

Original Research

Evaluation of renal drug dosing adjustment in chronic kidney disease patients at two university hospitals in Lebanon

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Abstract

Background: Inappropriate medication dosing in patients with chronic kidney disease can cause toxicity or ineffective therapy. Patients are at a high risk of developing related adverse events caused by the altered effect of drugs in conjunction with the use of polypharmacy to treat comorbid conditions. This necessitates adequate renal dosing adjustments.

Objective: The current study aims at assessing whether appropriate dosing adjustments were made in hospitalized patients with chronic kidney disease.

Methods: A retrospective descriptive study was conducted at two university hospitals in Beirut between January and December 2016. All adult CKD patients with creatinine clearance less than 60 ml/min and receiving at least one medication that require renal dosing adjustment were included. Kidney function was estimated from serum creatinine using Cockcroft-Gault equation, and dose appropriateness was determined by comparing practice with specific guidelines. The rates of renal drug dosing adjustment were investigated, in addition to the influence of possible determinants, such as the severity of renal impairment, reason of hospital admission, and other patient characteristics.

Results: 2138 patients admitted in 2016 were screened. 223 adults receiving 578 drug orders that require adjustment were included. Among the 578 orders, 215 (37%) were adjusted adequately, 284 (49%) were adjusted inadequately, and 79 (14%) were not adjusted at all. Beta-blockers were the most inadequately dosed (83.6%) class of medication, whereas lipid-lowering agents had the highest percentage of adequate dosing (65.1%). As per patient, 84.3% of patients appeared to be receiving at least one inappropriate drug dose.

Conclusions: Our study confirms that physicians are not prescribing appropriate dosing adjustments in chronic kidney disease inpatients, which may have deleterious effects. This highlights the need for more nephrology consultation and the implementation of physician education programs.

Keywords

Renal Insufficiency; Kidney Function Tests; Metabolic Clearance Rate; Drug Overdose; Medication Errors; Clinical Competence; Physicians; Retrospective Studies; Lebanon

INTRODUCTION

Chronic kidney disease (CKD) has globally become of substantial health and economic burden. An estimated 5–10 million people die annually from kidney disease.¹ In Lebanon, 10% of the population suffers from kidney disease at various stages, of whom 3500 patients are on dialysis.¹ With decreased renal function, the pharmacokinetics of many drugs are significantly altered so that the effect of usual doses becomes either augmented or diminished.²⁻⁴ Moreover, the patient's response may be changed due to the disease effect on multiple organ systems, making patients more susceptible to the effect of drugs.²⁻⁴ CKD patients are subject to significant accumulation of renally eliminated drugs.^{4,5} When a drug accumulates, the risk of side effects increases, and may lead to toxicities. In contrary, under-dosing in dialysis patients may decrease efficacy and result in suboptimal response. In hospitalized patients, toxic or ineffective doses increase the length of hospitalization and cost of

treatment, and thus, increase burden on both patient and healthcare systems.¹ Although adverse outcomes can often be delayed or prevented by inexpensive interventions, different studies have showed that during hospital stay, drug doses in patients with CKD are not adjusted properly in 25-77% of cases.^{6,7} In order to improve drugs' prescription in CKD patients, it would be necessary to have collaboration between all healthcare providers.⁸ The primary objective of the current study was to assess adherence to dosing guideline in hospitalized patients with renal impairment, whereas the secondary objective was to assess appropriateness of drug dosing adjustment in those patients recruited from two university hospitals in Beirut, Lebanon.

METHODS

Study population

A retrospective cross-sectional study was conducted between January and December 2016 at two university hospitals in Beirut, Lebanon. Databases of the two hospitals were computerized and established since 2008. Records of all patients admitted in 2016 to any hospital floor were screened. Initially, databases were searched using International Statistical Classification of Diseases and Related Health Problems (ICD-10) coding system for code of

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N18 (chronic kidney disease). However, since the use of coding system didn't yet become an obligatory practice in these hospitals, some doctors mentioned the N18 label to CKD patients, while others did not. The computerized typed reports were used as further reference.

Patients over 18 years of age, receiving at least one pharmacological agent requiring renal dose adjustment, with initial serum creatinine (SCr) level over 1.2 mg/dl (greater than the upper normal limit) were included in the study.⁹ SCr level was used in the initial selection of subjects rather than creatinine clearance (CrCl) because SCr values were available in all patients' medical files while CrCl values were not, and therefore was calculated by study investigators with values <60ml/min considered for analysis. Patients not receiving any pharmacological agent requiring adjustment, female patients who were pregnant and, patients with unreported age, weight or serum creatinine level were excluded from the study.

