Pattern and Predictors of Medication Dosing Errors in Chronic Kidney Disease Patients in Pakistan: A Single Center Retrospective Analysis

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Abstract

Background

Chronic kidney disease (CKD) alters the pharmacokinetic and pharmacodynamic response of various drugs and increases the risk of toxicity. The data regarding the pattern and predictors of medication dosing errors is scare from the developing countries. Therefore, the present study was conducted to assess the pattern and predictors of medication dosing errors in CKD patients in a tertiary care setting in Pakistan.

Methods

A retrospective study design was employed and medical charts of all those CKD patients who had an eGFR ≤60ml/min/1.73m², hospitalization ≥24 hours, and admitted in the nephrology unit during January 2013 to December 2014 were assessed. Descriptive statistics and the logistic regression analysis were done using IBM SPSS version 20.

Results

In total, 205 medical charts were assessed. The mean age of patients was 38.64 (±16.82) years. Overall, 1534 drugs were prescribed to CKD patients, of which, nearly 34.0% drugs required dose adjustment. Among those drugs, only 41.8% were properly adjusted, and the remaining 58.2% were unadjusted. The logistic regression analysis revealed that the medication dosing errors were significantly associated with the CKD stages, i.e. stage 4 (OR 0.054; 95% CI [0.017–0.177]; p <0.001) and stage 5 (OR 0.098; 95% CI [0.040–0.241]; p <0.001), the number of prescribed medicines ≥5 (OR 0.306; 95% CI [0.133–0.704]; p 0.005), and the presence of a comorbidity (OR 0.455; 95% CI [0.226–0.916]; p 0.027) such as the hypertension (OR 0.453; 95% CI [0.231–0.887]; p 0.021).

Conclusions

It is concluded that more than half drugs prescribed to CKD patients requiring dose adjustment were unadjusted. The predictors of medication dosing errors were the severe-to-end stages of
chronic kidney disease, the presence of a comorbidity such as hypertension, and a higher number of prescribed medicines. Therefore, attention should be paid to these risk factors.

Introduction

Chronic Kidney Disease (CKD) is a serious public health concern that affects nearly 10 to 15% of the adult population worldwide [1–4]. CKD is defined as a reduced GFR (glomerular filtration rate) for ≥ 3 months, that may or may not be coupled with a kidney damage, and classified into several stages on the basis of GFR [5]. CKD seriously alters the pharmacokinetic and pharmacodynamic response of various drugs that are mainly excreted from the body through renal route, either in an intact form or in a metabolite form, and increases the risks of toxicity by delaying drug excretion [2, 6].

Studies report that the doses of renally excreted drugs are not being adjusted properly in the hospitalized CKD patients all over the world [7–12]. The percentage of prescriptions having inappropriately adjusted drugs may range from 25–77% during the hospitalization of CKD patients [13–16]. Additionally, it has been reported that nearly 63% of these prescriptions potentially have adverse consequences, and nearly 3% potentially have fatal or severe consequences [17]. However, despite these facts and figures and the seriousness of chronic kidney disease, the renal functioning is still being assessed using serum creatinine values alone in usual clinical practices, especially in the developing countries, which indicates a higher risk of medication dosing errors in hospitalized CKD patients [7, 9].

To address the importance of the issue, a lot of work has been done worldwide to assess the pattern of medication dosing errors, however, very less attention has been paid to assess the predictors of medication dosing errors in CKD patients, especially in the developing countries [8, 9, 11, 12, 18]. From the developed world, a study conducted in the Netherlands has reported that the risk of unadjusted dose prescribing was higher in CKD patients with a creatinine clearance less than 35mL/min/1.73m² [14]. Another study conducted in the United States of America has reported that the inappropriate prescribing in CKD patients was associated with the older age above 85 years, obesity, and the presence of a comorbidity [19]. Likewise, a study conducted in Australia has also reported a higher risk of inappropriate prescribing in CKD patients with an older age, diabetes, and higher number of prescribed medicines [20].

Nevertheless, a few studies were also conducted in the developing countries, but unfortunately they did not yield significant outcomes. For instance, a study conducted in Palestine during 2007 reported that the age, gender, and the stages of chronic kidney disease were not associated with medication dosing errors in CKD patients [9]. Similarly, another study conducted in Ethiopia has endorsed the Palestinian study that gender and the stages of chronic kidney disease are not associated, but the age above 60 years is associated with medication dosing errors in CKD patients [21]. However, to get a clearer insight, more evidence based data is required from the developing countries such as Pakistan, where in the best of our knowledge no such studies are conducted. Therefore, the present study was conducted to assess the pattern and predictors of medication dosing errors in hospitalized CKD patients in Pakistan.

Material and Methods

Study Setting

The present study was conducted at the nephrology unit of a 1400-beds, fully equipped, tertiary care teaching hospital named Bahawal Victoria Hospital (BVH) that is situated in Bahawalpur,
Punjab, Pakistan. The hospital caters a large population living in the Southern Punjab region. In contrast to other units of BVH, the nephrology unit is comparatively new, and consists only of 15-beds. Patients at the nephrology unit of BVH are being served by trained nephrologists and nephrology residents.

