Research Article

Drug Dose Adjustment Practices in Patients with Renal Impairment at Ayder Referral Hospital, Mekelle, Northern Ethiopia

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Accepted on: 10-12-2014; **Finalized on:** 31-01-2015.

ABSTRACT

Significant renal impairment requires dose adjustment for certain drugs to avoid toxicity. The objective of this study was to assess the drug dose adjustment practices in patients with renal impairments in Ayder Referral Hospital, Mekelle, Ethiopia. A cross sectional study was carried out using patients' medical records in Ayder Referral Hospital from August 2012 to February 2013. Patients with serum creatinine level ≥ 1.2 mg/dL were purposely selected in the first stage of the study. The modification of diet in renal disease equation was used to calculate creatinine clearance. Patients with creatinine clearance of ≤50 mL/min were considered to have renal impairment and included for further processing. Based on the calculated creatinine clearance, the prescribed doses were compared to the recommended dose in renal failure. Among 422 patients, renal impairment was identified in 231 (54.7%) of patients. There were a total of 849 prescription entries for the 231 patients with renal impairment. Among the prescribed drugs, 42.5 % of them required dose adjustment for renally impaired patients. Of the drugs that require dose adjustment, 51% were inappropriately ordered (46.6% prescribed with inappropriate dosage and 4.4% being contraindicated). Dose adjustments were rationally performed in 49 % of the drugs. The group of drugs that needed dose adjustment was anti-microbial (59.2%) with ciprofloxacin being the most frequently prescribed one. Dosing errors were common among patients with impaired renal function in this study. Lots of work shall be done to alert clinicians about the need for dose adjustment in renal impairment.

Keywords: Renal impairment; dose adjustment; creatinine clearance; serum creatinine

INTRODUCTION

Effective drug therapy involves the delivery of an active drug to its site of action through absorption and distribution, followed by inactivation and removal of the drug from the body by metabolism and excretion.[1] The two principal organs responsible for the elimination of drugs and their metabolites from the body are liver and kidney.[2] Kidney is the main organ for keeping fluid and electrolytes balance as well as plays an important role in the disposition of many drugs.[3] The excretion of many drugs and their toxic metabolites depends on normal renal function.[4] Reduction in the normal function of kidney leads to accumulation of parent and toxic metabolites of drugs, which in turn increase the risk of different adverse effects.

Kidney disease is increasingly recognized as a significant health issue in the population. The incidence and prevalence of kidney failure are rising.[5] Chronic kidney disease compromise renal drug elimination and as a consequence there is toxicity associated with drug accumulation in the body. There are many drugs which require dose adjustment based on the degree of impairment of renal function. However, drug dosing errors are common in patients with renal impairment particularly in older patients.[6,7] Therefore, depending on the severity of renal dysfunction, the normal dosage regimen of a drug that is prescribed to renal patients has to be adjusted.[2] Dose adjustment is mostly important for drugs for which the fraction excreted unchanged is high[8,9], and for some drugs with narrow therapeutic window.[10]

Up to present, evaluating Glomerular Filtration Rate (GFR) has been the most reliable index and surrogate marker of overall kidney function.[11] It is generally accepted as the best overall measure of the functioning renal mass in both healthy and diseased states.[12]

The most convenient method to estimate the GFR is by calculating creatinine clearance (Crcl) based on serum creatinine concentration and requires only a single blood sample.[2]

Although several texts provide guidelines for drug administration in patients with renal insufficiency, there are limited data on the extent of applications in clinical practice in Ethiopia. To our knowledge there are only few studies which were performed in general hospitals of Ethiopia.

The aim of this study was, therefore, to assess the drug dose adjustment practices in patients with renal impairments in Ayder Referral Hospital (ARH), Mekelle, Ethiopia.

MATERIALS AND METHODS

The study was conducted in ARH located in Mekelle town, the regional state of Tigray, which is 783 km away from the capital city of Ethiopia, Addis Ababa. ARH is 400 bed teaching and referral hospital and it is the only referral hospital in the region. It provides general outpatient,

inpatient and emergency services for about eight million people in Tigray and neighboring regions.

