: Clinical pharmacology-Elsevier, Micromedex-Truven health analytics.
- Books: Include standard textbooks, Drug indexes & National formulary like Katzung et al, Renal Drug Hand Book, AHFS, BNF.
- Articles: Gilbert DN et al 16, Aronoff GR et.al 17

A baseline study was conducted for one month, to assess the pattern of prescribing a dose in the geriatrics and the clinical outcomes in geriatric patients. The included subject's creatinine clearance was calculated and estimated their drug dose. The follow-up was conducted for the patients during the hospital stay, and the observed outcome is recorded.

For the next five months, prescribers were suggested regarding dose adjustment of a patient based on their creatinine clearance. After reviewing the possibilities, the dose was modified by the prescriber based on creatinine clearance. A regular follow-up was carried out to assess the patient outcomes & also the doses were adjusted based on creatinine clearance in further follow up if necessary. If any adverse drug reactions were observed in patients and who require dose

adjustments were monitored until the patient was treated in the hospital.

RESULTS:

A) Baseline Study:

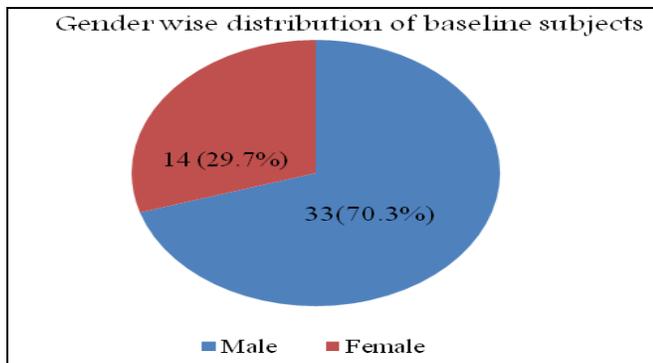


FIG.1: BASELINE GENDER DISTRIBUTION OF SUBJECTS

- Total numbers of subjects included in the baseline are 47.
- Out of which 33(70.3%) subjects are males & 14(29.7%) subjects are females

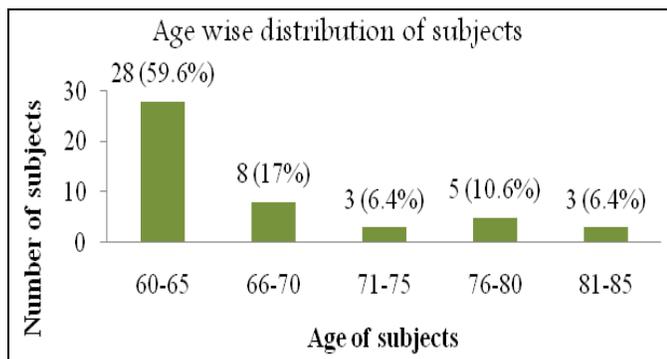


FIG.2: AGE WISE DISTRIBUTION OF SUBJECTS IN BASELINE

It was observed that in the subjects included between 60-65 years of age are higher incidence i.e 59.6%, 66-70 were 17%, 71-75 were 6.4%, 76-80 were 10.6%, 81-85 were 6.4%

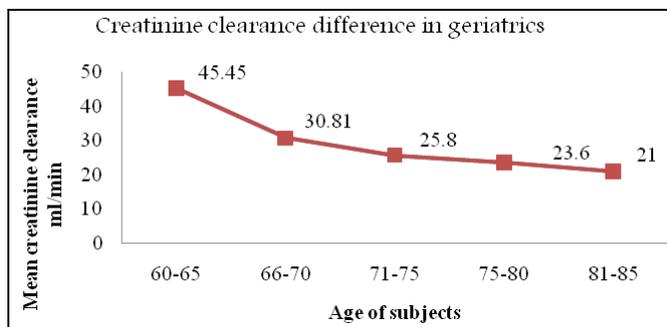


FIG.3: CREATININE CLEARANCE DIFFERENCE IN GERIATRIC PATIENTS (BASELINE)

The statistical parameters like mean and standard deviation of creatinine clearance were calculated for the included number of subjects. The mean creatinine clearance 45.45 ml/min was higher in 60-65 yrs of age. In 66-70 yrs creatinine clearance was 30.81ml/min, 71-75 yrs creatinine clearance was 25.8ml/min, 75-80 yrs creatinine clearance was 23.6ml/min, 81-85 creatinine clearance was 21ml/min. Thus, the above data provides that the Creatinine clearance was decreased as age increases.