A sample of 217 patients was targeted to allow for adequate power for bivariable and multivariable analyses to be carried out according to the Epi info sample size calculations with a population size of 400,000 patients with kidney diseases in Lebanon, a 28% expected frequency of appropriately adjusted drug doses according to a previous study in Ethiopia due to the lack of similar studies in Lebanon, and a 95% confidence interval.¹⁰

Outcomes

The primary outcome was to evaluate the frequency of medication orders with appropriate or inappropriate dose adjustment, or even non-adjustment. The secondary outcome was to assess the presence of at least one inappropriate or no drug dose adjustment per patient.

Dose appropriateness was determined by comparing practice with the guidelines: "Drug Dosing Adjustments in Patients with Chronic Kidney Disease" published by the American Academy of Family Physicians, and "Drug Information Handbook, 25th edition" published by Lexicomp®.¹¹ The "American College of Physicians' Drug Prescribing in Renal failure" fifth edition, was used in case of hemodialysis.¹²

The evaluation of dose appropriateness was performed by three clinical pharmacists independent from the study and who received thorough training to ensure consistency. For each drug order, when the dose prescribed for the patient was concordant with the dose recommended in the guideline for the patient's creatinine clearance level, it was recorded as adequately adjusted. However, when it was dosed inappropriately, we recorded it as either not adjusted at all, when CKD patients were given doses recommended for patients with normal renal function, or as inadequately adjusted, when doses given matched neither of the above two doses. Each prescribed order, thus, was labeled as one of three practice categories: adequately adjusted, inadequately adjusted, or not adjusted. This enabled to calculate the percent of each category with respect to the total orders and analyze its occurrence with respect to patient factors and drug classes.

Data collection procedures

Individual patient data were obtained from computerized patient records in both hospitals. Each patient was assigned a study ID. Patient characteristic including date of admission, floor, reason of admission, age, gender, weight, serum creatinine, blood urea nitrogen, dialysis status, and comorbidities were collected through Open Data Kit (ODK) collect android application, and directly uploaded to Microsoft excel 2010. However, medication regimens were copied from the hospitals' computerized prescriptions and recorded manually on a data collection sheet that holds the patient-specific study ID, where each medication order was also assigned an ID and written with its corresponding dose and dosing schedule.

From the above data, creatinine clearance of each patient was calculated based on the serum creatinine level, recorded prior to drug prescription, following the Cockcroft Gault (CG), the most frequently clinically used equation (i.e. the one used by physicians at the two hospitals) to estimate glomerular filtration rate (GFR).^{13,14} For obese patients, an adjustment factor of 0.4 was used based on a meta-analysis conducted by Wilhelm *et al.*¹⁵ The corresponding GFR category was assigned for each patient based on his current state according to "Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease".⁹ Patients included in the analysis belonged to the following GFR categories G3a (45-59 ml/min), G3b (30-44 ml/min), G4 (15-29 ml/min), and G5 (<15 ml/min).

Study drugs were divided into six different classes including: angiotensin-converting enzyme inhibitors (ACEI), beta-blockers, diuretics, antivirals, lipid-lowering agents, and miscellaneous drugs.

Data analysis

Data analysis was conducted using SPSS version 19.0. For study population and drug dosing analysis, descriptive statistics using frequency tables were used to obtain counts and percentages. Dosing appropriateness was compared among different patient/hospital characteristics and analyzed using Chi-square. A multivariable logistic regression was conducted taking the dose adjusted inappropriately as the dependent variable and taking all variables that showed a $p < 0.2$ in the bivariate analysis as independent variables. Statistical significance was set at p -value of less than 0.05.

Ethics Approval

A written informed consent from the patients was not needed since this study had no physiologic, psychologic, or social risks on the patients. The Institutional Review Board of each hospital approved the study protocol.

RESULTS

A total of 2138 patients with CKD were identified during the twelve-month study period. Based on the inclusion criteria, a total of 223 patients were considered for evaluation (10.4% of screened subjects). Those patients were prescribed 578 orders of our study medications. The clinical and demographic characteristics of all study patients

		Frequency (%)
Gender	Male	124 (55.6)
	Female	99 (44.4)
Age (mean) year		65.78 (range 19-96)
SCr (mean, SD)		4.48 (2.9)
BUN (mean, SD)		61.41 (49)
Estimated CrCl (mean) ml/min		21.42 (range 2.1-59)
Reason for admission	Renal	27 (12.1)
	Non-renal	196 (87.9)
GFR category	G3a	18 (8.0)
	G3b	27 (12.1)
	G4	84 (37.7)
	G5	94 (42.2)
Admission floor	IM	104 (46.6)
	CCU	57 (25.6)
	ICU	37 (16.6)
	Other	25 (11.2)
Dialysis	Yes	95 (42.6)
	No	128 (57.4)
Total		223 (100)