A cross-sectional study was conducted from August 2012 to February 2013 by reviewing patients' medical record after obtaining the ethical clearance from college of health sciences research and community service council, Mekelle University and permission from the hospital administration. The patient records were anonymized and de-identified prior to analysis. All the patients that fulfilled the inclusion criteria: age ≥16 years, serum creatinine level (Scr) of greater than or equal to 1.2 mg/dL, and patients prescribed with drugs were included in the study. A Scr value of 1.2 mg/dL was considered the upper normal value for Scr in clinical practice.[9] Most drugs need dosage adjustment when CrCl falls below 50 ml/min.[5] Therefore, CrCl was calculated for all patients and those with ≤ 50 ml/min were included in the final analysis.

The CrCl was calculated using the modification of diet in renal disease (MDRD) equation due to the reason that MDRD equation is based on more easily available information (gender, age, race and Scr) and it is a more practically useful method. For that matter it has been recommended as the preferred method recently.[5,13]

GFR (ml/min per 1.73 m^2) = 186 x $Scr^{-1.154}$ x $age^{-0.203}$

(Eq.1) multiplies if female by 0.742 and multiplies for black by 1.210.[14]

Dosages, dosing intervals and dose adjustments of the prescribed drugs were investigated based on the calculated CrCl. These were evaluated using the dose adjustment guidelines; drug prescribing in renal failure and dosing guidelines for adults[15], to assess whether they were appropriately adjusted according to the patient's renal function.

RESULTS AND DISCUSSION

Demographic Data of the Patients

Table 1: Age and sex distribution of the participants in ARH from August 2012 to February 2013

Age category	Sex		Total (%)
	Male	Female	
16-29	60	58	118 (28)
30-45	72	47	119 (28.2)
46-65	88	47	135 (32)
>65	30	20	50 (11.8)
			422 (100)

A total of 422 patients were included in this study (Table 1). Among the participants 59.2 % were male and the rest were female. The age of the study participants was in a range of 16–93 years, with mean age ± SD was 42.90 ± 17.340. Majority of the patients (32%) were in the age range of 46-65.

Occurrence of Renal Impairment

Of the total sample size, 231(54.7%) were found to have renal impairment (CrCl ≤ 50 ml/min) (Table 2). In a similar study by Sweileh and his coworkers[9] done in Palestine, a total of 91 patients with Scr >1.2 mg/dL were identified and 78 (85.7%) patients had a calculated creatinine clearance ≤ 59 ml/min. Higher percentage of patients found in the later study may be due to the higher cutoff point used in CrCl. The mean Scr level for the renally impaired patients was found to be 3.94 ± 3.02 (range: 1.4–14.4) (Table 2). This result is quite above the results obtained in a study done by Emami and coworkers[8] and Fahimi and coworkers[13] with values of 2.3 ± 2.0 (1.0-16.0), and 2.5 ± 1.9 (1.1-16.4), respectively. The higher value of Scr in this study suggests that patients come to the hospital after severely diseased. The mean CrCl of the patients was 28.84 ± 14.5 ml/min (range: 5–50). This is in agreement with a finding by Soetikno and his coworkers[16] which was 26.06 ± 12.44 ml/min.

Table 2: Renal function index in ARH from August 2012 to February 2013

Patient Characteristics	Mean ± SD
Scr (mg/dl)	3.94 ± 3.02
Crcl (ml/min)	28.84 ± 14.5
Creatine clearance category	Number (%)
10-50	198 (85.7%)
<10	33 (14.3%)

As it is presented in Table 3 below, the age range of the study participants with renal impairment was 17–93 years; with an average age ± SD was 45.23 ± 17.7. This result is a bit skewed to the aged ones. This might be due to the decline in renal function as a result of physiological and structural changes in the kidney that occur with aging.[10] It is a general fact that with an increase in age the possibility of renal impairment is higher. This is in line with the statement made by Greenberg and his coworkers[17] that elderly patients are at a higher risk for drug toxicity than adult age group. However, in this study a large percentage (35.5%) of patients with renal impairment was found in the age group of 46-65 than above 65 years old (15.2%). This discrepancy might be due to involvement of small number of elderly patients in the total sample.

