PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2007; **16**: 908–912
Published online 26 April 2007 in Wiley InterScience (www.interscience.wiley.com) **DOI**: 10.1002/pds.1412

ORIGINAL REPORT

Medication dosing errors in hospitalized patients with renal impairment: a study in Palestine†

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SUMMARY

Background and Aim Reduced renal function requires dose adjustment for certain drugs to avoid toxicity. The aim of this study was to determine whether appropriate dosage adjustments were made for drugs that are nephrotoxic, excreted, or metabolized (TEM medications) by the kidney in patients with renal impairment.

Methodology A cross-sectional study of a group of hospitalized patients was carried out at Al-Watni governmental hospital, Nablus, Palestine. All patients with creatinine clearance $\leq$59 ml/min were included in the analysis. Data regarding patients' clinical, laboratory findings and medications whether they were prescribed at hospital or at discharge were collected from patients' medical files. Evaluation of appropriate dosing was based on Physician Disk Reference (PDR). All data were collected for further research and subsequent statistical analysis using statistical package for social sciences (SPSS) for windows version 10.

Results A total of 78 patients had calculated creatinine clearance $\leq$59 ml/min. Those patients were prescribed a total of 1001 lines of prescription medication. Dosage adjustment was necessary for 193 TEM medications. Analysis of TEM medications with guidelines for adjustment indicated that 73.58%(142) were found to be inappropriate and 26.42% (51) were found to be appropriate. The most common inappropriate medications were ranitidine, antibiotics, and digoxin. Approximately 77.5% of the unadjusted medications were prescribed during hospitalization.

Conclusion In our study, a wide range of dosing errors was common among patients with renal impairment that was common during hospitalization. Continued medical education in the field of clinical pharmacokinetics is important for physicians. Copyright © 2007 John Wiley & Sons, Ltd.

KEY WORDS — dose adjustment; renal impairment

Received 9 August 2006; Revised 21 February 2007; Accepted 19 March 2007

INTRODUCTION

Renal impairment is a common health problem among elderly patients.[1] Many medications are detoxified and eliminated through the kidney and thus adequate renal function is important to avoid toxicity. The proper dosing of medications for patients with renal impairment can maximize therapeutic efficacy, minimize toxicity and cost.[2–5] Dose adjustment becomes very important when dealing with medications with potential nephrotoxicity and/or elimination through renal excretion or metabolism designated as TEM medications.

Studies have shown that an adverse drug event increases the length of hospitalization and con-

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sequently increases cost.[4,5] Despite the importance of dose adjustment among patients with renal impairment, such adjustments are rarely made.[6–8] A major reason for inappropriate dose adjustment is the underestimation of potential adverse consequences. Examples of drugs requiring dose adjustment in patients with renal impairment mostly include antibiotics, digoxin, H_2-receptor antagonists, and angiotensin converting enzyme inhibitors (ACE-I).[9] Dose adjustment in renal impairment can be accomplished by estimating creatinine clearance and adjusting the dose and/or dosing interval according to Physician Disk Reference (PDR).

This study was designed to determine whether appropriate dosage adjustments were made for TEM medications prescribed for hospitalized patients with renal impairment.

METHODOLOGY

This cross sectional study was conducted at Al-Watni governmental hospital, Nablus, Palestine, a medical hospital of 100 beds providing primary care to beneficiaries of governmental medical insurance. The data were obtained from patients'medical files at the internal ward after obtaining permission from the hospital administration. For a period of 4 months, all patients admitted to the internal ward who were prescribed at least one medication, hospitalized for $\geq$one night and had a serum creatinine level $>$ 1.2 mg/dL were included in the study. The choice of serum creatinine level $>$ 1.2 mg/dL as a cut off point in pre selection rather than creatinine clearance was based on several reasons. First; serum creatinine values were available in the patients' medical files, however, neither body weight nor creatinine clearance were available in the patients' medical files. Second, although body weight and CrCl were measured and calculated by the researchers for each admitted patient, the serum creatinine value is the only laboratory value available for the physician in the patients' medical files. So using the serum creatinine (SCr) values will mimic the current situation in the hospital. Finally, an SCr value of 1.2 mg/dL is considered the upper normal value for SCr in clinical practice.

