APPROPRIATENESS OF ANTIMICROBIAL DOSES IN PATIENTS WITH CHRONIC KIDNEY DISEASE

Alok Kumar 1,a and Dorchhom Khrime b

a Associate Professor and HOD Department of Nephrology Shri Guru Ram Rai Institute of Medical and Health Sciences, b Professor Department of Medicine Shri Guru Ram Rai Institute of Medical and Health Sciences

ABSTRACT

Introduction: Antimicrobials are commonly prescribed to hospitalized CKD patients. Studies showed that antibiotic dose was adjusted in CKD patients’ 40 – 62% prescriptions. Dose adjustment according to eGFR can reduce toxicity in these patients. It can also save extra costs due to excessive dosing. Unfortunately, there is limited data regarding drug dose errors in CKD from developing countries. Aim: The study aimed to evaluate the extent of dose adjustment according to eGFR in CKD patients at our institute. In addition, we also looked for adverse effects related to excessive doses in patients. Material and Methods: The study was conducted from July 2020 to March 2022. The study cohort comprised 254 CKD patients admitted in various departments, and the nephrology department was consulted. Investigators screened the records of patients. Patients were included in the study based on inclusion and exclusion criteria. Descriptive statistics were used to present the results. Results: Patients received 626 antimicrobials, with a mean of 2.46 per patient. About 539 antimicrobial drugs needed modification of doses, but no adjustment was made in 55.28% of prescriptions. Beta-lactum antibiotics were the most prescribed antibiotics. Only 51% of patients received the appropriate dose in the betalactam group. Amoxicillin clavulanate dosage was inappropriate in 75.28% of patients, followed by cefepime (57.4%), ceftizoxime (44.82%) and Piperacillin tazobactam (31.7%). Most patients (86.66%) on colistin received inappropriate doses. Patients on vancomycin and amikacin also received inappropriate dose adjustments in > 65% of patients. The fluconazole dose was adjusted in 61.8% of cases, while only 14% of patients received an adjusted dose of acyclovir. Adverse drug reactions due to inappropriate doses were observed in 19 patients. Conclusion: We found drug dose errors of antimicrobials in 55% of cases. Antibiotic dose adjustment had been observed in 40-60% of different studies. Increasing awareness about dose adjustment in CKD patients among physicians would help in minimizing dosing errors.

KEYWORDS Antibiotic doses, renal failure, dose adjustment

Introduction

Chronic kidney disease (CKD) is defined as “a decrease in glomerular filtration rate (GFR) <60 for ≥3 months”, that may or may not be coupled with a kidney damage and classified into five stages based on GFR [1]. Kidneys play major role in metabolism and excretion of various drugs. CKD may lead to accumulation of drug and its metabolites due to impaired excretion and metabolism of drug [2]. Chronic Kidney disease leads to impaired activity of drug transporters and drug metabolizing enzymes [3]. Many authors have reported that doses of renally excreted is not adjusted appropriately [4]. The percentage of drug prescriptions having inappropriately adjusted drugs doses according to estimated glomerular filtration rate (e GFR) may range from 25–77% in various studies [5]. Antimicrobials are commonly prescribed to hospitalized CKD patients. The most common dosing error is described during antimicrobial use in CKD patients [6]. Studies showed that antibiotic dose adjustment in patients with renal dysfunction was done in 40 –62% prescriptions [7]. Dosing errors cause most of the drug related adverse effects therefore these could be prevented by dose ad-
Dose adjustment according to eGFR can reduce drug related toxicity [8]. It can also save extra cost by excessive dosing [9]. Renal elimination of a drug correlates better with GFR than serum creatinine. It is better to use eGFR (estimated GFR) or CrCl (estimated creatinine clearance) for drug dose adjustment in CKD [10]. There are two approaches for dose adjustment in renal dysfunction i.e., to either lengthen the interval between doses or to reduce the dose. Some drugs need adjustment by both methods together [11]. The aim of study was to assess the extent of antimicrobial dose adjustment in hospitalized patients with CKD at our center. We also looked for adverse drug reactions those could be associated with use of inappropriate drug dosages in such patients.

**Material and Methods**

The present study is retrospective descriptive study which was conducted at our institute a tertiary care center. It was conducted from July 2020 to March 2022. The study cohort comprised of 254 CKD patients admitted in various departments of hospital for different reasons and nephrology department was consulted for management of renal dysfunction. Investigators screened the records of patients with renal dysfunction in the hospital. Patients were included in study on basis of inclusion and exclusion criteria.

**Inclusion criteria for the patients were as follows:**

1. e GFR < 60 ml/minute
2. Presence of CKD
3. Those were on antimicrobial agents.