From the data of the same Table, it can be easily understood that males seemed to be more prone to renal impairments than females. This is in line with the study done by Emami and his coworkers[8] with greater ratio of male to female (86:56). This difference in susceptibility to renal impairments based on gender could be attributed to the fact that, on average, women have a lower muscle

mass that results lower Scr and, thus, elevated GFR than men.[18]

Table 3: Distribution of renally impaired patients by age and sex in ARH from August 2012 to February 2013.

Patient Characteristics		Number (%)
Sex	Male	126 (54.5%)
	Female	105 (45.5%)
Age category		
	16-29	55 (23.8%)
	30-45	59 (25.5%)
	46-65	82 (35.5%)
	>65	35 (15.2%)

Appropriateness of overall drug dosages according to the Renal Function

There were 849 drugs prescribed for the 231 renally impaired patients. By considering the renal function of the patients, dose adjustment was required for 42.5% of the drugs. This is in agreement to Alahdal and Elberry[3] where 39% of the drugs prescribed for renally impaired patients required dose adjustment. The high prevalence, in both cases, might be because of the fact that nearly half of all drugs or their metabolites excreted via the kidney[3].

In this study, out of the 361 drugs which require dose adjustment 46.6% (Table 4) were not adjusted on top of the presence of 4.4% drugs which are totally contraindicated in patients with renal impairment. In a similar study conducted in the university hospital of Iran, it was found that proper dose adjustments were not performed in 54.4% of the case[9]. Another study conducted in France revealed that 34% of patients' prescriptions were with inappropriate dosage in addition to 14% being contraindicated[19]. Several explanations may be elucidated for the lack of dose adjustment practices. One of the reasons may be due to physicians' underestimation of the consequences of mild renal impairment in terms of subsequent iatrogenic risks or their poor knowledge of the medications requiring adjustment in the renal impairment[19]. Another reason could be prescribers might not estimate and review renal function results before prescribing. This is statement is supported by the finding obtained from a study done by Salomon and his coworkers[20] who assessed the resident's prescribing behavior in renal failure. According to this study, it was only a few residents (5%) requested drug dosage checking for patients with elevated serum creatinine and 35% of the physicians performed dosage adjustments only for Scr above 1.7 mg/dL. However, patients with less than this value can have a very low CrCl and necessitate dose adjustment. Moreover, the large number and the continuously increasing list of drugs that required dose adjustment makes it difficult for medical staffs to remain updated on the dose adjustment issues of individual drugs.

Table 4: Percentage of adjusted, non adjusted and contraindicated drugs prescribed for renally impaired patients in ARH from August 2012 to February 2013

Category	Frequency	Percent (%)
Adjusted drugs	177	49%
Non adjusted drugs	168	46.6%
Contraindicated drugs	16	4.4%
Total	361	100%

Appropriateness of Class of Drugs Prescribed

In the present study, the most common groups of drugs that required dose adjustment were anti-microbials (59.2%) followed by cardio-vascular (15.2%) and gastro-intestinal drugs (14.5%) (Figure 1). This result is supported by the results found by Alahdal and Elberry[3], that antibiotics (39.8%) were the most common group of drugs requiring dose adjustment. The possible reasons could be admissions in critical care unit that need empiric antibiotics, and preoperative use of antibiotics for prophylaxis in surgical wards among other reasons.[21]

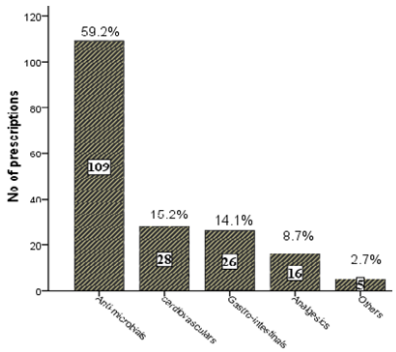

Figure 1: Class of drugs prescribed inappropriately for renally impaired patients in ARH from August 2012 to February 2013

Appropriateness of individual drug prescribed

As it is shown in Table 5, Ciprofloxacin (16 times), metochlopramide (15 times) and diclofenac (14 times) were the three most inappropriately dosed drugs. In a study by Falconnier and his coworkers[22], digoxin, amoxicillin, ciprofloxacin, flucloxacillin, and acyclovir were found to be the most inappropriately dosed drugs.

