Identifying the pattern and risk factors for potential medication dosing errors in chronic renal impairment of critically ill patients

Bafrin Sedaghat[1], Saeed Abbasi[2,3,4], Shadi Farsaei[1*]

[1]Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmacy, Isfahan University of Medical Sciences, Isfahan, Iran.
[2]Anesthesiology and Critical Care Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.
[3]Nosocomial Infection Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.
[4]Anesthesiology and Critical Care Department, Isfahan University of Medical Sciences, Isfahan, Iran.

Abstract

Different prescription entries usually complicate the drug therapy for critically ill patients; therefore, we conducted this prospective study to assess the rates for appropriate renal dosing modifications in chronic kidney disease (CKD) patients admitted to the ICU and reported possible related factors of misadjustments. We enrolled adult ICU patients who received at least one drug and experienced CKD with the estimated glomerular filtration rate (eGFR) $\leq$ of 59 ml/min on ICU admission. The latest Lexicomp drug information handbook recommendations were also applied as a standard guide for renal dosing changes. A total of 701 prescription entries were studied in 97 patients, and 13.8% (97 medications) required renal dose adjustment. Of the 97 drugs, 20.6% (20) had not been prescribed appropriately, according to eGFR. Antibiotics were the most likely medication group to require a dose adjustment and comprised the largest number of inappropriate prescriptions in our study. EGFR and the number of drugs that needed dose modification significantly affected renal dosing adjustment accuracy (p = 0.03 and 0.01, respectively). These results revealed a high percentage of appropriate renal dose adjustment in ICU compared to other studies that evaluated non-critically ill patients. However, more attention should be paid to patients with a higher number of prescribed medicines for renal dose modification and lower eGFR to reduce medication errors.

Keywords: Inappropriate prescribing, Critical Illness, Renal Insufficiency

1. Introduction

Medication dosing errors are crucial in hospitalized patients, leading to suboptimal treatment, severe adverse events, prolonged hospital stay, and increased mortality (1, 2). Patients with renal insufficiency are more frequently admitted to the hospital and more often at risk of medication dosing errors and toxicity related to delaying or decreasing renal excretion of drugs (3, 4). Previous studies revealed that up to 80% of medication dosing errors occurred in non-critically ill patients with chronic kidney disease (CKD). This problem is more critical in the intensive care unit (ICU) patients who receive various medications to control their acute conditions (5). The recent study declared that the incidence of ADRs may be as high as 36% in hospitalized patients, and critically ill patients are at incredibly high risk because of complex medical regimens with high-alert medications

Corresponding Author: Shadi Farsaei, Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmacy, Isfahan University of Medical Sciences, Isfahan, Iran.
Email: farsaei@pharm.mui.ac.ir

and challenging drug dosing (6).

Drug dosing is complex in acute renal failure (ARF) conditions; however, dosing recommendations in renal impairment are usually intended for CKD patients based on estimated glomerular filtration rate (eGFR) (7). Since a minor increment in serum creatinine (SCr) can cause a significant decrease in eGFR, it seems eGFR is more sensitive than SCr to evaluate renal function and medication dosing revision (8). However, SCr is still used to assess renal function and subsequent drug dosing changes even in the hospital setting, especially in developing countries (9). Modification of Diet in Renal Disease (MDRD) equation provides a more accurate estimate of GFR than Cockroft Gault's (CG) equation; however, available evidence does not support the superiority of the MDRD equation for drug dosing purposes (10, 11). Although both equations were validated for drug dosing, some concerns exist in critically ill patients who may not have stable renal function and creatinine levels at a steady state and require optimal drug levels for controlling acute conditions (12).

Various works have been conducted to address the importance of renal dosing modification to prevent the possible adverse consequence of errors. The literature review indicated that the rate of non-adherence to renal dosing guidelines in CKD hospitalized patients varied between 12% and 82% in different general wards and hospitals located in developing or developed countries. However, there is inadequate information regarding CKD patients admitted to ICUs (1, 4, 9, 13-20).

Retrospective research in the nephrology unit revealed severe end-stage chronic kidney disease (CKD), a higher number of prescribed medications, and the patients' comorbidities could predict medication dosing errors (9). Other conducted research found that appropriate prescribing in CKD patients was associated with different factors such as the stage of renal impairment (13), SCr level (13, 19), eGFR (19), age (18, 20), comorbidities (18, 20), obesity (18), and the type (13) and the number of prescribed medicines (20). However, we could not find any study regarding renal dosing of drugs in CKD patients and its risk factors in the ICU. Therefore, we designed this pilot survey to evaluate the prevalence of non-adherence to renal dosing guidelines among ICU patients with chronic renal insufficiency in a referral hospital. Besides, more analyses were conducted to found risk factors that could predict this non-adherence.