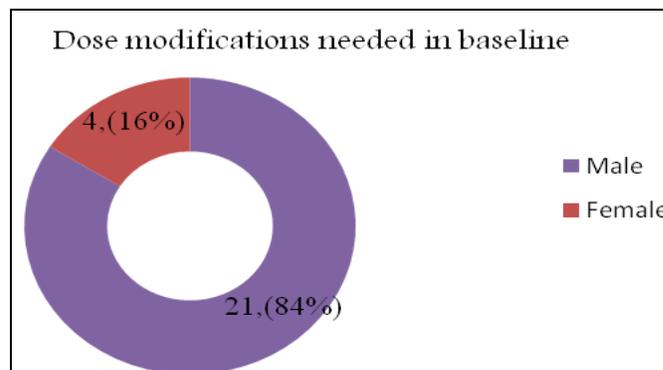


FIG.4: DOSE MODIFICATIONS NEEDED SUBJECTS IN BASELINE:

In a total of 47 subjects in the baseline, 25 subjects were needed dose modifications based on their Creatinine clearance rate. Among these 25 subjects 21(84%) subjects are males, 4(16%) subjects are females.

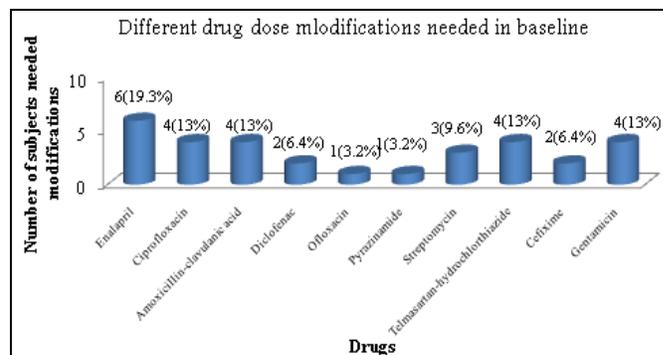


FIG.5: DIFFERENT DRUG DOSE MODIFICATIONS NEEDED IN BASELINE

Among 25 subjects, 19(76%) needed one drug dose modification i.e 19 drugs, remaining 6(24%) subjects needed two i.e 12 drug dose modifications. It was observed that Enalapril dose mode modification is more in patients 19.3%, Ciprofloxacin, Amoxicillin+clavulanic acid Telmisartan + hydrochlorothiazide, Gentamicin

require in 13%, Diclofenac, Cefixime in 6.4%, Ofloxacin, Pyrazinamide in 3.2% subjects.

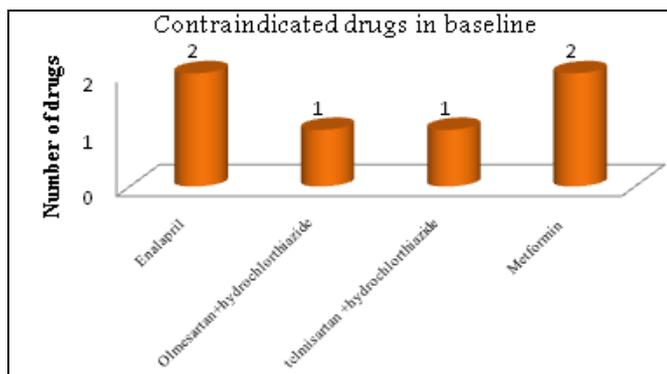


FIG.6: CONTRAINDICATED DRUGS IN BASELINE

Among 47 subjects 6(12%) have contraindicated drugs.

TABLE 1: ADVERSE DRUG REACTIONS OBSERVED IN BASELINE STUDY

Suspected Drug	Adverse drug reaction
Enalapril	Hypotension (n=2), hyperkalemia (n=3)
Pyrazinamide	Rashes(n=1), SGOT Levels raised (n=1)
Ofloxacin	Vomiting (n=2)
Amoxicillin+ clavulanic acid	Diarrhea (n=2)

n=number of patients

Among 25 drug dose modification required patients 11(44%) were experienced adverse drug reactions.