(n=223) are summarized in Table 1. The study population consisted of 124 (55.6%) males and 99 (44.4%) females. The mean age was 65.78 years (range 19-96); the mean actual body weight was 76.3 kg; 27 (12.1%) were admitted for a renal reason. Most of the patients 104 (46.6%) were admitted to internal medicine (IM) floor; 84 (37.7%) and 94 (42.2%) patients were in G4 and G5 stages of CKD, respectively. Patients receiving hemodialysis were 95 (42.6%) of study group.

Evaluation of renal dosing adjustment

A total of 578 orders of our study medication list was prescribed. Among these, 215 orders (37%) were adjusted adequately, 284 (49%), corresponding to the majority, were adjusted inadequately, and 79 orders (14%) were not adjusted at all.

Table 2 summarizes the total number of orders of each drug or drug class, with the counts and corresponding percentages of orders that were adjusted adequately, adjusted inadequately, or not adjusted. When type of medication and dose adjustment were evaluated, bisoprolol was the most frequently prescribed drug that required dose adjustment, it was adequately adjusted in 24/196 (12.2 %) and inadequately adjusted in 168/196 (85.8%) of cases; followed by ranitidine which was adequately adjusted in 42/68 (61.7%). Metoclopramide, ramipril, and simvastatin were adequately adjusted in 22/45 (48.8%), 22/35 (62.9 %) and 30/31 (96.8 %) patients respectively. Fenofibrate was associated with highest proportion of not adjusted doses 19/20 (95%), followed by oseltamivir and captopril, which were not adjusted in 5/8 (62.5%) and 3/5 (60%) of cases respectively.

Based on the age, data showed that greater proportion of inadequate dosing adjustment 168/303 (55.4%) was observed in patients aging 65 years and above.

Based on the GFR category, data showed that patients in stages 3a and 3b had a total of 76 and 78 drug orders, of which 25 (33%) and 28 (35.9%) were adjusted adequately. A total of 211/578 (36.5%) and 213/578 (36.8%) drug orders that required dose adjustment was prescribed to patients with stage 4 and 5 respectively.

Medication	Orders	Adjusted adequately		Adjusted inadequately		Not adjusted	
	n	n	%	n	%	n	%
All drugs	578	215	37.2	284	49.1	79	13.7
ACE-I*	42	24	57.1	7	16.7	11	26.2
Captopril	5	1	20	1	20	3	60
Ramipril	35	22	62.9	6	17.1	7	20
Beta blockers	202	28	13.9	169	83.6	5	2.5
Atenolol	6	4	66.6	1	16.7	1	16.7
Bisoprolol	196	24	12.2	168	85.8	4	2
Diuretics	16	3	18.7	12	75	1	6.3
Spironolactone	12	2	16.7	10	83.3	0	0
Thiazide diuretic	4	1	25	2	50	1	25
Antivirals*	9	4	44.4	0	0	5	55.6
Oseltamivir	8	3	37.5	0	0	5	62.5
Lipid-lowering agents*	63	41	65.1	1	1.6	21	33.3
Rosuvastatin	10	9	90	0	0	1	10
Simvastatin	31	30	96.8	0	0	1	3.2
Fenofibrate	20	0	0	1	5	19	95
Other drugs	246	115	46.7	95	38.6	36	14.6
Allopurinol	57	14	24.6	35	61.4	8	14
Gabapentin	5	3	60	2	40	0	0
Metoclopramide	45	22	48.8	16	35.6	7	15.6
Ranitidine	68	42	61.7	18	26.5	8	11.8
Pregabalin	10	6	60	2	20	2	20
Enoxaparin	25	5	20	13	52	7	28
Digoxin	21	12	57.1	8	38.1	1	4.8
Fluconazole	15	11	73.3	1	6.7	3	20

*. Medications that were less frequently prescribed (≤ 2) were not included in this table.

Table 3. Proportions of dosing adjustments per drug order according to different patient and hospital characteristics.

