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Drug Dosage Adjustment of Patients with Impaired Renal Function at Hospital Discharge in a Teaching Hospital

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ABSTRACT

Background: Inappropriate dosing and the risk of toxicities are common with the patients with impaired renal function. Therefore, appropriate dosing is obligatory to prevent the drug toxicities. The present study was performed to investigate the appropriateness of dosage adjustment of the drugs that are toxic to kidney and/or metabolized or eliminated (TEM) by kidney.

Methods: A retrospective studywas performed at the time of hospital discharge in the patients with impaired renal function. All patients with renal clearance ≤50 ml/min/1.73 m^2 were included for the analysis. Data with respect to patient's clinical, medications and their dosages, laboratory findings were extracted from medical record section.

Results: At discharge, there were a total of 848 prescribed drugs in 116 impaired renal function patients. Of them 404 were classified as TEM medication. Dose adjustment according to renal function was judged as necessary in 135 TEM medications and 28 were deemed to be used with caution. Among these, 108 (80% of 135) medications were considered appropriate in dosing, whereas 27 (20%) were inappropriate. Total 14 (10.37%) and 13 (9.63%) times of inappropriate dosing were found in those with moderate and severe renal impairment, respectively. The frequency of inappropriate dosing was not significantly different from moderate than that of the severe renal impairment ($p > 0.05$).

Conclusions: The results of the study demonstrated that dosage adjustment of TEM drugs in patients with impaired renal function is less than optimum in a considerable number of patients at hospital discharge. Awareness raising and monitoring system for inappropriate dosing is critical to improve the quality of care in patients with renal dysfunction.

Keywords: dose adjustment; renal drugs; renal impairment.

INTRODUCTION

Several studies have indicated that dosing error and the risk of toxicity are common with the patient with renal impairment.[1,2] The frequency of adverse drug effects increases with the number of medications used, degree of renal dysfunction, age of patients, and number of co-morbidities.[3,4] Many medications and their metabolites are eliminated through the kidney. Incorrect dosing of such drugs can cause adverse drug events (ADEs) ranging from mild discomfort to serious injuries. For instance, Imipenem and Cilastatin may excessively accumulate in renal impaired patients leading to seizures if doses are not reduced.[5]

Adverse drug reactions are responsible for about 7% of all hospital admissions.[6] Most of the drug related problems (50%-73%) are detectable and preventable, often caused by dosing errors.[7] On the other hand, dosage adjustment can result in minimization of morbidity caused by excessive dosing, save the cost and prevent drug-related toxicity.[8] Despite the importance of dosage

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adjustment among patients with renal impairment, such adjustments are rarely made.[9,10] The current study was aimed to investigate the frequency of inappropriate dosing according to the degree of renal impairment of the patients at hospital discharge.

METHODS

This study was carried out at Tribhuvan University Teaching Hospital (TUTH), the largest tertiary hospital in Nepal with over 500 beds.The research design was a cross-sectional retrospective study. All patients with renal impairment discharged between February 2012 and March 2013 were enrolled. Renal impairment was defined as having an estimated glomerular filtration rate (eGFR) ≤50 ml per minute per 1.73 m^2. All TEM classes of drugs administered to the patients on a daily basis were considered for evaluation. Medications with potential nephrotoxicity and/or elimination through renal excretion or metabolism were designated as TEM medications. Serum creatinine (SCr) was extracted from the record of laboratory data. For the patients who had more than three SCr values, the one closest in time before starting the renally eliminated drug(s), was used as a reference for the estimation of renal status. The dose per day of a prescribed drug was calculated by multiplying the unit dose (mg) and frequency. Renal failure was defined as having creatinine clearance less than 50 ml/min and was subdivided into 3 category: mild (30-50 ml/min), moderate (10-29 ml/min) and severe (<10 ml/min). The Cocroft- Gault equation was used for the estimation of creatinine clearance (CrCl). The study variables included age, sex, serum creatinine, weight, medications and their corresponding doses. For each patient, the total numbers of medications were identified in each prescription. Prescription of any TEM medication was judged 'inappropriate' when the dosage was not in compliance with the adjustment required with regard to the patient's CrCl.[11]

The reliability on the judgment of the appropriateness of dosage adjustments was assessed using Kappa statistics calculated from the independent evaluation of dosage adjustments made by clinical experts in 82 medications prescribed in 20 renal impaired cases. Kappa value was 0.817 implying high agreement of judgment between two raters.

A descriptive analysis was made for age, body weight, creatinine value (mg/dL), days of hospital stay and average prescribed drugs per prescription. Chi-square test was applied to test the relationship between renal status and dosage adjustment. A p-value <0.05 was considered statistically significant. Data were analyzed using PSPP free software program.

The study proposal was ethically cleared by the Nepal Health Research Council (Ref. no.1137) and the permission was given by the hospital administration for the data collection.