B) Study:

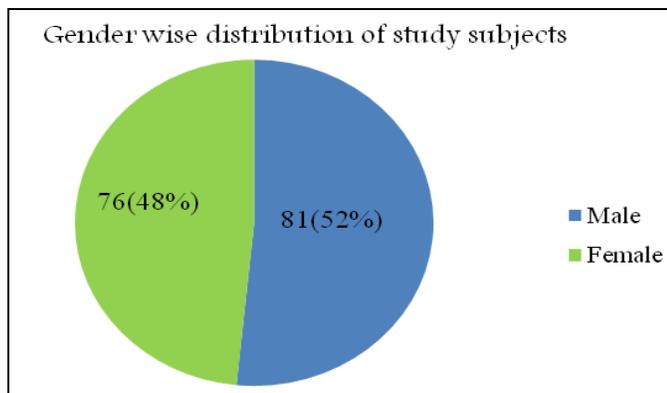


FIG.7: GENDER DISTRIBUTION OF STUDY SUBJECTS

Total Number of subjects included in the study were 157, Out of 157 subjects 81(52%) subjects were males & 76 (48%) subjects were females.

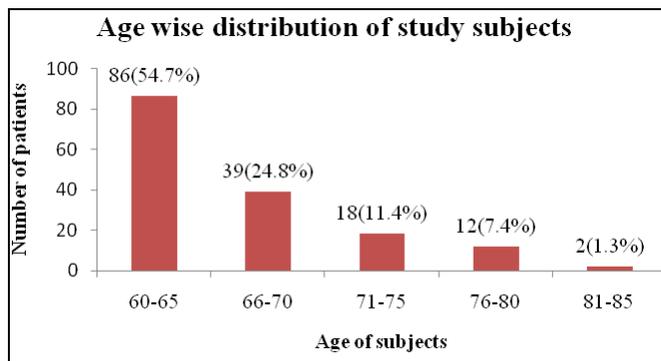


FIG. 8: AGE WISE DISTRIBUTION OF STUDY SUBJECTS

It was observed that the subjects included between 60-65 years of age are higher incidence i.e 59.6%, 66-70 were 17%, 71-75 were 6.4%, 76-80 were 10.6%, and 81-85 were 6.4%

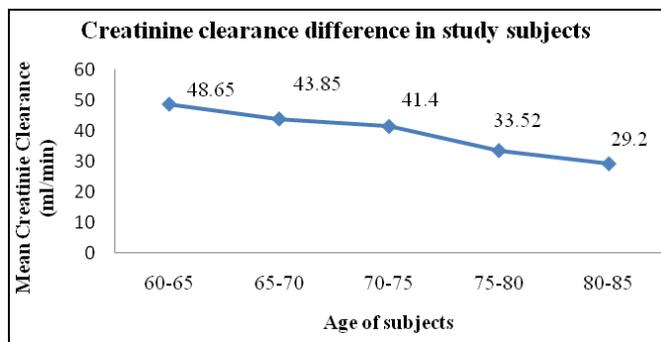


FIG.9: CREATININE CLEARANCE DIFFERENCE IN STUDY SUBJECTS

The statistical parameters like mean and standard deviation of creatinine clearance were calculated for the included number of subjects. The mean creatinine clearance 45.45 ml/min was higher in 60-65 yrs of age. In 66-70 yrs creatinine clearance was 30.81ml/min, 71-75 yrs creatinine clearance was 25.8ml/min, 75-80 yrs creatinine clearance was 23.6ml/min, 81-85 creatinine clearance was 21ml/min. Thus, the above data provides that the Creatinine clearance was decreased as age increases.

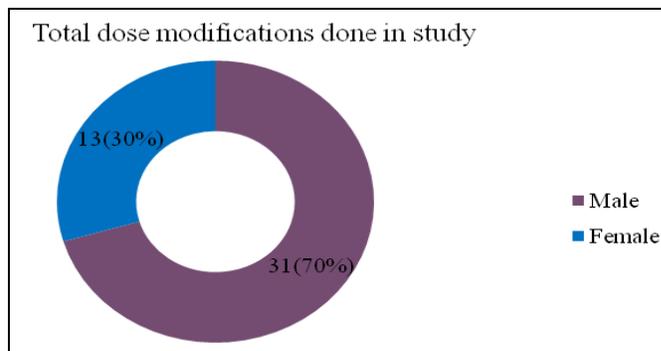


FIG.10: TOTAL DOSE MODIFICATIONS DONE IN STUDY

Of total 157 subjects, dose modification was done for 44(28%) subjects. In this 31(19.7%) Subjects were males 13(8.3%) subjects were females.