Ethical Considerations
This study was approved by the Pharmacy Research Ethics Committee of The Islamia University of Bahawalpur, Pakistan (Reference: 21-2015/PREC). Informed consent could not be obtained from the patients (or next of kin/caregiver in the case of children) for their clinical records to be used in this study. However, permissions were obtained from the hospital administration to access and use the data. Moreover, to ensure the patients' privacy, the data was anonymized and de-identified prior to analysis.

Study Design and Sampling Procedure
A retrospective study design was employed and medical charts of all those chronic kidney disease patients, who were admitted in the nephrology unit of BVH during January 2013 to December 2014, for a minimum of 24 hours, with a confirmed CKD diagnosis, and had serum creatinine values mentioned in their medical charts, were included. The stages of chronic kidney disease were not mentioned in the majority of medical charts, therefore, the glomerular filtration rate (GFR) of patients was measured using the Modification of Diet in Renal Disease (MDRD) equation, and only those charts were included that had an eGFR less than 60ml/min/1.73m². Which means, patients included in the study had stages of chronic kidney disease as follows: stage 3 (CrCl 30–59 ml/min), stage 4 (CrCl 15–29 ml/min), and stage 5 (CrCl < 15 ml/min). All those medical charts not meeting the abovementioned criteria were excluded. A special data collection form was designed and used to collect the required data (S1 Table).

Measurement of GFR
In usual clinical practice, creatinine clearance is measured using Cockcroft and Gault’s equation [22]. However, in the present study, the authors were unable to calculate the creatinine clearance values using Cockcroft and Gault’s equation due to lack of data regarding patients’ weight. Therefore, an alternative equation, the Modification of Diet in Renal Disease (MDRD) was used to measure the glomerular filtration rate (GFR). The GFR was estimated by the three-variable version of the MDRD-formula: eGFR (ml/min./1.73m²) = 175 x (serum creatinine (μmol/l)/88.4) – 1.154 x (age in years) – 0.203 (x 0.74 if female) [23].

Dosing Guidelines and the Assessment of Medication Dosing Errors
Due to the unavailability of any single national drug dosing guideline for CKD patients in Pakistan, four reputed references such as the British National Formulary (BNF-58) [24], the Drug Prescribing in Renal Failure-2007 [25], the Drug Prescribing in Renal Failure: Dosing Guidelines for Adult [26], and the Drug Dosing in Elderly Patients with Chronic Kidney Disease guidelines by Lassiter et al [27], were used. The dose adjustment guidelines were adopted from these references and tabulated in consultation with the nephrologists for all those drugs that were classified as the most commonly prescribed drugs in the unit, during a pilot study (Table 1). At the end, the doses of drugs were assessed for appropriateness individually for each and every patient using these dose adjustment guidelines.
Data Analysis

Statistical analysis was carried out using IBM SPSS version 20. Descriptive statistics were applied on independent variables such as the age, gender, stages of chronic kidney disease, the number of prescribed drugs, the length of hospitalization of patients, comorbidities of patients, and the pattern of medication dosing errors. Similarly, the descriptive statistics were applied to assess the central tendencies of dose adjustment numerical variables. The binary logistic regression analysis was done using following independent variables to assess the predictors of
medication dosing errors in chronic kidney disease patients: Gender (Male, Female), Age (< 20 years, 20–40 years, 41–60 years, > 60 years), CKD Stage (Stage 3, Stage 4, Stage 5), Length of hospitalization (< 7 days, ≥ 7 days), Number of prescribed medicines (< 5, ≥ 5), Comorbidity (Yes, No), Diabetes (Yes, No), Hypertension (Yes, No), and Antibiotics prescribed (Yes, No). Variables with a p-value < 0.1 in the univariate analysis were further studied in the multivariate analysis. A p-value < 0.05 was considered significant throughout the statistical analysis.

Results

In this study, nearly 205 medical charts of chronic kidney disease (CKD) patients were assessed. Of which, nearly 61.0% patients were males and 39.0% were females. Nearly 92 (44.9%) patients were aged between 20–40 years, followed by 60 (29.3%) who were aged between 41–60 years, and only 10.7% who had an age above 60 years. The mean age of CKD patients was 38.64 ±16.82 (SD) years. The average length hospitalization of CKD patients was 8.95 days (Range: 1–31 days). Furthermore, it was observed that the majority N = 155 (75.6%) of patients had CKD stage 5, followed by nearly 15.1% who had CKD stage 4, and the remaining 9.3% patients had CKD stage 3. The Hypertension (69.3%), Diabetes (19.1%) and Hepatitis C (4.8%) were observed as three topmost comorbidities in CKD patients (Table 2).