On the basis of the guidelines of the National Kidney Foundation, renal impairment is classified into five stages. Patients included in the analysis were those who belonged to stages 3, 4 and 5. Patients in stage 1 or 2 who usually have adequate kidney function were not included. Creatinine clearance was calculated for all patients and those with CrCl $\leq$59 ml/min were included in the analysis. Creatinine clearance was calculated using the Cockroft Gault equation. CrCl $\leq$59 ml/min was considered the threshold for renal impairment. Patients included in the analysis belonged to the following stages of renal impairment: stage 3 (CrCl 30–59 ml/min), stage 4 (CrCl 15–29 ml/min), and stage 5 (CrCl $<$ 15 ml/min). The following parameters were collected for all patients included in the study: age, gender, SCr, serum glucose level, blood urea nitrogen (BUN), co-morbid condition, weight, medications prescribed during hospitalization and at discharge, and their corresponding doses.

For each patient, the total lines of prescriptions were identified in each order. Medications with potential nephrotoxicity and/or elimination through renal excretion or metabolism were designated as TEM medications. Based on updated drug references, some TEM medications require dose adjustment and some do not. The regimen for any TEM medication was rated 'appropriate' when the dosage was suitable based on the patient's CrCl. Prescription of any TEM medication was rated 'inappropriate' when the dosage prescribed was not in conformity with the adjustment required with regard to the patient' CrCl. All 'inappropriate' TEM medications were distributed based on renal impairment category, and whether they were prescribed at the hospital or at discharge. The reference used to check for the appropriateness of the dose was the PDR and the Drug Information Handbook. Administered doses of each studied drug were compared with the recommended doses. We examined the variables of age, sex, SCr, and weight to determine whether they were individually correlated with dosing error. All data were entered into the Statistical Package for Social Sciences Program (SPSS) and analyzed descriptively, and Chi-square with the classical P value of $<$0.05 was used.

RESULTS

A total of 91 patients with SCr $>$1.2 mg/dL were identified during the 4-months study period. Based on the inclusion criteria, a total of 78 patients were considered for evaluation. Those 78 patients were designated as the renal impairment group which consisted of 47 men and 31 women. The renal impairment group had a mean age of 62.88 $\pm$ 12.09 years (range: 21–96 years). The mean SCr level for the renal impairment group was 2.66 $\pm$ 2.4 mg/dL (range: 1.22–16.41) and the mean CrCl was 35.86 $\pm$ 14.98 ml/min (range: 5.5–59). Most of the patients (52) were in stage 3 and 17 patients were in stage 4. Few patients (9) were in

DOI: 10.1002/pds

Table 1. Patterns of prescribing appropriate and inappropriate TEM medications

Drugs	% Dose increase	Appropriate TEM	Inappropriate TEM				Inappropriate	
			Stage 3 ($n=52$)	Stage 4 ($n=17$)	Stage 5 ($n=9$)	Total	At hospital	At discharge
Ratio		0.6	1.5	2.5	2.6			
Ranitidine	200–300	2	55	25	7	87	62	25
Antibiotics	200–300	12	3	10	9	22	20	2
Digoxin	200–300	15	8	0	0	8	7	1
Other CV drugs	200–400	15	4	3	5	12	11	1
Metoclopromide	150–200	0	2	3	1	6	5	1
Others	>100	7	5	1	1	7	5	2
		51	77	42	23	142	110	32
	Total		193			Total	142	

stage 5 (Table 1). Cardiovascular diseases such as hypertension (HTN), congestive heart failure (CHF), and ischemic heart diseases (IHD) were present in approximately two-thirds of the patients, while diabetes mellitus was present in one-third of the patients. Most patients were hyperglycemic and uremic upon admission.