2. Materail and Methods
2.1. Clinical study

We conducted a prospective study among critically ill patients hospitalized at the largest referral teaching hospital (Alzahra hospital affiliated with Isfahan University of Medical Sciences) situated in Isfahan, Iran.

More than 900 ICU patients were screened for the study inclusion and exclusion criteria. Of those, 123 adult patients were recruited in this survey on ICU admission from October 2018 until July 2019 based on the inclusion criteria defined as the age at least 18 years and CKD with an eGFR between 10 and 59 ml/min. CKD confirmation was based on patients' past medical history registered in the medical chart and SCr levels from recent available laboratory results. Patients who experienced ARF or inconsistencies in SCr levels were excluded during the follow-up period. We defined ARF as a greater than 0.3 mg/dl increment in SCr level within three days after the index test date. Another exclusion criterion was less than seven day follow-up period.

We estimate GFR according to the CG equation for renal dosing of medications: eGFR (ml/min): (140 - age in years) x weight in kg/(72 x serum creatinine level in mg/dl) adjusted by sex (x 0.85 in women) (21).

We use the MDRD equation to estimate GFR to determine stages of chronic kidney disease: eGFR (ml/min) The eGFR was assessed by the MDRD equation: eGFR (ml/min./1.73 m2)=175 x (serum creatinine (μmol/l)/88.4)-1.154 x (age in years)-0.203 (x 0.74 if female) and stages of chronic kidney disease were classified as follows: stage 3 (eGFR 30-59 ml/min), stage 4 (eGFR 15-29 ml/min), and stage 5 (eGFR <15 ml/min) (22). Moreover, we used the Lexicomp drug information handbook recommendation for renal dosing adjustment according to calculated eGFR (23).

A pharmacist collected data of all prescribed drugs of eligible patients on the admission date and reported the rate of inappropriate dosing

adjustment among drugs required dose modification based on the patients' renal function. Therefore, we registered dosing of drugs, together with the demographic data (age and sex), kidney function results (SCr, BUN (blood urea nitrogen), and physician administrative service information. The APACHE score of the patient was also calculated on the beginning day of the study.

We defined non-adherence in patients with 20% lower (underdosing) or higher (overdosing) cumulative daily dose than the Lexicomp drug information handbook recommendation. Moreover, we described the reason for non-adherence by asking open-ended questions from attending physicians and nursing and statistically analyzed the factors possibly related to the non-adherence.

2.2 Statistical analysis

Results were described with the absolute numbers (percentage) or average (standard deviation). The Kolmogorov-Smirnov statistic tested the normality of the data. Differences between groups of patients were evaluated using the independent sample t-test or Mann–Whitney U test for continuous variables and chi-squared test or Fisher's exact test for categorical variables. The data were analyzed with SPSS version 12 (SPSS Inc, Chicago, IL), and a p-value <0.05 was considered statistically significant.

2.3 Ethical consideration

The research ethics committee of Isfahan University of Medical Sciences approved the use of data from medical records. Hospital administration is permitted to access and use the data following the permission obtained from this committee. We also handled all data for the present study anonymously

3. Results

Among 910 screened adult ICU patients, a total of 123 patients were recruited in this study. After excluding 26 patients who underwent inconsistency in SCr (21 patients) or staying in ICU less than seven days (4 patients), 97 patients completed the study.

These enrolled patients aged between 32-90 years old with a female/male ratio of 0.89. They

Table 1. Demographic and clinical characteristics of the study population.

Parameter	N = 97
Male Sex, n (%)	45 (46.4)
Age (year), median (IQR)	71 (61-78.5)
Reason for ICU admission, n (%)	
Trauma	5 (5.2)
Surgery	21 (21.6)
Other medical complications	71 (73.2)
Comorbid disease, n (%)	
CVD	26 (26.8)
HTN	66 (68)
Diabetes	32 (33.0)
Chronic lung disease	13 (13.4)
Cirrhosis	-
Neurologic disorders	21 (21.6)
Number of comorbidities, median (IQR)	1 (1-2)
APACHE II score, Mean ± SD	17.1 ± 5.6
Serum creatinine (mg/dl), median (IQR)	1.4 (1.1-1.7)
BUN (mg/dl), median (IQR)	22.0 (16.5-32.0)
Creatinine clearance (ml/min), median (IQR)	49.6 (37.95-53.86)
30-59 (stage 3), n (%)	81 (83.5)
15-29 (stage 4), n (%)	10 (10.3)
< 15 (stage 5), n (%)	6 (6.2)
Prescribed medications that required dose adjustment, n (%)	77 (78.6)
Vancomycin, n (%)	25 (25.8)
Cephalosporines, n (%)	53 (54.6)
Carbapenem, n (%)	9 (9.3)
Fluoroquinolones, n (%)	5 (5.1)
Metronidazole, n (%)	2 (2.1)
Gabapentin, n (%)	3 (3.1)
Treatment services, n (%)	
Surgery	53 (54.6)
Internal medicine	18 (18.6)
Neurology	12 (12.4)
Others	14 (14.4)