Table 2. Patient characteristics.

| Variables                  | Frequency | %   |
|----------------------------|-----------|-----|
| Age                        |           |     |
| < 20                       | 31        | 15.1|
| 20–40                      | 92        | 44.9|
| 41–60                      | 60        | 29.3|
| > 60                       | 22        | 10.7|
| Gender                     |           |     |
| Male                       | 125       | 61.0|
| Female                     | 80        | 39.0|
| Length of hospitalization  |           |     |
| < 7 days                   | 97        | 47.3|
| ≥ 7 days                   | 108       | 52.7|
| Number of medicines        |           |     |
| < 5 drugs                  | 45        | 22.0|
| ≥ 5 drugs                  | 160       | 78.0|
| CKD Stage                  |           |     |
| Stage 3                    | 19        | 9.3 |
| Stage 4                    | 31        | 15.1|
| Stage 5                    | 155       | 75.6|
| Comorbidity present        |           |     |
| Yes                        | 159       | 77.6|
| No                         | 46        | 22.4|
| Antibiotics prescribed     |           |     |
| Yes                        | 156       | 76.1|
| No                         | 49        | 23.9|
| Comorbidities†             |           |     |
| Hypertension               | 146       | 69.3|
| Diabetes                   | 40        | 19.5|
| Hepatitis C                | 10        | 4.8 |
| Anemia                     | 7         | 3.3 |
| Urinary Tract Infection    | 5         | 2.4 |
| Renal Stone                | 4         | 1.9 |
| System Lupus Erythematous  | 3         | 1.4 |
| Ischemic Heart Disease     | 3         | 1.4 |
| Hepatitis B                | 2         | 1.0 |

† = Variable with tick multiple option (Individual frequencies are based on total 205 patients)

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Further analysis showed that overall 1534 drugs were prescribed to CKD patients, of which, nearly 522 (34.0%) required dosage adjustment. Of those 522 drugs, the majority N = 304 (58.2%), were unadjusted, and the remaining N = 218 (41.8%) were properly adjusted (Table 3).

Moreover, the descriptive statistics revealed that the most common unadjusted drugs were amikacin (100.0%), linezolid (100.0%), cephalosporin antibiotics (100.0%), chloroquine (100.0%), spironolactone (100.0%), amoxicillin (79.4%), metoclopramide (87.5%), sodium bicarbonate (97.9%), rosuvastatin (71.4%), trandolampin (85.7%) ranitidine (65.5%), paracetamol (79.3%), domperidone (88%), and acetylsalicylic acid (81.8%). In contrast, the most accurately adjusted drugs were captopril (90.7%), bisprolol (66.6%), furosemide (52.6%), atenolol (58.8%), lisinopril (68.7%), and ofloxacin (100.0%), ciprofloxacin (91.3%), piperacillin/tazobactam (63.6%), vancomycin (66.6%), gabapentin (100%), pregabalin (100.0%) and cetirizine (100.0%). For further details please see Table 4.

The logistic regression analysis was carried out to assess the predictors of medication dosing errors in CKD patients. The multivariate analysis confirmed that out of the nine studied variables, only the stages of chronic kidney disease i.e. CKD stage 4 (OR 0.054; 95% CI [0.017–0.177]; p < 0.001) and CKD stage 5 (OR 0.098; 95% CI [0.040–0.241]; p < 0.001), the number of prescribed medicines ≥ 5 (OR 0.306; 95% CI [0.133–0.704]; p 0.005), and the presence of a comorbidity (OR 0.455; 95% CI [0.226–0.916]; p 0.027) such as the hypertension (OR 0.453; 95% CI [0.231–0.887]; p 0.021) were associated with the medication dosing errors (Table 5).

Discussion
The present study showed that nearly 34.0% of drugs prescribed to chronic kidney disease (CKD) patients required dose adjustment. Of which, only 41.8% drugs were properly adjusted, and the remaining 58.2% were unadjusted. Amazingly, the medication dosing errors in the present study were much lower than the studies reported from Palestine, India and South Africa, whereby the percentages of unadjusted drugs were nearly 73.6%, 81.1%, and 59.0% respectively [9, 28, 29]. The comparatively lower percentage of unadjusted drugs in Pakistan could be due to differences in the selected patients in the abovementioned studies. The lower medication dosing errors as compared to other underdeveloped countries could also be due to the better knowledge of practicing physicians regarding the management of chronic kidney disease, as the CKD patients in the present study received medical care directly from trained nephrologists.

In marked contrast, the same percentage of medication dosing errors in Pakistan was comparatively higher than the studies reported from Bosnia and Herzegovina, Australia, France, Saudi Arabia, Indonesia, and even Nepal, whereby the percentages of unadjusted drugs were nearly 52.6%, 44.8%, 34.0%, 53.1%, 20.0%, and 13.5% respectively [7, 8, 12, 18, 30, 31]. This clearly reflects that Pakistani physicians are lacking knowledge as compared to those in the developed countries [32]. The better dose adjustment in CKD patients in high income

Table 3. Frequency and central tendencies of adjusted and unadjusted prescribed drugs.

| Variable                        | Frequency | Percentage | Mean ± SD | Median (IQR) |
|---------------------------------|-----------|------------|-----------|--------------|
| Total drugs prescribed          | 1534      | 100.0%     | 7.48 ± 2.551 | -            |
| Number of drugs requiring dose adjustment | 522/1534 | 34.0%      | -         | 2 (3)        |
| Number of drugs properly adjusted | 218/522 | 41.8%      | -         | 1 (2)        |
| Number of drugs unadjusted      | 304/522   | 58.2%      | -         | 1 (1)        |