**Exclusion criteria in the study included:**

1. e GFR > 59 ml/minute
2. Age < 16 years
3. Acute Kidney injury

Patient chart review was used to collect individual patient data including age, sex, weight, serum creatinine, blood urea nitrogen. Patient file was screened for information on co-morbid condition, reason for admission, medications prescribed during hospitalization.

We calculated eGFR by Cockcroft Gault equation as shown below for men and women respectively [12]:

**Men:**

\[ \text{CrCl (ml/min)} = (\frac{140- \text{age}}{\text{weight (kg)}}) \times \text{SCR (mg/dl)} \times 72 \]

**Women:**

\[ \text{CrCl (ml/min)} = (\frac{140- \text{age}}{\text{weight (kg)}}) \times 0.85 \times \text{SCR (mg/dl)} \times 72 \]

The CKD staging was determined for the individual patients according to “Kidney Disease: Improving Global Outcomes” (KDIGO 2012) guidelines. The identified patients were classified in stages as follows. Those with GFR stages G3a (45-59 mL/min), G3b (30-44 mL/min), G4 (15-29 mL/min), and G5 (< 15 ml/minute) [13]. Dosage appropriateness was checked by comparing the practice with the established recommendation on drug dosages provided in “Drug Information Handbook, 25th edition” published by Lexicomp® [14].

**Data analysis**

Data analysis was done on excel 2016. Descriptive statistics was used to present the results such as frequency and percentage for categorical data, while mean (SD) was used for numerical data.

Unadjusted dose of each drug was main outcome measure in form yes or no.

**Results**

The study group comprised of 254 patients. There were 160 males and 94 females with gender ratio of 1.7:1. The subjects had mean age of 42.5±12.9 years (23 to 78 years). They had mean eGFR of 33.2±18.5 ml/minute/173 m2. Table 1 shows the basic demographic data of study group. Table 2 shows the number of patients in different stages of CKD. Most of the patients were in CKD stage 3. There were 112 (44%) patients in stage 3 CKD. Chart 1 shows the different causes of CKD. Most common cause of CKD was diabetic nephropathy in the group. Diabetic nephropathy caused CKD in 84(33%) patients.

Patients received total 626 antimicrobials with mean of 2.46 per patient. About 539 antimicrobial drugs needed modified doses but no adjustment was done in 298 (55.28%) prescriptions. Chart 2 shows frequency of various renally excreted antibiotics prescribed in the patients and dose adjustment. Beta lactum antibiotics were most prescribed antibiotics. Only 51% of patients received appropriate dose in beta lactum group. Beta lactum antibiotics included Piperacillin tazobactam (48%), Amoxicillin clavulanate (28.8%), cefepime (13.6%) and ceftizoxime (9.4%). Amoxicillin clavulanate dosage were inappropriate in 75.28% patients followed by cefepime (57.4%), ceftizoxime (44.82%) and Piperacillin tazobactam (31.7%). Most patients (86.66%) on colistin received inappropriate doses. Patients on vancomycin and amikacin also received inappropriate dose adjustments in > 65% patients.
Table 1 Showing the demographic data of group.

| S.no | Parameter      | value          |
|------|---------------|----------------|
| 1    | Age           | 42.5±12.9 years|
| 2    | S. creatinine | 2.4± 2.1 mg%  |
| 3    | Mean e GFR    | 33.2±18.5 ml/min/1.73 m² |
| 4    | TLC           | 13220±822/ mm³ |
| 5    | Hb            | 9.8±1.2 gm%   |

Table 2 Patients in different stages of CKD.

| S.no | Stage of CKD by GFR | No of patients |
|------|---------------------|----------------|
| 1    | 3                   | 112            |
| 2    | 4                   | 87             |
| 3    | 5                   | 55             |

Chart 3 Doses adjustment of antifungals and antivirals. These drugs were prescribed in 77 patients and 53 % (n=41) patients received unadjusted doses. Fluconazole dose was adjusted in 61.8% cases while only 14% patients received adjusted dose of acyclovir. Valacyclovir was adjusted 25% cases. Patients on Tigecycline, clindamycin and linezolid received sub-therapeutic doses in 25.22 % cases. Chart 4 shows suboptimal doses in patients on non-renal excreted antibiotics. Adverse drug reactions due to inappropriate doses were observed in 19 patients. Seizures were seen in 5 patients on cefepime and 2 patients on imipenem. Encephalopathy was observed in 9 patients. Eight patients on acyclovir had encephalopathy and one patient on ceftizoxime had encephalopathy. Five patients had developed ototoxicity who were on amikacin. Patients with severe CKD (eGFR< 30 ml/minute) had statistically lesser chances of inappropriate antibiotics dosing than patients with moderate (eGFR ≥ 30 ml/minute) renal failure. Patients with severe CKD had inappropriate dose in 128 of 288 doses but patients with moderate CKD had inappropriate doses in 170 of 252 doses. Z test with two tail showed Z value of 5.364 and P was < .00001.