		Adjusted Adequately		Adjusted inadequately		Not adjusted	
		n	%	n	%	n	%
Age	Less than 65	118	42.90	116	42.20	41	14.90
	65 and above	97	32.00	168	55.40	38	12.50
Gender	Male	127	39.30	155	48.00	41	12.70
	Female	88	34.50	129	50.60	38	14.90
Reason for admission	Renal	28	43.10	27	41.50	10	15.40
	Non-renal	187	36.50	257	50.10	69	13.50
Floor	IM	104	42.40	105	42.90	36	14.70
	CCU	50	29.90	96	57.50	21	12.60
	ICU	31	33.30	47	50.50	15	16.10
	Other	30	41.10	36	49.30	7	9.60
GFR category	G3a	25	33.00	40	52.60	11	14.40
	G3b	28	35.90	43	55.10	7	9.00
	G4	74	35.10	104	49.30	33	15.60
	G5	81	38.00	101	47.40	31	14.60
Patient on dialysis	Yes	94	43.50	88	40.70	34	15.70
	No	121	33.40	196	54.10	34	12.40

Of the 211 drug orders, 74 (35.1 %) were adequately adjusted for patients with stage 4. Of the 213 drug orders, 81 (38 %) were adequately adjusted for patients with stage 5 (Table 3).

As per each patient, the average number of drugs received by one patient was calculated to be 2.59. The number of patients receiving at least one inappropriate drug dose was 188 accounting for 84.3% of 223 patients.

Multivariable analysis

The results of a logistic regression, taking the inappropriate vs appropriate drugs doses adjustment as the dependent variable, showed that patients aged 65 years and above had more drugs adjusted inappropriately compared to those aged less than 65 years (OR=0.64). Patients admitted to the CCU floor (aOR=1.384) had more drugs adjusted inappropriately compared to those who did not enter the CCU floor, whereas patients who were not on dialysis had more inappropriate drug adjustment compared to those who were on dialysis (aOR=0.586) (Table 4).

DISCUSSION

Several studies conducted worldwide have focused on the evaluation of medication dosing in patients with renal impairment. Yet, none of the published studies was, to our knowledge, carried in Lebanese hospitals. Our objective was to assess whether proper medication dosing was practiced at two university hospitals in Lebanon. The results of our study demonstrate that among 578 medication orders only 37% of prescription orders were adjusted adequately, and the remaining 63% of inappropriately dosed orders were divided into a majority adjusted inadequately with a rate of 49%, and 19% not adjusted at all. Moreover, among the 223 patients selected in our study, 84.3% received at least one medication without the correct adjustment dose.

Our results were comparable to those obtained by Declodt *et al.* who reported that 32% of 117 prescription

entries were adequately adjusted at a hospital in South Africa, and a slightly lower adequate adjustment rate when compared to 49% found by Getachew *et al.* in Addis Ababa, Ethiopia.^{10,16} Several studies had described rates of inappropriately dosed drug orders: Alahdal *et al.*, in a study conducted at a university hospital in Saudi Arabia, reported a rate of 53.1%, and another study in Paris by Salmon *et al.*, showed a rate of 34%, both rates were lower than the 63% obtained in our study.^{17,18} Altunbas *et al.* reported significantly lower rates of 12.6%, but the rate was explained by authors by the fact that the study patients had higher degrees of renal dysfunction, compared to other studies, and thus required nephrology consultation and more careful drug prescription.¹⁹ Another similar study was carried out at a governmental hospital in Palestine, indicated that only 26.42% of medications were found to be appropriately adjusted, compared to 73.58% inappropriately adjusted medication orders.²⁰

The rate of inappropriate prescriptions obtained in our study is considered to be high. Several reasons may contribute to inappropriate drug dosing in renal failure.^{16,19,21} These include not reviewing renal function tests before prescribing, which was reflected by the high number of exclusions due to missing serum creatinine level in our patients' charts. Moreover, physicians' lack of knowledge concerning all drugs that require dosage adjustment which was revealed here by the high rates of drugs "not adjusted at all". Furthermore, underestimating the impact of mild renal disease by physicians resulted in higher rates of inadequate adjustment in G3a/3b CKD stages versus more advanced disease stages.