IQR (Interquartile range), SD (Standard deviation)

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countries could be due to the incorporation of advanced computerized dose adjustment systems and clinical pharmacists [33, 34]. Beside developed countries, the Nepal and Indonesia have also incorporated clinical pharmacists in their clinical settings that perhaps resulted in lower medication dosing errors. Therefore, we are suspecting that the lack of clinical pharmacists and computerized dose adjustment programs in the Pakistani clinical settings could have caused higher medication dosing errors. In addition, several other factors such as the

| ATC Classification                        | Drug Name          | N of drugs needing adjustment | N (%) of adjusted drugs | N (%) of unadjusted drugs |
|------------------------------------------|--------------------|------------------------------|-------------------------|---------------------------|
| Alimentary tract and metabolism          | Metoclopramide     | 72                           | 9 (12.5)                | 63 (87.5)                 |
|                                          | Sodium Bicarbonate | 48                           | 1 (2.1)                 | 47 (97.9)                 |
|                                          | Ranitidine         | 32                           | 1 (34.4)                | 21 (65.6)                 |
|                                          | Domperidone        | 25                           | 3 (12.0)                | 22 (88.0)                 |
|                                          | Acesulfamum acid   | 11                           | 2 (18.2)                | 9 (81.8)                  |
| Antiinfectives for systemic use          | Ciprofloxacin      | 46                           | 42 (91.3)               | 4 (8.7)                   |
|                                          | Amoxicillin        | 34                           | 7 (20.6)                | 27 (79.4)                 |
|                                          | Piperacillin/Tazobactam | 11              | 7 (63.6)                | 4 (37.4)                  |
|                                          | Vancomycin         | 6                            | 4 (66.6)                | 2 (33.3)                  |
|                                          | Amikacin           | 4                            | -                       | 4 (100.0)                 |
|                                          | Levofloxacin       | 2                            | 1 (50.0)                | 1 (50.0)                  |
|                                          | Linezolid          | 2                            | -                       | 2 (100.0)                 |
|                                          | Cefixime           | 1                            | -                       | 1 (100.0)                 |
|                                          | Cefotaxime         | 1                            | -                       | 1 (100.0)                 |
|                                          | Cephalexin         | 1                            | -                       | 1 (100.0)                 |
|                                          | Ofloxacin          | 1                            | 1 (100.0)               | -                         |
| Antineoplastic and immunomodulating agents | Azathioprine     | 3                            | 1 (33.3)                | 2 (66.6)                  |
| Antiparasitic products, insecticides and repellents | Chloroquine | 1 | - | 1 (100.0) |
| Blood and blood forming organs           | Tranexamic Acid    | 7                            | 1 (14.3)                | 6 (85.7)                  |
| Cardiovascular system                    | Captopril          | 54                           | 49 (90.7)               | 5 (9.3)                   |
|                                          | Furosemide         | 38                           | 20 (52.6)               | 18 (47.4)                 |
|                                          | Atenolol           | 17                           | 10 (58.8)               | 7 (41.2)                  |
|                                          | Lisinopril         | 16                           | 11 (68.7)               | 5 (31.3)                  |
|                                          | Enalapril          | 12                           | 8 (66.6)                | 4 (33.3)                  |
|                                          | Amiloride          | 9                            | 4 (44.5)                | 5 (55.5)                  |
|                                          | Rosuvastatin       | 7                            | 2 (28.6)                | 5 (71.4)                  |
|                                          | Spironolactone     | 7                            | -                       | 7 (100.0)                 |
|                                          | Bispironol        | 3                            | 2 (66.6)                | 1 (33.3)                  |
| Musculoskeletal system                   | Diclofenac         | 6                            | 2 (33.3)                | 4 (66.6)                  |
|                                          | Mefenamic acid     | 2                            | -                       | 2 (100.0)                 |
| Nervous system                           | Paracetamol        | 29                           | 6 (20.7)                | 23 (79.3)                 |
|                                          | Gabapentin         | 2                            | 2 (100.0)               | -                         |
|                                          | Pregabalin         | 1                            | 1 (100.0)               | -                         |
| Respiratory system                       | Cetirizine         | 2                            | 2 (100.0)               | -                         |
|                                          | Sum                | 513                          | 209                     | 304                       |
|                                          | Others             | 9                            | 9                       | -                         |
| Total                                    |                    | 522                          | 218                     | 304                       |

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negligence and traditional clinical practices of physicians, the lack of laboratory support, and the lack of standard dosing guidelines could also have caused higher medication dosing errors in our study setting [8, 9].