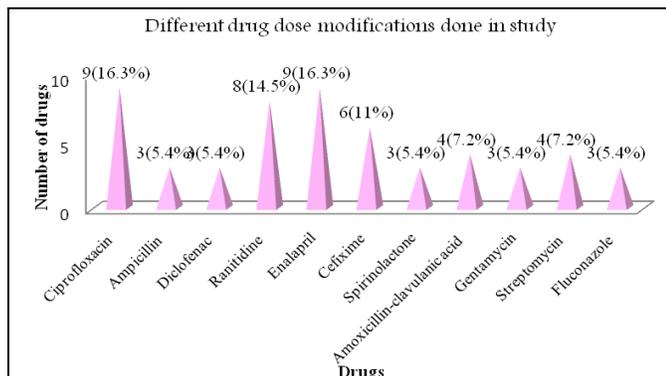


FIG. 11: TOTAL NUMBER OF DRUG DOSE MODIFICATIONS DONE IN STUDY

Among 44 subjects, 33 subjects needed one drug dose modification i.e 33 drugs, remaining 11 subjects needed two drugs i.e 22 drug dose modifications. Among all the drugs, it was observed Enalapril (16.3%) and ciprofloxacin (16.3%) needed higher dose modifications

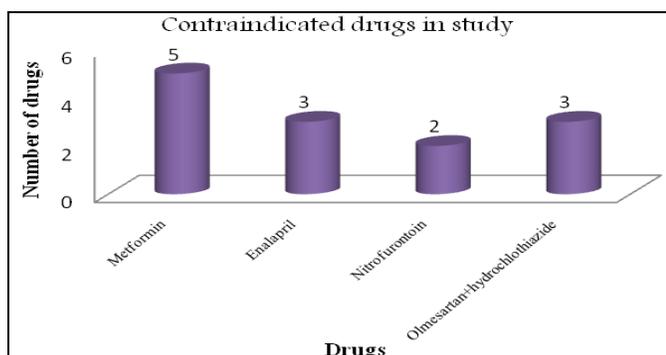


FIG.12: CONTRAINDICATED DRUGS IN STUDY

Among 157 subjects (13)8% have contraindicated drugs.

TABLE 2: ADVERSE DRUG REACTIONS OBSERVED IN NORMAL STUDY

Suspected Drug	Adverse drug reaction
Diclofenac	Gastric irritation(n=2)
Ciprofloxacin	Nausea(n=3)
Spironolactone	Hyperkalemia(n=2)
Pyrazinamide	Hyperuricemia(n=1)
Ofloxacin	Vomiting(n=0)
Pyrazinamide	Rashes(n=0), SGOT Levels raised (n=0)

The observed adverse drug reactions were observed even after dose adjustment some are before dose adjustment. Among 44 dose modification subjects 8(18%) were experienced adverse drug reactions.

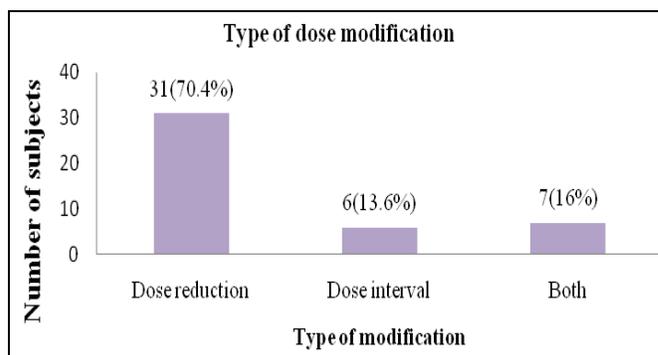


FIG.13: TYPE OF DOSE MODIFICATIONS DONE IN THE SUBJECTS

It was observed that 31 (70.4%) subjects dose was reduced, in 6(13.6%) subjects dose interval was reduced. In 7(16%) subjects both dose and dose interval was reduced.