RESULTS

Of the 116 patients identified as having moderate to severe renal impairment, 75 (65.25%) were men. The subjects had an average age of 47.47±15.55 years (range 18-66 years) with mean SCr 5.16 ± 1.93 mg/dLand the mean CrCl 15.10 ± 7.05 mL/min/1.73 m^2 (range 2.09-32.45). Most of the patients 74 (62.41%) were having moderate renal dysfunction while 42 (37.29%) having severe renal impairment.

Table 1. Patient characteristics.

Variables	
Number of patients	116
Age, mean ± SD (years)	47.47 ± 15
Male, n (%)	75 (65.25)
Female, n (%)	41 (64.75)
SCr (mg/dL), range	5.16 (2.17-9.80)
CrCl (mL/min/1.73m2), mean ± SD	15.10±7.05
Moderate renal failure, n (%)	74 (62.41)
Severe renal failure, n (%)	42 (37.29)
Average no. of drugs per patient at hospital discharge, mean ± SD	6.78 ± 2.23
Average no. of TEM drugs per patient at hospital discharge, mean ± SD	3.42± 1.25
Average no. of TEM drugs needing dose adjustment mean ± SD	1.65 ± 0.88

A total of 848 medications were prescribed for 116 patients with impaired renal function, with an average of 6.78 medications per patient (Figure 1). Among these, a total of 404 drugs were classified as TEM drugs (Figure 1). Overall, the average number of TEM medications per patients was 3.42 ± 1.25 (range: 2-7). According to the guidelines for dosage adjustment, a total of 163 TEM medications need dose adjustment or should be used with cautions.

The appropriateness of dosage adjustment for TEM drugs were assessedat hospital discharge: 80% of TEM medications were dosed appropriately, while 20% was inappropriate (Table 2).

Of 135 TEM medications needed dose adjustment, 90 and 45 drugs were prescribed for the patient with moderate and severe renal impairment respectively at hospital discharge. Analysis showed that 10.37% and 9.63% of drugs were inappropriately dosed for moderate and severe cases respectively (Table 2).

Table 2. Pattern of appropriate and inappropriate drugs at hospital discharge.

Drugs	Frequency of prescribing	Inappropriate dosage adjustment		n (%)	P (x^2)
		Moderate (a) impairment	Severe (b) impairment		
Digoxin	1	0	0	0 (00)	
Aml-At	6	2	1	3 (50)	1.00
Bisoprolol	1	0	0	0 (00)	
Met-Ram	1	0	0	0 (00)	
Atenolol	19	2	1	3 (15.79)	0.94
Enalapril	6	0	0	0 (00)	
Clonidine	6	1	0	1 (16.67)	0.27
Enoxaparin	1	0	0	0 (00)	
Rosuvastatin	1	0	0	0 (00)	
Tramadol	1	0	0	0 (00)	
Codein+ PCM	2	0	0	0 (00)	
Gabapentin	2	0	0	0 (00)	
Colchicine	3	1	1	2 (66.67)	0.39
Allopurinol	8	0	0	0 (00)	
Metoclopramide	2	0	0	0 (00)	
Leveteracetam	1	0	0	0 (00)	
Tranexamic acid	1	1	0	1 (100)	
Ranitidine	4	1	1	2 (50.00)	0.25
Cetrizine	1	0	1	1 (100)	
Amikacin	1	0	0	0 (00)	
Norfloxacin	1	0	0	0 (00)	
Ciprofloxacin	1	0	0	0 (00)	
Levofloxacin	1	0	0	0 (00)	
Clarithromycin	1	1	0	1 (100)	
Amoxicillin	1	0	1	100	
AMX-CLV	2	0	2	2 (100)	
Metronidazole	4	0	0	0 (00)	
Cefixime	12	5	4	9 (75)	0.16
Cefadroxil	1	0	0	0 (00)	
Cefpodoxime	12	0	0	0 (00)	
Ethambutol	8	0	1	1 (12.50)	0.17
Pyrazinamide	9	0	0	0 (00)	
Sulfamethoxazole	5	0	0	0 (00)	
Fluconazole	4	0	0	0 (00)	
Cyclophosphamide	2	0	0	0 (00)	
Lamivudine	3	0	0	0 (00)	
Total	135	14 (10.37)	13 (9.62)	27 (20)	

Note: a:moderate renal function patients (CrCl: 29-10 mL/min/1.73 m2) b: severe renal function patients (CrCl<10 ml/min/1.73m2), Aml-At: amlodipine-Atenolol, Met-Ram: metoprolol-ramipril, AMX-CLV: Amoxicillin-Clavulanic acid, PCM: Paracetamol

Atenolol was the most frequently prescribed cardiovascular drugs that needed dosage adjustment (19/135) followed by Clonidine (6/135), Enalapril (6/135), Digoxin (1/135), Enoxaparin (1/135), Bisoprolol (1/135) and Tranexamic acid (1/135) respectively. The dose was considered inappropriatein 15.79% of Atenolol prescription, followed by that of Clonidine (16.67%). In medications for arthritis and gout, 66.67% of Colchicine dose was not adjusted properly.