Another important aspect of the present study is the strange age distribution of CKD patients, which is likely different from those in the developed and the underdeveloped countries [8, 12, 30]. This difference could be due to several reasons. For instance, the average life expectancy of a normal person in Pakistan is only 65 years, which is much lower than the western counterparts [35]. Therefore, there are likely chances that the CKD patients are dying at an earlier age, even before reaching the national average life-expectancy. There is another possibility that the prevalence of CKD is itself higher in the younger population due to a higher prevalence of hypertension, diabetes and smoking in Pakistan [36, 37]. A recent study has also reported that the prevalence of CKD is higher in patients aged <50 years in Pakistan, and the underlying causes of CKD were the glomerulonephritis, diabetic nephropathy, renal stones and the hypertension [38]. However, further studies are required to assess both these aspects as reliable evidence is lacking.

Furthermore, the assessment of the pattern of medication dosing errors has revealed that the majority of drugs prescribed without any dose adjustment were metoclopramide, sodium bicarbonate, ranitidine, domperidone, acetylsalicylic acid, amoxicillin, linezolid, cephalosporin antibiotics, diclofenac, mefenamic acid, spironolactone, and rosuvastatin. These findings are in line with previous studies with the exception of ciprofloxacin and the cardiovascular medicines that were prescribed more appropriately in our study setting [9, 21]. These findings show that physicians working in the Pakistani public sector hospitals are underestimating the adverse outcomes associated with several important medicines. For instance, the medicines such as

### Table 5. Predictors of medication dosing errors in chronic kidney disease patients.

| Variables                  | N (patients) | patients with unadjusted drugs | UA (OR [95% CI]) | p value | MA (OR [95% CI]) | p value |
|----------------------------|--------------|--------------------------------|------------------|---------|------------------|---------|
| Gender                     |              |                                 |                  |         |                  |         |
| Female                     | 80           | 59 (73.8%)                      | Ref              |         |                  |         |
| Male                       | 125          | 92 (73.6%)                      | 1.062 [0.564–1.999] | 0.852   |                  |         |
| Age                        |              |                                 |                  |         |                  |         |
| < 20                       | 31           | 21 (67.7%)                      | Ref              |         |                  |         |
| 20–40                      | 92           | 66 (71.7%)                      | 0.863 [0.261–2.853] | 0.809   |                  |         |
| 41–60                      | 60           | 48 (80.0%)                      | 0.931 [0.329–2.631] | 0.892   |                  |         |
| > 60                       | 22           | 16 (72.7%)                      | 1.500 [0.484–4.651] | 0.483   |                  |         |
| CKD Stage                  |              |                                 |                  |         |                  |         |
| Stage 3                    | 19           | 5 (26.3%)                       | Ref              |         |                  |         |
| Stage 4                    | 31           | 12 (38.7%)                      | 0.056 [0.018–0.172] | <0.001  | 0.054 [0.017–0.177] | <0.001  |
| Stage 5                    | 155          | 134 (86.5%)                     | 0.099 [0.042–0.233] | <0.001  | 0.098 [0.040–0.241] | <0.001  |
| Length of hospitalization  |              |                                 |                  |         |                  |         |
| < 7 days                   | 97           | 69 (71.1%)                      | Ref              |         |                  |         |
| > 7 days                   | 108          | 82 (75.9%)                      | 0.825 [0.445–1.528] | 0.540   |                  |         |
| Number of medicine         |              |                                 |                  |         |                  |         |
| < 5 drugs                  | 45           | 25 (55.6%)                      | Ref              |         |                  |         |
| > 5 drugs                  | 160          | 126 (78.8%)                     | 0.355 [0.178–0.710] | 0.003   | 0.306 [0.133–0.704] | 0.005   |
| Comorbidity                |              |                                 |                  |         |                  |         |
| Yes                        | 46           | 28 (60.9%)                      | Ref              |         |                  |         |
| No                         | 159          | 123 (77.4%)                     | 0.458 [0.231–0.909] | 0.025   | 0.455 [0.226–0.916] | 0.027   |
| Diabetes                   |              |                                 |                  |         |                  |         |
| No                         | 165          | 118 (71.5%)                     | Ref              |         |                  |         |
| Yes                        | 40           | 33 (82.5%)                      | 0.535 [0.220–1.288] | 0.162   |                  |         |
| Hypertension               |              |                                 |                  |         |                  |         |
| No                         | 59           | 36 (61.0%)                      | Ref              |         |                  |         |
| Yes                        | 146          | 115 (78.8%)                     | 0.422 [0.219–0.814] | 0.010   | 0.453 [0.231–0.887] | 0.021   |
| Antibiotics prescribed     |              |                                 |                  |         |                  |         |
| No                         | 49           | 34 (69.4%)                      | Ref              |         |                  |         |
| Yes                        | 156          | 117 (75.0%)                     | 0.756 [0.372–1.533] | 0.437   |                  |         |

UA (univariate analysis), MA (multivariate analysis); Significance: p < 0.05.

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amikacin, and cephalosporin antibiotics that are well reported to induce nephrotoxicity [21]. Moreover, the linezolid use has also been linked with the CKD and thrombocytopenia, therefore, the dose of linezolid should also be adjusted in order to reduce the likelihood of thrombocytopenia in CKD patients [39]. However, the Pakistani nephrologists should be commended for adjusting several important medicines such as the cardiovascular medicines, piperacillin/tazobactam, ofloxacin, ciprofloxacin, vancomycin, gabapentin, and pregabalin.

