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

S. K. Shama, P. Chandra Sai *, A. Ramya, V. Raghuram and T. V. A. Seshu Babu

Department of Pharmacy Practice, Chalapathi Institute of Pharmaceutical Sciences, Guntur, Andhra Pradesh, India
Department of General Medicine, Government General Hospital, Guntur, Andhra Pradesh, India.
Department of Pharmacy Practice, Chalapathi Institute of Pharmaceutical Sciences, Acharya Nagarjuna University, Guntur, Andhra Pradesh, India.

INTRODUCTION: Aging is associated with deleterious effects at the cellular level and altered homeostatic mechanisms that are liable to diseases and death. As the man gets older the physiological changes are inevitable. These physiological changes alter the pharmacokinetics and pharmacodynamics of the drug. 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 function. 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 decreased.

The creatinine clearance is most extensively used method to measure glomerular filtration rate. Creatinine clearance decreases 1% every year after...
40 years of age. 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. 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 reactions. 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 minimized. The clinical pharmacist helps in drug dosage modification and provides the pharmaceutical care in geriatrics.

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. 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 weight.

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.
- 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:

- 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

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.

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%

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%, Ciprofl oxacin, Amoxicillin+clavulanic acid Telmisartan + hydrochlorothiazide, Gentamicin

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

FIG.1: BASELINE GENDER DISTRIBUTION OF SUBJECTS

FIG.2: AGE WISE DISTRIBUTION OF SUBJECTS IN BASELINE

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

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

TABLE 1: ADVERSE DRUG REACTIONS OBSERVED IN BASELINE STUDY

<table>
<thead>
<tr>
<th>Suspected Drug</th>
<th>Adverse drug reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enalapril</td>
<td>Hypotension (n=2), hyperkalemia (n=3)</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Rashes(n=1), SGOT Levels raised(n=1)</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>Vomiting (n=2)</td>
</tr>
<tr>
<td>Amoxicillin+ clavulanic acid</td>
<td>Diarrhea (n=2)</td>
</tr>
</tbody>
</table>

n=number of patients

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

B) Study:

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

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%

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.
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.

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

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

**TABLE 2: ADVERSE DRUG REACTIONS OBSERVED IN NORMAL STUDY**

<table>
<thead>
<tr>
<th>Suspected Drug</th>
<th>Adverse drug reaction</th>
<th>Number of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac</td>
<td>Gastric irritation (n=2)</td>
<td>2</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Nausea (n=3)</td>
<td>3</td>
</tr>
<tr>
<td>Spiromolactone</td>
<td>Hyperkalemia (n=2)</td>
<td>2</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Hyperuricemia (n=1)</td>
<td>1</td>
</tr>
<tr>
<td>Ofloxicin</td>
<td>Vomitting (n=0)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Rashess (n=0), SGOT Levels raised (n=0)</td>
<td>0</td>
</tr>
</tbody>
</table>

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/min 18.

According to National kidney foundation K/DOQI staging system >60ml/min (mild), 60-30ml/min (moderate), <30ml/min (severe) renal failure 19. In our study it is observed that geriatric patients have a moderate renal failure. For calculating estimated glomerular filtration rate (Cr.cl) by using Cockgraft Gault equation was widely used, simple and many drug manufacturers used this equation for monographs 20.

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 reactions 23. 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:

2. Fauci, Braunwald: Harrison’s Principles of Internal Medicine; Aging, Mcgraw hill medicine, 18th edition vol 1, 2008; p 112.
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.
8. Richard j. glassock, M.D: Ageing and the glomerularfiltration rate truths and consequences;