Among the drugs which were totally unadjusted in all cases, lamivudine were prescribed more frequently (13 cases) followed by Gentamicin, cephalexin, fluconazole and metformin, each was prescribed 3 times. A study from Saudi Arabia found augmentin, cotrimoxazole, glibenclamide, metochlopramide and atenolol were totally unadjusted drugs.[3]

Of the most frequently prescribed drugs, enalapril was the most adjusted (83.9%) one. A different result was obtained by Decloedt and his coworkers[14] where ethambutol was the most adjusted drug.

Sixteen contraindicated drug orders in renal failure were identified for tenofovir, spironolactone and aspirin (Table 5). However, in a study by Emami and his coworkers[8] nineteen contraindicated drug orders were obtained for the following four drugs: spironolactone, glyburide, metformin and phenazopyridine. In both studies, looking into individual drugs, there were differences in the type of inappropriately prescribed as well as contraindicated drugs. This profound variation may be attributed to the variation in prevalence of disease type, formulary of individual country, and/or the use different guidelines' recommendations on drug dosage adjustment in renal impairment.

Drugs with Potential Nephrotoxicity

The finding of this result also indicates that there are nephrotoxic drugs prescribed such as gentamicin and NSAIDs (diclofenac and aspirin) (Table 5).

Table 5: The rate of prescribed drugs which needed dose-adjustment using guidelines in ARH from August 2012 to February 2013.

Drugs	Adjusted drugs (n)	Non-adjusted drugs (n)	Contraindicated drugs (n)
Acyclovir	-	2	-
Allopurinol	1	2	-
Amoxicillin	4	8	-
Aspirin	7	-	2
Atenolol	6	4	-
Augmentin	3	3	-
Captopril	2	-	-
Cefotaxime	1	-	-
Ceftazidime	1	5	-
Cephalexin	-	3	-
Cimetidine	21	11	-
Ciprofloxacin	9	16	-
Clarithromycin	7	13	-
Diclofenac	8	14	-
Digoxin	2	4	-
Enalapril	26	6	-
Ethambutol	7	10	-
Fluconazole	-	3	-
Gentamicin	-	3	-
HCT	16	5	-
Lamivudine	-	13	-
Metformin	-	3	-
Methyl dopa	2	2	-
Metoclopramide	8	15	-
Norfloxacin	9	5	-
Pen.G	1	1	-
Rifampin	12	4	-
Spironolactone	14	4	5
Stavudine	-	1	-
Tenofovir	-	-	9
TMP/SMX	8	5	-
Vancomycin	2	5	-
Total	177	168	16

n = number of drugs

Patients with poor kidney function are at increased risk of developing kidney injury from nephrotoxic medications. In the contrary to this study, Soetikno and his coworkers[16] in Indonesia found that only in few cases where nephrotoxic drugs such as aminoglycosides were prescribed. This difference may be due to the status of the hospital (i.e., drug prescriptions in hospitalized patients, particularly with renal dysfunction, are closely monitored either by residence on ward or by supervisors and/or the use of well developed guidelines for dose adjustment during renal failure).

CONCLUSION

Renal impairment was occurred in 54.7% of the patients. 42.5% of the studied drugs required dosage adjustment based on patients' renal function. Of all the "must to adjust" drugs, 46.6% of them were with inappropriate dosage and 4.4% were contraindicated. The most common group of drug that need dose adjustment was anti-microbial with ciprofloxacin being in the forefront. The most nephrotoxic drugs prescribed includes gentamicin and NSAIDs (diclofenac and aspirin). This study showed that dosing errors are common among patients with impaired renal function. From this we can grasp the idea that prescribers do not give due attention about patients' renal function while they are prescribing. Lots of work shall be done to alert clinicians about the need for dose adjustment in renal impairments. On the top of that, we strongly recommended continuous presence of clinical pharmacist at physician round to review all medications as an effective solution to reduce dosing errors and overall improvements in pharmaceutical care.

Acknowledgement: We would like to acknowledge both the ARH laboratory and patient card archive staffs.

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Source of Support: Nil, **Conflict of Interest:** None.