DISCUSSION: A total number of 204 (47 baseline+157 study) subjects were included in this prospective interventional study conducted for 6 months duration. The baseline study was conducted to observe the drug prescribing pattern of drugs in geriatrics with respect to creatinine clearance rate. In a one-month baseline study, total 47 subjects were included. Out of which 70% were males and 30% were females. In our study we observed geriatric patients of age 60-65 yrs were more, as age increases the number of admitted patients were decreased. It was observed that there is less number of healthy and live geriatrics. The Creatinine clearance 45.4ml/min was more in 60-65 yrs of age and it was decreased as age increases 21 ml/min was low in 81-85 yrs of age. In another study stated that in geriatrics the Creatinine clearance was decreased as age increases and it is mostly <60ml/min¹⁸.

According to National kidney foundation K/DOQI staging system >60ml/min (mild), 60-30ml/min (moderate), <30ml/min (severe) renal failure¹⁹. In our study it is observed that geriatric patients have a moderate renal failure. For calculating estimated glomerular filtration rate (Cr.cl) by using Cockcroft Gault equation was widely used, simple and many drug manufacturers used this equation for monographs²⁰.

In baseline study, 25(53%) patients require dose modifications based on Creatinine clearance rate. Among them, males (84%) were more than

females(16%). Among 25 subjects 76% require one drug dose modification and 24% require two drug dose modification. It was observed that Enalapril(19.3%) is the highest percentage require dose modification among the drugs. In our study found that antihypertensives, antidiabetics, antimicrobials, H₂ receptor antagonists, Analgesics and some antifungals require dose modifications. Anita Conforti et al; kirsch-Volk et al; also observed similar results in drug dose modification 21, 22. In this baseline study, 6 subjects were contraindicated to drugs. It was observed that metformin is the most contraindicated drug when the Creatinine clearance was 60ml/min clearance was 60ml/min thereby it signifies that metformin is not recommended in geriatrics. Among 25 drug dose modifications required patients 11(44%) were experienced adverse drug reactions mostly type A (augmented). In another study indicated that the geriatric patients with decreased renal function admitted due to type A adverse drug reactions²³. Thus, the drug dose modifications were needed to decrease the plasma levels and to avoid toxicity.

In the next 5 months of interventional study 157 subjects were included. Among them 52% subjects were males and 48% subjects were females. In study also males were more than females but there is no much difference as previous in baseline. Subjects of age 60-65 yrs were 54.7% and the numbers of subjects were decreased as age increases. In the study population, Creatinine clearance of 60-65 yrs (48.6ml/min) and it was decreased as age increases. A total of 44(28%) subjects require drug dose modification based on creatinine clearance. With the suggestion of Pharmacist, the physicians modified the drug dose regimen in study population. Enalapril, ciprofloxacin were the highest percentage of drugs which require dose modification in the study.

In study period also Enalapril and ciprofloxacin needed higher number of dose modification as in baseline. In contraindicated drugs metformin was highly observed. Among dose modifications, dose was reduced for 70.4% of subjects, dose interval was increased for 13.6% of subjects, both dose and dose interval was reduced for 16% of subjects. Among 44 dose modified subjects 8(18%) were experienced adverse drug reactions. Some adverse

drug reactions were observed even after dose adjustment, may be because of other pharmacodynamic parameters. The adverse drug reactions observed in study were decreased compared to baseline like, Diarrhea(n=0), Hypotension(n=0), Hypokalemia(n=0) etc, thereby we can understand that adverse reactions and toxicity were decreased due to either change of drug dose or drug interval in geriatrics. Pharmacist plays an immodest role in calculating and assessing the dosage regimen in geriatrics. Pharmacist role is important in vulnerable patients like geriatrics. Long term studies and effective methods like therapeutic drug monitoring were required for better results and therapeutic recommendations.

CONCLUSION: The renal function which estimated by Creatinine clearance was decreased as age increases. So drug dose adjustments are necessary to avoid adverse effects based on their Creatinine clearance. The dose adjustment was needed either by increasing dose interval, dose reduction or contraindicated drugs. The patient's higher plasma levels were reduced by changing the dosage regimen. There was a significant difference was observed in the outcome of the patient after dose adjustments. The patient's side effects were reduced and expected toxicity was avoided. The Pharmacist play's a pivot role in calculating the dosage regimen and to improve the quality of life in geriatrics.