About 46% (63/135) of the prescribed TEM drugs requiring dose adjustment were antimicrobials including Cephalosporin (18.51%), anti-tuberculosis (22.95%), antifungal (2.96%), SMZTMP (3.7%), Quinolones (2.22%), Aminoglycoside (0.74%), Macrolides (0.74%). Among the prescriptions of the TEM antimicrobials, 75% of Cefixime, 100% of Amoxicillin/Clavulunic acid, 100% of Amoxicillin, 100% of Clarithromycin, 12.50% of Ethambutol were inappropriately dosed at hospital discharge (Table 2).

The frequency of inappropriate dosing of the TEM drugs was not significantly different between patients with moderate renal impairment and those with severe impairment ($p>0.05$).

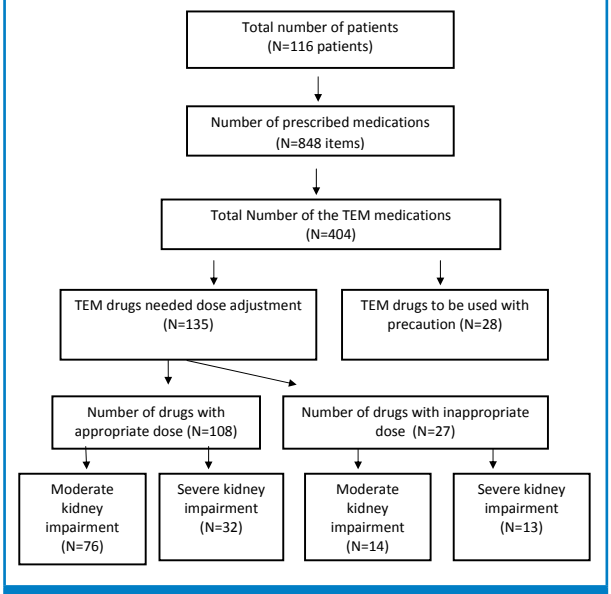

Figure 1. Appropriateness of dosing of the TEM medications in the study.

DISCUSSION

Several pharmacokinetic parameters are adversely affected in Chronic Kidney Disease (CKD), secondary leading to a reduced oral absorption, glomerular filtration rate, altered tubular secretion, reabsorption and changes in intestinal, hepatic and renal metabolism,[12] subsequently leading to exaggerated pharmacologic activity and toxicity. Therefore, appropriate adjustment of the dose may assist to individualize the drug therapy according to the renal function and could contribute to the drug safety. The several studies have shown that there are widespread overdosing rates in the hospitalized patient.[10,11,13] Van Dijak et al. found that 41.1% drugs were not properly adjusted at hospital discharge.[14] In our study, we found that 20% of the TEM drugs at hospital discharge were inappropriately dosed in patients with renal dysfunction. The reason behind the lower rate of inappropriate dosing in our study could be the application of the maximum limit on per day basis for judging overdosing. Our study showed that Atenolol, Clonidine, Colchicine, Ranitidine, Cetrizine, Clarithromycin, Amoxicillin-Clavulunic acid, Cefixime, Ethambutol were marked with higher dose than recommended at hospital discharge. Each patient with renal impairment received an average of 3.42±1.25 TEM medications. Apparently, 20% of the drugs were inappropriately dosed, reflecting that renal function was not a prime consideration in many occasions by the prescribers. There are many explanations for such findings.

Physicians may not review the result of the renal function test because of the overwhelming of the other clinical information. Furthermore, it is obvious that CrCl should be calculated and documented for all of the patients with impaired renal function for the benefit of dosage adjustment. The calculation of CrCl with the Cocroft and Gault formula taking into account patient's weight, age and SCr provides an accurate assessment of the renal function. Prescriber might have used different methods from the one in the study to assess the renal impairment, such as the one using only serum creatinine as an indicator of renal impairment rather than calculating CrCl. Moreover, clinicians may not exclusively consider the dose regimen based on the pharmacokinetic parameters for some drugs like beta-blocker (Atenolol), ACE inhibitor (Enalapril), instead it may require to adjust according to the clinical outcomes such as blood pressure and heart rate of the patients.

As a result of the problems identified in this study, a strategy towards the education and awareness raising regarding the dosage adjustment of the TEM drugs among the health care team could be helpful to reduce the problems. Furthermore, implementing the computing system would be the best strategy to providing the lab data in the form that is convenient to be used by prescribers to assess and monitor renal function of the patients, thereby, reducing the inappropriate dosing.[15,16] Moreover, having a clinical pharmacist to review medication profiles and frequent monitoring the creatinine clearance according to the lab data would be the another solution to minimize the dosing error.

CONCLUSIONS

The results of the study demonstrate that the information on renal function is underused by the physicians in the prescribing of the TEM drugs during hospital discharge in a considerable number of patients with renal dysfunction. Such patients are at risk to develop adverse outcomes. Thus, in light of this information, strategies should be made to increase the compliance of the dosing guideline to avert the potential hazardous effects.

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