Lastly, the regression analysis confirmed that the age, gender, and the lengthy hospitalization of patients were not associated with the medication dosing errors. These findings are in line with previous studies elsewhere [9, 21]. However, the number of prescribed medicines ≥ 5, the presence of a comorbidity, such as hypertension, and the severe-to-end stages of chronic kidney disease were significantly associated with the medication dosing errors. To the best of our knowledge, these findings are comparatively new and not studied before in the developing countries. We also found that diabetes, that is one of the major underlying causes of CKD, was not associated with medication dosing errors, which is in contrast to an Australian study [20]. Moreover, the antibiotic prescribing was also not associated with medication dosing errors. Therefore, attention should be paid to the abovementioned significant predictors of medication dosing errors and thus the doses of drugs should be prescribed carefully and appropriately to avoid the risk of drug related toxicities and adverse outcomes.

Strengths and Limitations
There present study has several strengths. For instance, this is the first study of its kind that is performed in Pakistan. Second, as compared to the past more detailed pattern and predictors of medication dosing errors were studied and identified. Despite these strengths, the study has several limitations. First, a retrospective study design was employed which restricted us from suggesting interventions and observing actual adverse drug reactions. Second, the MDRD equation was used due to lack of data regarding patients’ weight, which is considered unsuitable for patients with higher muscle mass and for those suffering from serious disorders such as cancer [40]. Third, due to the lack of data, the most responsible diagnosis for hospital admission could not be identified, and the diagnosis of CKD could not be verified using the baseline serum creatinine values. Moreover, the lack of data also restricted us to study only those charts that had mentioned serum creatinine values. Fifth, due to the lack of funding, the present study was conducted at only one tertiary care hospital, therefore, these findings should be carefully generalized to across the Pakistan.

Clinical Implications and Future Recommendations
The medication dosing errors in CKD patients is a global concern. It has been reported that CKD alters the pharmacokinetic parameters of drugs such as the bioavailability, protein binding, biotransformation, volume of distribution, and renal excretion of drugs which makes CKD patients more prone to severe adverse outcomes [9]. Therefore, physicians should take extra care while prescribing drugs to CKD patients. One important point that we want to mention here is; due to the lack of consensus among dose adjustment guidelines, confusion exists among nephrologists regarding the dose adjustment of several renally excreted drugs. The best example here is sodium bicarbonate. Some studies and guidelines show that it is beneficial for CKD patients and some do not [24, 41]. Therefore, it is suggested that nephrologists should make a universal consensus and develop internationally applicable dose adjustment guidelines to ensure appropriate drug dose adjustment to save CKD patients from drug related adverse outcomes.
Furthermore, the clinical pharmacists should be incorporated in clinical settings, especially in the developing countries, and allowed to intervene and ensure safe prescribing in CKD patients by playing their role as an active healthcare team member. Additionally, educational programs should be designed to improve and refresh the knowledge of physicians regarding the management of CKD. Apart from that, further research should be conducted to assess the impact of more variables such as the specific drug classes and the specific comorbidities on the medication dosing errors in chronic kidney disease patients. In addition, epidemiological studies should be done to assess the changing pattern of CKD disease and to identify the underlying causes of CKD disease especially in the developing countries such as Pakistan.

Conclusions

It is concluded that the occurrence of medication dosing errors was high in hospitalized chronic kidney disease patients in Pakistan. More than half drugs prescribed to CKD patients requiring dose adjustment, were unadjusted. The predictors of medication dosing errors in CKD patients were the severe-to-end stages of chronic kidney disease, the number of prescribed medicines \( \geq 5 \), and the presence of a comorbidity such as hypertension. Therefore, physicians are advised to take care of these predictors of medication dosing errors while prescribing drugs to chronic kidney disease patients to minimize the risk of drug related toxicities and adverse outcomes.

Supporting Information

S1 Table. Data Collection Form. (PDF)

Acknowledgments

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Author Contributions

Conceived and designed the experiments: AS IM. Performed the experiments: AS. Analyzed the data: AS. Contributed reagents/materials/analysis tools: AS IM. Wrote the paper: AS. Approved final version of the manuscript: AS IM.