Chart 4 Showing non renal excreted antibiotics.

Discussion

CKD patients are at high risk for medication dosing-related errors because various pharmacokinetic parameters are deranged in CKD leading to impaired oral absorption, glomerular filtration rate, altered tubular secretion, and reabsorption with alterations in renal, intestinal, and hepatic metabolism. These changes could lead to exaggerated pharmacologic toxicity and activity [15]. This study demonstrated that total 539 antimicrobial agents were administered which needed dose modification due to renal dysfunction. But no adjustments were made in 55% patients. Hassan et also found that no dose adjustment was made in 59.5% patients [16]. Another study showed that no dose adjustment was done in 51.5% antibiotics doses [17]. Though a study from the India found no dose adjustments were made in 81% drugs [18]. It could be due to increased awareness now as study by Prajapati et al was done a decade earlier. Mean age of the patients was 42.5±12.9 years in the study. It is comparable to data provided by other Indian authors [19,20]. Though data from west shows higher mean age (60-68 years) of CKD patients [21,22]. It could be due to higher life expectancy the western population. The present study showed Diabetes was the commonest cause of CKD. Other studies also reported similar observation [19,20,21]. Other causes of CKD were CGN, CIN and hypertension in the study. Modi et al and Singh et al also described same causes for CKD. There were 64% males in
this study. It is comparable to observation by Saleem et al [23]. Patients had mean eGFR of 33.2 ml/minute/173 m2. Fahimi et al also found mean eGFR of 34.4 ml/minute [7]. But some authors observed mean eGFR of ≤ 15 ml/minute [16,24].

Patients received mean antimicrobials of 2.46 per patient. Other studies showed that mean antibiotics of 2.4 and 2.6 in their patients [17,24]. We found that dose adjustment was done in 45% of antimicrobial doses. Prajapati et al found that only 18% of drugs were adjusted according to GFR [18]. Other study showed that 43.7% antibiotics doses were appropriate [7]. A recent study also described drug dose adjustment rate of 40% in CKD patients [16]. Beta lactum antibiotics were most frequently (48%) prescribed antibiotics. Other studies also reported same pattern in their patients [17,23]. Colistin (14%), Amoxicillin clavulanate (25%), Vancomycin (35%) and Amikacin (35%) were least frequently adjusted antibiotics in the study population. Vancomycin and Amoxicillin clavulanate had been described with least dose adjustment in CKD by other authors as well [18,7]. Acyclovir dose was adjusted in 14% doses in present study but Brandariz et al reported adjustment in 55% cases [25].

Valacyclovir dose was adjusted in 25% in comparison to 55% adjustment rate by others [25]. We observed dose adjustment of Fluconazole in 61% while Hasan et al reported in 40%. Though it has not been reported earlier we found Tigecycline, clindamycin and linezolid were used in lower doses than recommended doses in CKD. These drugs do not need adjustment as these are not excreted by kidney. It could lead to subtherapeutic blood levels and reduced efficacy. Our study found that there were statistically higher dosing errors in patients with moderate renal failure (eGFR ≥ 30 ml/minute) than patients with severe renal failure. It could be due to early referral of advance renal failure to nephrologist. It was observed by Prajapati et al also [18]. Some studies found that dosing errors were higher in patients with severe CKD [16,23]. Nineteen patients developed adverse reactions those could be attributed due to inappropriately higher doses of antibiotics. Five patients on cefepime and two patients on imipenem developed seizures. Other studies also reported seizures with cefepime and imipenem [26,27]. We observed encephalopathy in 10 patients due to acyclovir and cefotizoxime. There are reports of encephalopathy due to these agents in other studies also (25,28). Antimicrobials should be prescribed in patients of CKD with precautions and dose should be adjusted according to eGFR.

**Conclusions**

Errors of drug doses are common in patients with CKD all over the world. Though we found drug dose errors of antimicrobials in 55% cases. Antibiotic dose adjustment had been observed 40-60% in different studies. Rate of adjustment was found least with Colistin, Amoxicillin clavulanate and acyclovir. Nineteen patients developed neurotoxicity due to inappropriate doses. Present study found that patients with moderate renal failure had significantly higher probability of getting unadjusted doses according to eGFR. Usage of higher doses could lead to more toxicity and increased cost of treatment.

Therefore, it would be appropriate to increase awareness about dose adjustment in CKD patients among physicians.

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**Conflict of interest**

There are no conflicts of interest to declare by any of the authors of this study.

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