Evaluation of Antibiotic Dose Adjustment in Patients with Renal Insufficiency in a Tertiary Care Center

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ABSTRACT

Introduction: Renal dysfunction may lead to accumulation of drugs and their metabolites. It may lead to toxicity of drugs. Therefore many drugs need adjustment of doses in renal failure. Appropriate dose adjustment can optimize therapeutic efficacy and minimize toxicity of drug.

Material and methods: The study is retrospective and cross sectional. Records of all patients with renal dysfunction in any department where nephrology unit was consulted were screened. Inclusion criteria were eGFR of < 60ml/minute, age>16 years and administration of at least 1 antibiotic. Prescribed dosage of the drug was compared with dosage recommended by guidelines to assess appropriateness of dose in renal dysfunction. GFR was calculated by Cockcroft Gault equation.

Results: Study group comprised of 242 patients. Gender ratio was 1.23:1(male: female). Mean age of patients was 43.8± 11.3 years. Patients received 615 antibiotics. There was need of antibiotic dose adjustment in 562(91.39%) antibiotic dosages. Physicians did not do any dose adjustment for Amoxicillin clavulanate, Ceftazidime and Vancomycin. There was no adjustment of doses in 63.22% patients and partial dose adjustment was done in 23.96% cases. Only 31 patients (12.8%) got appropriate doses as per GFR. Appropriate doses were given in 31.49 % doses.

Conclusion: This study showed that there was no adjustment done in drug doses in 63% patients with renal insufficiency and 23.9% got adjustment for some drugs. 24 patients (9.9%) developed adverse drug reaction attributable to excessive doses. There is need to create awareness among physicians for drug dose adjustment in renal dysfunction.

Keywords: Renal dysfunction, appropriate drug doses, estimated glomerular filtration rate, drugs, toxicity of drug

INTRODUCTION

Kidneys have major role in excretion and metabolism of many drugs. There is rise in patients with renal insufficiency with aging population. Some kind of renal dysfunction is observed in 10% patients.[1] Impairment of renal function can lead to impaired excretion of drug and its metabolites.[2] It may lead to accumulation of drug and its metabolites. Chronic renal failure is also responsible for impaired activity of drug transporters and drug metabolizing enzyme.[3] Therefore many drugs need dosage adjustment in renal failure according to severity of renal dysfunction. Drug related problems are commonly due to medication dosing errors in renal failure.[4] Appropriate dosage adjustment for drugs in renal failure can optimize efficacy and help in reducing toxicity and cost.[5] Inappropriate dosing in patients with kidney dysfunction can lead to either toxicity or ineffective therapy.[6] Renal elimination of drug correlates better with the glomerular filtration rate (GFR) than serum creatinine level. It is better to use eGFR (estimated GFR) or eCrCl (estimated creatinine clearance) for drug dose adjustment in patients with renal dysfunction.[2] There are two major approaches for dose adjustment in renal failure i.e. either to lengthen the interval between doses or to reduce the dose. Occasionally both interval and dose adjustments are needed to adjust dose in renal insufficiency.[7]

Objectives of the study were to determine the percentage of antibiotics needed dosage adjustment in patients with renal failure and to determine percentage of antibiotics with inappropriate doses whether high or sub therapeutic. We also looked for adverse effects due to inappropriately high doses of drugs.

MATERIAL AND METHODS

The study was retrospective descriptive study. The study was done in at our institute a tertiary care center and teaching hospital in uttarakhand. Hospital has all medical and surgical departments with indoor beds more than 800. The study period was January 2013 to May 2015. Study sample comprised of 242 patients, which was based on inclusion exclusion criteria.

Records of all patients with renal dysfunction in any department where nephrology unit was consulted were screened. Serum creatinine of 1.4 mg% was kept as cut off. Inclusion criteria were as follows.

1. Patients with eGFR < 60 ml/minute were included.
2. Patients with age of more than 16 years and of either sex were included
3. Patients who received at least one antibiotic

Patients with eGFR > 60 ml/minute and who were not on any antibiotic were excluded from the study. Data were collected by investigators on the extraction of data from patient files. Patient chart review was used to collect individual patient data including age, sex, serum creatinine, blood urea nitrogen, and co-morbid condition, reason for admission, medications prescribed during hospitalization and medications that need dose adjustment. Actual weight was recorded and for those who were critical and immovable patients, either

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the patient, if conscious, or the care giver was asked to provide the most recent weight of the patient. Any adverse event which could be attributed to drug was also noted. There were 242 patients who fulfilled inclusion criteria.