APACHE, acute physiology and chronic health evaluation; BUN, blood urea nitrogen; CVD, cardiovascular disease; HTN, hypertension; IQR, interquartile range; SD, standard deviation
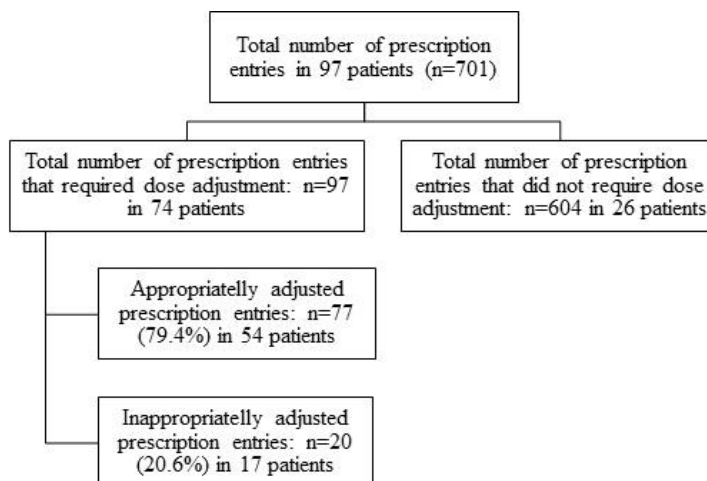
Figure 1. Appropriateness of dosing adjustment in the study population.

were admitted to ICU because of internal medicine complications (72%), surgery (21%), and trauma (5%) reasons. The average SCr of patients for at least seven days follow-up was 1.79 mg/dl, and most patients (82.7%) had eGFR 30-59 ml/min. Table 1 indicated a summary of patient demographic and clinical data.

Dose adjustment required for 97 (13.8%) of 701 medications ordered in 97 patients. Most of these drugs were prescribed by surgeons (54.1%), Nephrologists (12.2%), and specialists of internal medicine (18.3%).

Further analysis revealed that two-thirds (71/97) of patients had at least one drug that should be adjusted based on their kidney function. However, dose adjustments were non-adhered to the guideline in 17 (17.5%) patients or 20 (20.6%) prescription entries which was described in figure 1. Among these 20 dosing errors, six belonged to inattention to eGFR, corrected by phar-

macist intervention, and 14 related to patients' critical condition with severe sepsis, which remained unchanged.

More descriptive statistics indicated that all medications of 76% (54/71) of patients were appropriately adjusted, 5.6% (4/71) of patients had some drugs inappropriately revised, while all drugs of 18.4% (13/71) of patients were inappropriately dosed base on renal function.

Antibiotics were the most common drugs that needed dose adjustment (90/97 orders, 92.8%) and remained the only unadjusted medications group in our study. Fluoroquinolones and cephalosporins were the most miss-dosed drugs, followed by vancomycin and meropenem, demonstrated in figure 2.

Table 2. presented the variables which associated appropriate drug dosing based on renal function. The statistical tests revealed a lower eGFR, and the higher number of drugs that need
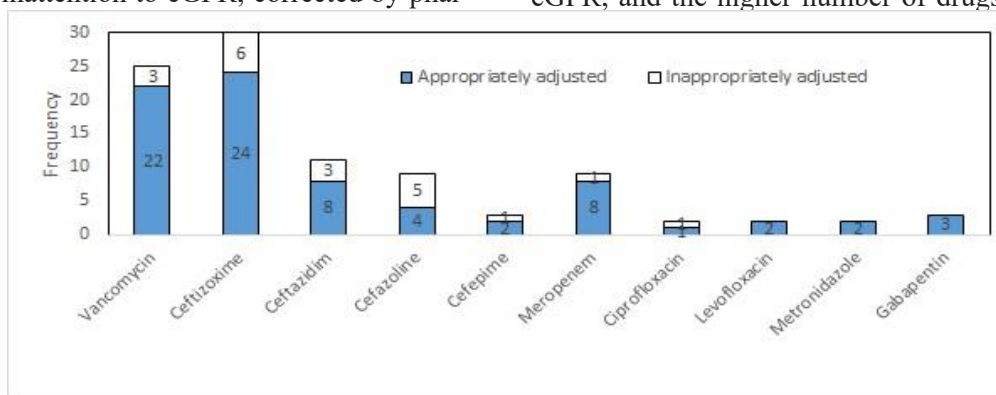
Figure 2. Frequency of appropriately adjusted medications