We found a positive association between age greater than 65 years and inadequate dose adjustment; this can be attributed to polypharmacy and incorrect GFR estimation.^{10,22} It was noticed that patients admitted to the CCU had higher rates of inadequate adjustment. The latter finding can be explained by the fact that beta-blockers were among the most commonly prescribed class of medication requiring adjustment similar to the results

Table 4. Relationship between independent variables and percentage of at least one inappropriately adjusted drug orders.				
	Drugs adjusted inappropriately † Count (%)		P value	Odds Ratio (OR) ‡ 95% CI
	Yes	No		
Age			0.007*	0.65 (0.44, 0.95)
	Less than 65	157 (57.09) ^a	118 (42.91) ^b	
	65 and above	206 (67.98) ^a	97 (32.02) ^b	
Gender			0.235	0.97 (0.66,1.44)
	Male	196 (60.38) ^a	127 (39.62) ^a	
	Female	167 (65.49) ^a	88 (34.51) ^a	
Reason for admission			0.298	0.83 (0.45, 1.50)
	Renal	37 (56.92) ^a	28 (43.08) ^a	
	Non-renal	257 (57.88) ^a	187 (42.11) ^a	
GFR category			0.170	
	G3a	51 (67.10) ^a	25 (32.90) ^a	0.75 (0.34, 1.65)
	G3b	50 (64.10) ^a	28 (35.90) ^a	0.85 (0.43, 1.67)
	G4	137 (64.92) ^a	74 (35.08) ^a	0.85 (0.53, 1.37)
	G5	132 (61.97) ^a	81 (38.03) ^a	
Patient on Dialysis			0.015*	0.59 (0.36, 0.95)
	Yes	122 (56.48) ^a	94 (43.52) ^b	
	No	241 (66.57) ^a	121 (33.43) ^b	
Coronary Care Unit department		117 (70.06) ^a	50 (29.94) ^b	1.38 (0.73, 2.61)

†. Drugs adjusted inappropriately are the sum of inadequately adjusted and not adjusted at all.
 *. The Chi-square statistic is significant at the 0.05 level.
 ‡. The reference category is drugs adjusted adequately.
 Note: Values in the same row and subtable not sharing the same subscript are significantly different at p< 0.05 in the two-sided test of equality for column proportions. Cells with no subscript are not included in the test. Tests assume equal variances. Nagelkerke R²= 31.7%

obtained by Bailie *et al.*²³ Furthermore, the inadequate adjustment rate of beta-blockers in the present study was 83.6% far more than the 3.78% attained with Altunbas *et al.*¹⁹

Other finding in our study reported that dialysis patients had lower rates of inadequate adjustment. It seems that physicians were more careful in medication prescription, made appropriate dose adjustments, and more nephrologist consultations among dialysis patients were noted.²¹

This study was subject to some limitations. It was confined to two hospitals, which limits the generalizability of the results. The study was planned as a retrospective, cross sectional study, and thus, data collection may be vulnerable to missing and incomplete data, the method which prescribers used to assess the severity of renal impairment could not always be determined, and we did not evaluate the outcomes. The SCr value of 1.2 mg/dL is considered cut off point for patient inclusion, and this value, alone, cannot confirm the presence of renal impairment as those below 1.2 mg/dL may have severe renal impairment particularly in some special population such as very old or amputated patients. However, because hospital data lack consistent CrCl estimation rates, a cutoff point to start with was necessary. A cutoff point lower than 1.2 would have included huge number of non-CKD patients. Physicians may have referred to guidelines that are different from the ones we used in our study. In addition, the dose of some medications may be adjusted based on different endpoints other than estimated GFR. Moreover, the experience with the use of certain medications in renal dialysis patients is limited and no clear adjustment guidelines.²⁴ Lastly, GFR may become extremely difficult to estimate and unreliable in critically ill patients who experience rapidly changing renal function.¹⁶

In consideration of the high prevalence of CKD among medical inpatients, and the significant impact of improper dosing of medications, several methods have been suggested to improve drug dose adjustment recommendations. The collaboration with clinical pharmacists, who are uniquely trained in therapeutics and provide comprehensive drug management to both patients, physicians, and all members of the care team, has been shown to be a vital step towards improving patient care.^{17,25} Moreover, improving education, via standardization of prescription sources, updated prescription protocols, and pocket tables with dosing guidelines, as a complete interventional program, have been showed by Martinez-Anton *et al.* to reduce the rate of prescribing errors from 34.2% to 21.7%.²⁶ Furthermore, computerized systems are becoming significantly helpful in this area. It has been shown that using computerized physician order entry and clinical decision support system was able to decrease rates of medication dosing errors.¹⁹

CONCLUSIONS

In conclusion, the frequency of appropriate dosing adjustment as to renal clearance for all non-antimicrobial drugs in patients with CKD at two Lebanese university hospitals was low. Although the rates of inappropriate dosing were relatively low in statins and ACE inhibitors, it was fairly high in bisoprolol and ranitidine dosing. In Lebanon, problems at the organizational and professional levels are contributing to the incidence of medical errors and the associated suboptimal responses.²⁷ Therefore, increasing nephrology consultation rate and implementation of physician education programs may be helpful to reverse this trend.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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