Cockcroft Gault equation[8] was used to calculate glomerular filtration rate from serum creatinine (SCr) as shown below for men and women respectively:

Men: CrCl (ml/min)=[(140-age)×weight (kg)]SCr (mg/dl)×72

Women: CrCl (ml/min)=[(140-age)×weight (kg)]×0.85(SCr (mg/dl)×72)

Prescribed dosage of the drug was compared with dosage recommended by guidelines to assess appropriateness of dose in renal dysfunction.[9]

STATISTICAL ANALYSIS

SPSS version 16.0 was used to analyze data. Description of data was done with help of descriptive statistics like mean, standard deviation and percentage

RESULTS

In the study group of 242 patients, there were 135 males and 107 females in the group. Mean age of patients was 43.8± 11.3 years (17-82 years). Demographic data for the patients is shown in table 1. Patients received 615 antibiotics with a mean of 2.54 per patient. Maximum number of patients were in GFR 15-29 ml/ minute group. Chronic kidney disease (CKD) was cause of renal insufficiency in in 77% patients (n=202) and Acute kidney injury (AKI) was responsible in 33% (n=40) patients. Figure 1 shows different causes of CKD in this cohort. Most commonly used antibiotics were Piperacillin tazobactam, Meropenem, Amoxicillin clavulanate, Ceftriaxone, Imipenem, Teicoplanin, Levofloxacin and Ciprofloxacin. Other antibiotics were Linzolid, Vancomycin, Ceftazidime, Cefuroxime, Cefoperazone, Polymixin and Colistin. Table 2 shows the frequency of different antibiotic usage and dose adjustment done.

There was need of antibiotic dose adjustment in 562(91.39%) antibiotic dosages and 8.59% doses did not need any adjustment. Piperacillin tazobactam (120 doses) was most commonly used but adjustment of dose was done in 58.5% doses only. Meropenem and Imipenem dose adjustment was done in 49% and 21% doses. Levofloxacin and Ciprofloxacin doses were not adjusted in 87.5% and 83.3% cases. Cefoperazone was used in appropriate dose in all cases. Linzolid and Clindamycin doses were not appropriate in 41.6% and 31.25% cases as doses were reduced but no adjustment is needed in renal failure. There was no adjustment of doses in 153(63.22%) patients and partial dose adjustment was done in 58 (23.96%) cases. Only 31 patients (12.8%) got appropriate doses as per GFR. Appropriate doses were given in 31.49 % doses only while remaining 68.51% doses were inappropriate.

Most of the patients (88.63%) with GFR 30-60 ml/minute got inappropriate doses and 67% patients with GFR 29-15 ml/minute got inappropriate doses. 70% of patients with GFR<15 ml/minute got inappropriate doses and 71.4% patients on dialysis received inappropriate doses

Adverse drug reactions due to inappropriate doses were seen in 24 patients. Seizures were noted in 5 patients on imipenem and 2 patients on Ceftazidime. Encephalopathy could be attributed to ceftazidime, Piperacillin tazobactam and Amoxicillin clavulanate in 10 patients. Ototoxicity was seen in 4 patients on vancomycin. Hemorrhagic complications were observed in 2 patients on ceftazidime.

Serial No	Parameter	value
1	Age (years)	43.8±11.3
2	Males	135
3	Females	107
4	Mean S.creatinine (mg %)	2.6±1.1
5	Mean Urea (mg %)	86±11.7
6	Mean eGFR(mi/min)	28.7±8.9
7	Hemoglobin (gm %)	9.2±1.9
8	Total Leukocyte count (permm3)	12900±587