Table 2. Factors associated with medication dosing errors in ICU chronic kidney disease patients.

Variables	Appropriately dosing adjustment (n = 80)	Inappropriately dosing adjustment (n = 17)	P-value
Age, (years), median (IQR)	71 (61-78)	74 (64-83)	0.25*
Male sex, n (%)	36 (45.0)	9 (52.9)	0.60†
APACHE score, mean ± SD	17.0 ± 5.9	17.68 ± 4.19	0.57‡
Serum creatinine (mg/dl), median (IQR)	1.3 (1.1-1.7)	1.5 (1.2-1.9)	0.10*
BUN (mg/dl), median (IQR)	22 (16-32)	26 (19-33)	0.31*
eGFR, (ml/min), median (IQR)	50.34 (38.4-55.3)	45.3 (35.7-49.4)	0.03*
Stage of renal impairment, n (%)			0.49†
Stage 3	67 (83.8)	14 (82.4)	
Stage 4	9 (11.3)	1 (5.9)	
Stage 5	4 (5)	2 (11.8)	
Reason for ICU admission, n (%)			0.38†
Surgery	18 (22.5)	3 (17.6)	
Internal medicine	59 (73.8)	12 (70.6)	
Trauma	3 (3.8)	2 (11.8)	
Comorbid disease, n (%)			
CVD	21 (26.3)	5 (29.4)	0.77†
HTN	55 (68.8)	11 (64.7)	0.78†
Diabetes	26 (32.5)	6 (35.3)	1†
Chronic lung disease	9 (11.3)	4 (23.5)	0.23†
Cirrhosis	-	-	-
Neurologic disorders	15 (18.8)	6 (35.3)	0.19†
Number of comorbidities, median (IQR)	1 (1-2)	2 (1-3)	0.12*
Number of all prescribed medications per patient, median (IQR)	7 (5-9)	6 (4-7)	0.10*
Number of medications require dose adjustment per patient, median (IQR)	1 (0-1)	1 (1-3)	0.01*
Treatment services, n (%)			0.26†
Surgery	42 (52.5)	11 (64.7)	
Internal medicine	17 (21.3)	1 (5.9)	
Neurology	11 (13.8)	1 (5.9)	
Other	10 (12.5)	4 (23.5)	

* P-values are based on Mann-Whitney Test. † P-values are based on Chi-square test or Exact-Fisher Test. ‡P-values are based on Independent t-Test. APACHE, acute physiology and chronic health evaluation; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; IQR, interquartile range; SD, standard deviation.

adjustment were significantly associated with medication dosing errors (p=0.03 and 0.01, respectively). However, other variables, including age, sex, APACHE score, SCr, BUN, the reason for admission, stage of renal impairment, number of prescribed medications per patient, and attending physician service, were not statistically different on the proportion of appropriately adjusted prescriptions.

4. Discussion

Our research showed a high prevalence of 82.5% adherence to renal dosing guidelines on ICU admissions. The present study's adherent rate was much higher than the studies reported in underdeveloped countries such as Pakistan, South

Africa, Palestine, and India, which had 41.8%, 41.0%, 26.4%, and 18.9%, respectively (9, 14, 15, 24). However, this is comparable to research conducted in developed countries with a nearly 50%-87% adherence rate (16, 25-28). Although the different sets of our study (ICU) compared to previous research (internal medicine wards), make comparison difficult to some extent. Perhaps our population's critical condition attracted more attention than internal patients for their therapies which could justify this high prevalence rate in our study.

Moreover, the lower percent of inattention to eGFR among the self-reported reasons for dosing errors confirms the higher knowledge and awareness of attending physicians in our study. Indeed incorporating different specialties and fellowships in the management of patients in our ICU could minimize medical errors. Our hospital is the largest teaching hospital in Iran, which trains residents and specialists that encourage more attention to prevent medication errors. In addition, antibiotics, the most prescription entries that required dose adjustment in our study, were the most critical and familiar group of medications for dosing adjustment.