The total number of lines of prescriptions for the patients in the renal impairment group was 1001, an average of 12.83 medications per patient. Analysis of all medications showed that a total of 774 belonged to the TEM group. An average of 9.9 ± 4.7 (range: 1–27) TEM medications were prescribed per patient. Based on the patients' CrCl values, 193 TEM medications have guidelines for dose adjustment. Analysis of the TEM medications with guidelines for adjustment showed that 73.6% were found to be inappropriate and 26.4% were found to be appropriate (Figure 1). Of the 78 patients studied, 63 patients were having at least one inappropriate medication and only 15 patients had all their TEM medications being appropriate. Based on the stage of renal impairment, data showed that a total of 23 inappropriate TEM medications were prescribed to patients in stage 5, a ratio of 2.6 TEM per patient (Table 1). It is noteworthy that most of these medications should be avoided when CrCl $\leq$15 ml/min. Patients in stage 4 were prescribed 42 inappropriate TEM medications, a ratio of 2.5 TEM per patient (Table 1). Patients in stage 3 were prescribed a total of 77 inappropriate TEM medications, a ratio of 1.5 TEM per patient (Table 1). Approximately, 77.5% of the inappropriate TEM medications were prescribed during the hospital stay and 22.5% were prescribed at discharge. Analysis of the data showed that ranitidine was the most (87) inappropriate TEM prescribed followed by antibiotics (22) and digoxin (8), cardiovascular medications (12), and metoclopromide (6). The inappropriate TEM antibiotics include amikacin, trimethoprim/sulfamethoxazole, ciprofloxacin and cefuroxime.

Analysis of inappropriate doses of TEM medications showed that the patients in the study were exposed to an average of 1.5–3 folds greater than the recommended dose. Finally, analysis of factors that could influence the inappropriate prescribing of TEM medications indicated that age, gender, SCr, CrCl and stage of renal impairment were not significantly influential on the frequency of inappropriate prescribing ($p > 0.05$).

DISCUSSION

Patients with renal impairment, often have alterations in pharmacokinetic parameters such as drug bioavailability, protein binding, biotransformation, volume of distribution, and renal excretion.[10] This is mostly important for drugs for which the fraction excreted unchanged (fe) is high. To avoid the risk of drug toxicity among patients with reduced renal function, medication doses should be adjusted based on the estimated CrCl, co-morbid disease and co-prescribed medications. Several recent studies have indicated that dosing errors and the risk of toxicity are common among patients with renal impairment. In agreement with other studies, our results showed a widespread dosing errors among patients with renal impairment.[6,11]

In our study, ranitidine, antibiotics, digoxin, other cardiovascular medications, and metoclopromide were commonly prescribed in inappropriate doses. Several case reports have indicated the toxic effects of ranitidine, both at therapeutic and overdoses. Acute interstitial nephritis, Fanconi syndrome, bradycardia,