References

1. Schieppati A, Remuzzi G. Chronic renal diseases as a public health problem: Epidemiology, social, and economic implications. Kidney Int. 2005; 68(S98):S7–S10.
2. Leendertse AJ, Dijk EAv, Smet PAD, Egberts TC, Bemt PMvd. Contribution of Renal Impairment to Potentially Preventable Medication-Related Hospital Admissions. Ann Pharmacother. 2012; 46:625–33. doi:10.1345/aph.1Q633 PMID: 22570433
3. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. JAMA. 2007; 298(17):2038–47. doi:10.1001/jama.298.17.2038 PMID: 17986697
4. Hallan SI, Coresh J, Astor BC, Asberg A, Powe NR, Romundstad S, et al. International Comparison of the Relationship of Chronic Kidney Disease Prevalence and ESRD Risk. Journal of the American Society of Nephrology. 2006; 17(8):2275–84. doi: 10.1681/asn.2006121273 PMID: 16790511
5. Hartmann B, Czock D, Keller F. Drug Therapy in Patients With Chronic Renal Failure. Deutsches Ärzteblatt International. 2010; 107(37):647–56. doi: 10.3238/arztebl.2010.0647 PMID: PMC2956196.
6. Verbeeck R, Musumba F. Pharmacokinetics and dosage adjustment in patients with renal dysfunction. Eur J Clin Pharmacol. 2009; 65(8):757–73. doi: 10.1007/s00228-009-0678-8 PMID: 19543887
7. Alahdal AM, Elberry AA. Evaluation of applying drug dose adjustment by physicians in patients with renal impairment. Saudi Pharmaceutical Journal. 2012; 20:217–20. doi: 10.1016/j.jspj.2011.12.005 PMID: 23960796
8. Salomon L, Deray G, Jaudon MC, Chebassier C, Bossi P, Launay-Vacher V, et al. Medication misuse in hospitalized patients with renal impairment. International Journal for Quality in Health Care. 2003; 15(4):331–5. doi: 10.1093/intqhc/mzg046 PMID: 12930048
9. Sweileh WM, Janem SA, Sawalha AF, Abu-Taha AS, Zyoud SeH, Sabri IA, et al. Medication dosing errors in hospitalized patients with renal impairment: a study in Palestine. Pharmacoepidemiology and Drug Safety. 2007; 16(8):908–12. doi: 10.1002/pds.1412 PMID: 17464934
10. Haider SI, Ahmad M, Masood I. Evaluation Of The Rational Use Of Medicines In Renal Impaired Patients In The Public Sector Hospitals Of Punjab, Pakistan. Value in Health. 2014; 17(3):A129. doi: 10.1016/j.jval.2014.03.747
11. Drenth-van Maanen AC, van Marum RJ, Jansen PAF, Zwart JEF, van Solinge WW, Egberts TCG. Adherence with Dosing Guideline in Patients with Impaired Renal Function at Hospital Discharge. PLoS ONE. 2015; 10(6):e0128237. doi: 10.1371/journal.pone.0128237 PMID: 26053481
12. Pillans PJ, Landsberg PG, Fleming AM, Fanning M, Sturtevant JM. Evaluation of dosage adjustment in patients with renal impairment. Internal Medicine Journal. 2003; 33(1–2):10–3. doi: 10.1046/j.1445-5994.2003.00330.x PMID: 12534872
13. Cantu T, Ellerbeck E, Yun S, Castine S, Kornhauser D. Drug prescribing for patients with changing renal function. American Journal of Health-System Pharmacy. 1992; 49(12):2944–8.
14. van Dijk EA, Drabbe NR, Krijtjbosch M, De Smet PA. Drug Dosage Adjustments According to Renal Function at Hospital Discharge. Annals of Pharmacotherapy. 2006; 40(7–8):1254–60. doi: 10.1345/aph.1G742 PMID: 16804098
15. Hu K-T, Matayoshi A, Stevenson FT. Calculation of the Estimated Creatinine Clearance in Avoiding Drug Dosing Errors in the Older Patient. The American Journal of Medical Sciences. 2001; 322(3):133–6. PMID: 00000441-200109000-00004.
16. Papaioannou A, Clarke J-A, Campbell G, Bébard M. Assessment of Adherence to Renal Dosing Guidelines in Long-Term Care Facilities. Journal of the American Geriatrics Society. 2000; 48(11):1470–3. doi: 10.1111/j.1532-5415.2000.tb02639.x PMID: 11083325
17. Hug BL, Witkowski DJ, Sox CM, Keohane CA, Seger DL, Yoon C, et al. Occurrence of adverse, often preventable, events in community hospitals involving nephrotoxic drugs or those excreted by the kidney. Kidney Int. 2009; 76(11):1192–9. doi: 10.1038/ki.2009.353 PMID: 19759525
18. Sah S, Wanakamanee U, Lerkjantobditt S, Regmi B. Drug Dosage Adjustment of Patients with Impaired Renal Function at Hospital Discharge in a Teaching Hospital. Journal of Nepal Health Research Council. 2014; 12(26):54–8. PMID: 25574986
19. Hanlon JT, Wang X, Handler SM, Weisbord S, Pugh MJ, Semla T, et al. Potentially Inappropriate Prescribing of Primarily Renally Cleared Medications for Older Veterans Affairs Nursing Home Patients. Journal of the American Medical Directors Association. 2011; 12(5):377–83. http://dx.doi.org/10.1016/j.jamda.2010.04.008. doi: 10.1016/j.jamda.2010.04.008 PMID: 21450179
20. Khanal A, Peterson GM, Castellino RL, Jose MD. Potentially Inappropriate Prescribing of Renally Cleared Drugs in Elderly Patients in Community and Aged Care Settings. Drugs & Aging. 2015; 32(6):391–400. doi:10.1007/s40266-015-0261-1