The medication regimen's complexity may harm dosing modification in renal insufficiency. In this context, the low percentage of prescription entries (13.8%) requiring dose adjustment in our examination could influence appropriate drug dosing. Whereby its rate was much higher in the survey from different studies in France (71%) (28), Saudi Arabia (39%) (25), Pakistan (34%) (9), Ethiopia (31%) (13), Netherlands (23.9%) (19), Bosnia and Herzegovina (19.6%) (26), Palestine (19.3%) (15), Nepal (19.2 %) (27), and South Africa (19%) (14).

Moreover, clinical pharmacist incorporation in our ICU setting in recent years could lower medication errors, which were also indicated in previous reports (29).

We also want to mention the lack of consensus in various guidelines for dose modification in different studies, which may play a role in multiple non-adherence rates in previous reports.

Furthermore, as the first pilot study of its kind performed in ICU, our findings indicated lower eGFR, and the higher number of drugs that need adjustment might harm dosing modification in renal insufficiency. As mentioned before, a higher number of prescribed medications and a complicated medication regimen could negatively affect dosing adherence. Therefore, similar to previous research, the number of drugs required dose adjustment per patient was significantly higher in our inquiries' inappropriately dosing adjustment group (20).

The prior investigation stated that dose adjustments are often neglected in the severe stages of kidney insufficiency (9, 19), aligning with our results. However, the study in Ethiopia reported that elevated Scr caused physicians to pay more attention to medication prescription and lower dosing errors, which contrasts with previous research and our findings (9, 13, 19). In general, attention to these mentioned predictors could ameliorate medication dosing.

It is necessary to adapt the dosing of drugs based on individual requirements to prevent the toxic effects of overdosing and maximize therapeutic drug efficiency. Renal function is one of the most important characteristics that could affect drug dosing, and adjusting the dose of prescribed medication in this situation is along with the worry of under-dosing. In contrast to recent research, lack of knowledge or inattention to the eGFR was not the primary source of non-adherence in our investigation. Instead, most attending physicians declared uncertainty of sufficient antibiotic level to control sepsis was the main reason that they didn't tend to reduce antibiotic dose in the early encounter to CKD patients, especially those with severe sepsis.

The earlier review declared postponed renal dose reduction of some antibiotics, such as cephalosporins with a broad therapeutic index, could ameliorate outcomes in patients with an active infection (7). Recent research also revealed that adjustment in antibiotic dose according to eGFR in ICU patients with renal insufficiency significantly increased the risk of treatment failure and death (30). However, these outcomes came from the population of chronic and acute kidney failure, which is different from our study, which included only chronic kidney disease.

Therefore it seems that in higher SCr, physicians decided to use higher doses of antibiotics than the amount required based on renal function besides the awareness for needing dose adjustment because of the uncertainty of the optimal level of antibiotics vital for controlling the sepsis of critically ill patients. This customized dosing regimen was also recommended, particularly in the presence of septic shock in Roberts' et al. study. However, they suggested that extensive prospective studies are now required to determine the value of this antibiotic dosing (12).

Since most antibiotics' pharmacokinetics are modified in critically ill patients, standard drug dosing regimens could lead to inadequate drug concentrations and treatment failure. This condition will be pronounced in organ insufficiency conditions such as CKD. Consequently, dosing adjustment in ICU patients with renal insufficiency is a global concern that could be improved by antibiotics' therapeutic drug monitoring (TDM) as a promising tool to optimize antibiotic therapy. Unfortunately, TDM is not widely available in developing countries' hospitals, but it seems necessary to integrate TDM as a part of an antimicrobial stewardship program. For this reason of limitation, some attending physicians didn't adjust doses of antibiotics despite renal impairment and then followed patients' clinical response for any required dose adjustment. Implementing a renal dosing service based on clinical pharmacists' intervention and alerts by computerized dose adjustment programs seems useful for improving drug dosing; however, these effects' significance was stated variously in conducted studies (29, 31, 32).

5. Conclusion

Our findings are the first report of medication dosing in chronic renal impairment in the ICU setting and revealed a high percentage of appropriate renal dose adjustment in ICU compared to other studies that evaluated non-critically ill patients. In addition, our results suggested that more attention should be paid to patients with a higher number of prescribed medicines for renal dose modification and lower eGFR to reduce medication errors. However, since antibiotics were the only drug class missed dosed, further studies are necessary to focus on different categories of medications in the larger population.

Conflict of Interest

There is no conflict of interest in this study.

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