REFERENCES:

1. Leonshargel: Applied Biopharmaceutics and Pharmacokinetics; Applications of pharmacokinetics to clinical situations, Fifth edition, 2004; pg 567-573.
2. Fauci, Braunwald: Harrison's Principles of Internal Medicine; Aging, Mcgraw hill medicine, 18th edition vol 1, 2008; p 112.
3. Allan J. Mclean: Aging, Biology and Geriatric Clinical Pharmacology, Pharmacology Review; 2004; 56:163-184.
4. Matteo Tosato et.al: The aging process and potential interventions to extend life expectanc; Clinical Interventions in Aging 2007; 2(3) 401-412.
5. Christian Aymanns et.al: Review on Pharmacokinetics and Pharmacodynamics and the Aging Kidney; American society Nephrology, 2010; 5: 314-327.
6. Bradley K Williams et.al: Drug therapy considerations in older adults; Prescribing Challenges in the elderly patients; Pharmaceutical care in the elderly patients; California state board of pharmacy, Vol.1; Edition 7; 9.
7. Kim Petrone MD et.al: Approaches to Appropriate Drug Prescribing for the Older Adult; Primary Care Clinics Officers Practice (2005); 32: 755-77.
8. Richard j. glasscock, M.D: Ageing and the glomerularfiltration rate truths and consequences;

- International Journal of Pharmaceutical Sciences and Research, 2009; vol. 120
9. Modig et al: The assessment of renal function in relation to the use of drugs in elderly in nursing homes; a cohort study; *BMC Geriatrics*, 2011; 11:1.
 10. Claudio pedone: Estimating renal function in older people, A comparison of three formulas Age and Ageing; 2006; 35: 121–12: 6.
 11. Eric. T. Herfindal: Text book of therapeutics Drug and disease management, Geriatric drug therapy; Lippincott Williams& Wilkins Eight edition, 2006;pg 1836-37.
 12. Fanak Fahimi et al: The Rate of Antibiotic Dosage Adjustment in Renal Dysfunction; *Iranian Journal of Pharmaceutical Research*, 2012; 11 (1): 157-161.
 13. Peggy Soule Odegard: Considerations for the Pharmacological Treatment of Diabetes in Older Adults, *Diabetes Spectrum*; 2007; Vol 20, (4).
 14. Ali J. Olyaei and William M. Bennett: Drug Dosing and Renal Toxicity in the Elderly Patient; *American Society of Nephrology*.
 15. Estela Iraci et al: Weight and height prediction of immobilized patients; 2006; 19(6):655-661.
 16. Glibert DN et al: the Sanford guide to antimicrobial therapy 2008; 38th ed.
 17. Aronff GR et.al: Drug prescribing in renal failure 1999; 4th ed.
 18. Thomas C. Dowling et al: Glomerular Filtration Rate Equations Overestimate Creatinine Clearance in Older Individuals Enrolled in the Baltimore Longitudinal Study on Aging (BLSA); Impact on Renal Drug Dosing, *Pharmacotherapy*, 2013 Sep; 33(9): 912–921.
 19. Myrna y.munar: Drug Dosing Adjustments in Patients with Chronic Kidney Disease, *American Family Physician*; 2007; May 15, 75(10):1487-1496.
 20. James M. Wooten: Pharmacotherapy Considerations in Elderly Adults; *Southern Medical Journal*; 2012; 105(8):437-445.
 21. Anita Conforti et al: Adverse drug reactions in elderly patients; an Italian observational prospective hospital study; *Drug, healthcare and patient safety*, 2012:4 75-80.
 22. Karsch-Völk et al: Kidney function and clinical recommendations of drug dose adjustment in geriatric patients; *BMC Geriatrics*, 2013; 13:92.
 23. Anders helleden et.al: Adverse Drug Reactions and Impaired Renal Function in Elderly Patients Admitted to the Emergency Department, 2009; 26(7):595-606.

How to cite this article:

Shama Sk, Sai PC, Ramya A, Raghuram V and Seshu Babu TVA: A Study on Drug Dose Administration in Geriatrics with Respect to Creatinine Clearance Rate. *Int J Pharm Sci Res* 2015; 6(11): 4721-27.doi: 10.13040/IJPSR.0975-8232.6(11).4721-27.

All © 2013 are reserved by International Journal of Pharmaceutical Sciences and Research. This Journal licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 3.0 Unported License.

This article can be downloaded to **ANDROID OS** based mobile. Scan QR Code using Code/Bar Scanner from your mobile. (Scanners are available on Google Playstore)

1.