DOI: 10.1002/pds

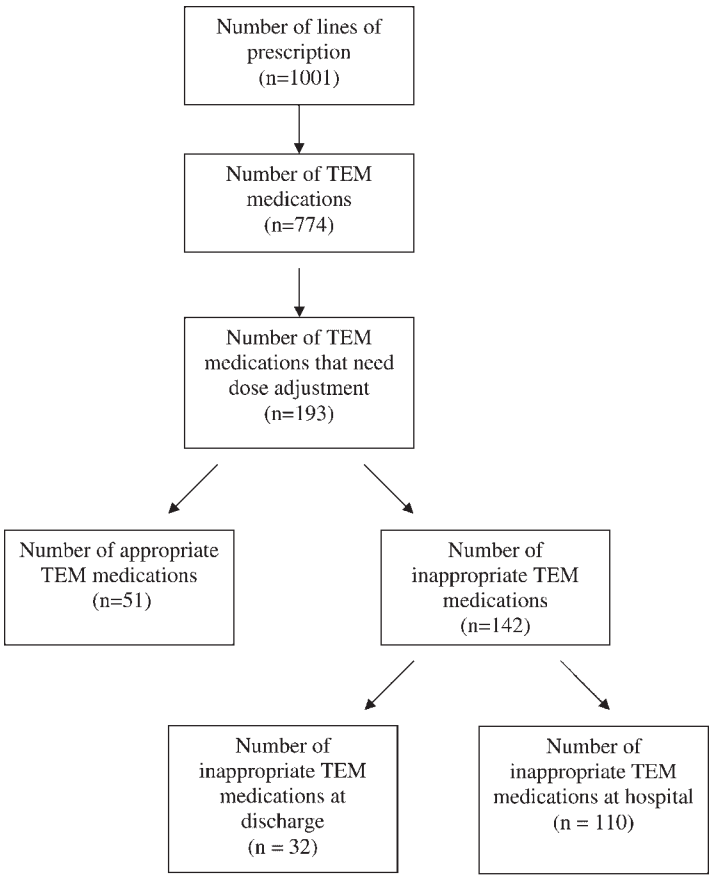

Figure 1. Appropriateness of prescriptions among the patients ($n = 78$) in the study. TEM medications are those with potential nephrotoxicity and/or renal elimination or metabolism

cardiac arrest, AV block, bone marrow hypoplasia, as well as, hematological toxicities have been reported following administration of ranitidine.[12–14] Such adverse effects and toxicities could be hazardous among the patients in the study given that most of them have renal as well as heart problems. Renal impairment negatively affects bone marrow and hematopoeisis leading to substantial anemia. Such adverse effects might worsen the blood profile of the patient.

In our study, digoxin, was administered in inappropriate doses. Digoxin is well known to have a narrow therapeutic window and serious adverse effects in overdose. Digoxin may cause several problems such as ventricular arrythmias, AV block, sinus bradycardia, SA arrest, and hyperkalemia. Again, such adverse effects might be harmful for the patients in our study who already have cardiac problems.[15]

In our study, 22 TEM antibiotic medications were prescribed to the 78 patients. These antibiotics include amikacin, gentamicin, ciprofloxacin and cefuroxime. Several case reports and studies have indicated that these antibiotics could induce nephrotoxicity in the form of interstitial nephritis or proximal tubular damage.[16–22] The toxic renal effects of the inappropriate antibiotics could lead to further accumulation of medication in the plasma and consequently increased risk of medication toxicity.

In our study, each patient with renal impairment received an average of 2.47 drugs eliminated and/or metabolized or excreted primarily by the kidney which necessitates dose reduction by a factor that is dependant on their creatinine clearance. Several reasons could be cited for this inappropriate dosing. The large number and the continuously increasing TEM medications list makes it difficult for medical staff to remain updated on dose adjustment issues.

DOI: 10.1002/pds

Furthermore, it seems that there is an underestimation or lack of knowledge of the importance regarding CrCl in determining the appropriate medication dose. In our study, CrCl and body weight needed to calculate the CrCl were missing from most of the patients' medical files. It is important that CrCl be calculated and documented for all patients for dose calculation. Using SCr level as the only indicator of renal function is not accurate. In our study, approximately 15% of the patients with normal or borderline SCr, were having low CrCl suggesting that normal SCr does not exclude renal impairment. A third possible reason is the lack of continuing medical education (CME) that focuses on the importance of this issue. Charts for dose adjustments are needed and should be available for the prescriber. Better pharmcotherapeutic monitoring is needed and could be achieved through clinical pharmacists' participation. Another professional source for information regarding dose adjustment is the poison control and drug information center. Finally, cost which is one of the motivations for dose adjustment may be ignored by the physician especially for drugs with wide therapeutic window (e.g., ranitidine).

Despite explicit need for dose titration in patients with renal impairment, adjustment should not be made based on pharmacokinetic considerations only. For example, cardiovascular medications such as ACE inhibitors (e.g., enalapril) or β-blocking agents (e.g., atenolol), spironolactone diuretic should be prescribed according to clinical end points such as blood pressure or heart rate.

This study showed that dosing errors are common among hospitalized patients with impaired renal function. Most of these dosing errors were made during hospital stay suggesting that better patient observation and dose calculation is needed. Continued medical education in the field of clinical pharmacokinetics is also required for all health practitioners. In conclusion, hospitalized patients are at risk for adverse outcomes due to prescribing errors related to inappropriate use of medication dose. This information should be considered in the development of strategies to prevent adverse patient outcomes resulting from such errors.

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DOI: 10.1002/pds