21. Getachew H, Tadesse Y, Shibeshi W. Drug dosage adjustment in hospitalized patients with renal impairment at Tikur Anbessa specialized hospital, Addis Ababa, Ethiopia. BMC Nephrology. 2015; 15(158):1–9.
22. Cockcroft DW, Gault MH. Prediction of Creatinine Clearance from Serum Creatinine. Nephron. 1976; 16(1):31–41. PMID: 1244564
23. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A More Accurate Method To Estimate Glomerular Filtration Rate from Serum Creatinine: A New Prediction Equation. Annals of Internal Medicine. 1999; 130(6):461–70. doi: 10.7326/0003-4819-130-6-199903160-00002 PMID: 10075613
24. British Medical Association and the Royal Pharmaceutical Society of Great Britain. British National Formulary. 58th ed. United Kingdom: BMJ Publishing Group; 2009.
25. Munar MY, Singh H. Drug Dosing Adjustments in Patients with Chronic Kidney Disease. American Family Physician. 2007; 75(10):1487–96. PMID: 17555141
26. Bennett WM, Aronoff GR, Morrison G, Golper TA, Pulliam J, Wolfson J, et al. Drug Prescribing in Renal Failure: Dosing Guidelines for Adults. American Journal of Kidney Diseases. 1983; 3(3):155–93. PMID: 6356890
27. Lassiter J, Bennett WM, Olyaei AJ. Drug Dosing in Elderly Patients with Chronic Kidney Disease. Clinics in Geriatric Medicine. 2013; 29(3):657–705. doi: 10.1016/j.cger.2013.05.008 PMID: 23849014
28. Prajapati A, Ganguly B. Appropriateness of drug dose and frequency in patients with renal dysfunction in a tertiary care hospital: A cross-sectional study. Journal of Pharmacy and Bioallied Sciences. 2013; 5(2):136–40. doi: 10.4103/09757406.111829 PubMed Central PMCID: PMID: PMCPMC3697192.
29. Decloedt E, Leisegang R, Blockman M, Cohen K. Dosage adjustment in medical patients with renal impairment at Groote Schuur hospital. SAMJ: South African Medical Journal. 2010; 100(5):304–6. PMID: 20460024
30. Markota NP, Markota I, Tomic M, Zelenika A. Inappropriate drug dosage adjustments in patients with renal impairment. Journal of Nephrology. 2009; 22(4):497–501. PMID: 19662605
31. Soetikno V, Effendi I, Nafrialdi, Setiabudy R. A survey on the appropriateness of drug therapy in patients with renal dysfunction at the Internal Medicine Ward FMUI/Dr. Cipto Mangunkusumo Hospital. Medical Journal of Indonesia. 2009; 18(2):108–13.
32. Tamizuddin S, Ahmed W. Knowledge, attitude and practices regarding chronic kidney disease and estimated GFR in a tertiary care hospital in Pakistan. Journal of Pakistan Medical Association. 2010; 60(5):342–6.
33. Marasinghe KM. Computerised clinical decision support systems to improve medication safety in long-term care homes: a systematic review. BMJ Open. 2015; 5(5). doi: 10.1136/bmjopen-2014-006539
34. Erfer A, Beyer M, Petersen JJ, Saal K, Rath T, Rochon J, et al. How to improve drug dosing for patients with renal impairment in primary care—a cluster-randomized controlled trial. BMC Family Practice. 2012; 13(91):1–8. doi: 10.1186/1471-2296-13-91
35. WHO. Pakistan: Statistics 2013 [cited 2016 02 April]. Available from: http://www.who.int/countries/pak/en/.
36. Gilani SI, Leon DA. Prevalence and sociodemographic determinants of tobacco use among adults in Pakistan: findings of a nationwide survey conducted in 2012. Population Health Metrics. 2013; 11:16–. doi: 10.1186/1478-7954-11-16 PMID: 23850735.
37. Alam A, Amanullah F, Baig-Ansari N, Lotia-Farrukh I, Khan FS. Prevalence and risk factors of kidney disease in urban Karachi: baseline findings from a community cohort study. BMC Research Notes. 2014; 7:179–. doi: 10.1186/1756-0500-7-179 PMID: PMC3972995.
38. Kifayat U, Ghias B, Imtiaz M, Kinza K, Farina K. Epidemiology of chronic kidney disease in a Pakistani population. Saudi Journal of Kidney Diseases and Transplantation. 2015; 26(6):1307–10. doi: 10.4103/1319-2442.168694 PMID: 26586079
39. Bassetti M, Righi E. Safety profiles of old and new antimicrobials for the treatment of MRSA infections. Expert Opinion on Drug Safety. 2016; 15(4):467–81. doi: 10.1517/14740338.2016.1142528 PMID: 26764972
40. Stevens LA, Levey AS. Use of the MDRD Study Equation to Estimate Kidney Function for Drug Dosing. Clinical Pharmacology & Therapeutics. 2009; 86(5):465–7. doi: 10.1038/clpt.2009.124
41. de Brito-Ashurst I, Varagunam M, Raffney MJ, Yaqoob MM. Bicarbonate Supplementation Slows Progression of CKD and Improves Nutritional Status. Journal of the American Society of Nephrology. 2009; 20(9):2075–84. doi: 10.1681/asn.2008111205 PMID: 19608703