Table-1: Showing demographic data

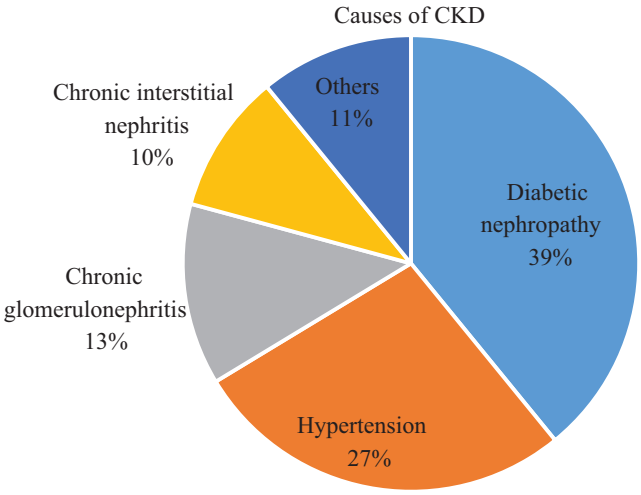

Figure-1: Showing causes of CKD

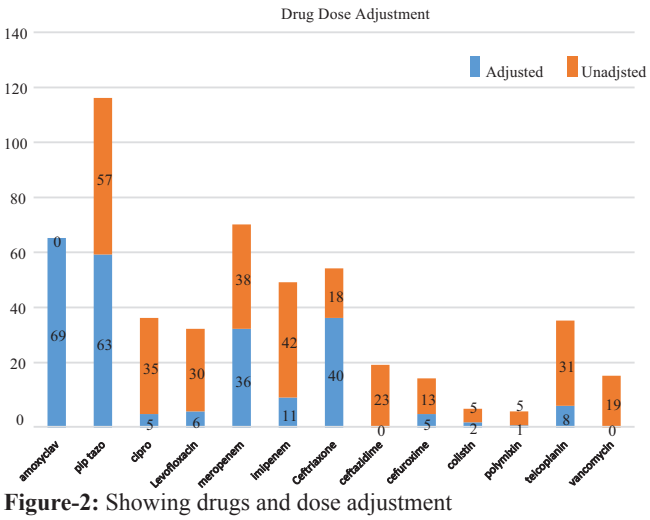

Figure-2: Showing drugs and dose adjustment

DISCUSSION

Our study looked into the drug dose adjustment in hospitalized patients with renal insufficiency for various reasons. There was no adjustment of doses in 153(63.22%) patients and partial dose adjustment was done in 58 (23.96%) cases.

In our study 153 patients received no dose adjustment while it is reported 39.3% by Fahimi et al and 31% by Henok et al.[10,11] Fifty eight (23.96%) patients received adjustment for at least one drug but Henok et al reported in 41% patients.[11] All drugs were adjusted according to GFR in 12.8% patients in our study. Henok et al reported adjustment in all drugs in 28 % patients and another study reported adjustment for all drugs in 23.4 % cases.[11,12] Study by Prajapati et al from India also showed that adjustment was done in 18.89% prescriptions only but prescriptions were adjusted in 31.49 % prescriptions in our study.[13] Similar rates of drug dose adjustment are described by Decloedt et al. (32 %) and Sweileh et al. (26.42 %).[14,15] Prescriptions were adjusted in 43% in another study.[10] There was no adjustment was done for ceftazidime, vancomycin and Amoxicillin clavulanate. Fahimi et al also reported that Vancomyin doses were least frequently adjusted.[10] There has been description of least adjustment of Amoxicillin, levofloxacin and ciprofloxacin.[13] Authors also described that antimicrobials needed drug adjustment most commonly. Though it had not been reported by other studies we found use of sub therapeutic doses of Linzolid and Clindamycin in 41.6 and 31.25% doses used in patients with renal failure. It may lead to poor control of infection.

We found that dosing errors were high in early stages of renal failure. Doses were inappropriate in 88.63% in patients with GFR 30-60 ml/minute while it was 70% in advance stages of renal failure. Prajapati et al also observed same finding in their study.[13] There are higher chances of adverse reactions due to use of higher doses of antibiotics. We found association of seizures and encephalopathy with Imipenem, Ceftazidime, Piperacillin tazobactam and Amoxicillin clavulanate in our patients with inappropriately high doses. There are several reports of neurotoxicity with use of imipenem, cephalosporins and other beta lactam antibiotics in renal insufficiency.[16-18] We found bleeding complications in two patients on ceftazidime. Third generation cephalosporins and beta lactum antibiotics can interact with function of platelet membranes through interference with ADP receptors and can lead to hemorrhagic complications in uremia.[19]

CONCLUSION

Current study showed that there was no adjustment done in drug doses in 63% patients with renal insufficiency and 23.9% got adjustment for some drugs. Linzolid and Clindamycin doses were sub therapeutic in 41.6% and 31.25% cases. 24 patients (9.9%) developed adverse drug reaction attributable to excessive dose given according to GFR. Errors in drug dosage could lead to toxic effects or sub therapeutic doses. It would result increased financial burden due to high dose of antibiotic and increased duration of hospitalization. There is need to educate physicians about need of adjustment of drug dosages in patients with renal dysfunction.

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