ASSESSMENT OF DRUG DOSE ADJUSTMENT IN PATIENTS WITH KIDNEY DISEASE: OPPORTUNITIES FOR PHARMACIST INVOLVEMENT

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ABSTRACT
The present observational study was performed on drugs requiring dose adjustment in kidney disease to assess the frequency and potential consequences of overlooked dosage adjustment in hospitalized patients. Medication records and data of 142 patients were collected on random basis from February 2008 through June 2010. Selected patients with elevated serum creatinine who were prescribed at least one drug needing dose adjustment were kept for further study. Eight hundred and thirty drug orders were evaluated in which dose adjustment was required in 193 (23.2%) of cases. Proper dose adjustments were performed in 88 (45.5%) of cases and not performed in 105 (54.4%) orders. According to our study, inappropriate dose adjustment in renal dysfunction shows a great need for pharmacist involvement in the process to improve drug dosing and avoid adverse drug reactions. Sub-grouping patients according to kidney function and following established dosing guidelines is recommended.

Keywords: Kidney disease, Dose adjustment, GFR, Jelliffe.

INTRODUCTION
Kidney disease is a recognized health care complication with the estimated prevalence of 1400 per million in the United States.1 Acute Kidney Injury (AKI) and Chronic Kidney Disease (CKD) are among important therapeutic problems often under-diagnosed, despite established classifications, necessitating attempts to improve drug dosing and disease management in kidney dysfunction.2-4 Dosing errors are common in this patient population, caused by advanced disease and adverse drug reactions (ADR), particularly in older patients.1 The incidence of ADRs is closely associated with number of medications used, patient’s age and other underlying diseases.5 Although worsening of renal function is correlated with increased age and higher expected ADRs, no recognized association has been found between correct dose adjustment in kidney disease and shortening of hospital stay.1,6 According to several studies, the rate of ADR is much higher in CKD and hemodialysis patients than those without renal insufficiency due to complex drug regimens and concomitant diseases.7 Furthermore, the length of hospital stay, associated costs and mortality rate increases with each adverse drug event.1,2 It is also established that a considerable number of drug-related hospital admissions are preventable and dose-related.8 Many drugs require dose adjustment in renal failure.9 Creatinine clearance or Glomerular Filtration Rate (GFR) are estimated using the existing equations for the purpose of staging CKD and drug dose adjustment.5,7 It is also established that a considerable number of drug-related hospital admissions are preventable and dose related.10-12 Even though roughly 20% of hospitalized patients suffer from kidney disease, dose adjustments are often overlooked in this patient population due to creatinine-blind range in early stages of the disease.11 According to several studies, the rate of noncompliance with renal dosing guidelines is 19-67% and 69% in hospital and ambulatory settings, respectively.10,12 While drug dosage adjustment alerts have been implemented in a number of studies13-15, the results are variable and have not shown significant reduction in inappropriate dosing. Given the fact that half of medication errors occur at ordering stage, implementing a renal dosing service within the hospital and clinical pharmacists’ intervention can improve drug dosing and save on drug costs.15-18

The objectives of the present study were to: 1) determine the percentage of drugs which needed dose adjustment in patients with kidney disease, 2) assess adjusted versus overlooked dosages according to dosing guidelines and 3) detect drugs with the most inappropriate dosage according to kidney function.

MATERIALS AND METHODS
Setting
The study was performed from February 2008 to June 2010 at Masih Daneshvar Hospital, a 446-bed teaching affiliate of Shahid Beheshti University of Medical Sciences in Tehran, Iran. The hospital consisted of surgical, oncology, Intensive Care Unit (ICU) and internal wards and is the educational collaboration center of the WHO Eastern Mediterranean region, the Middle East office of the International Union Against Tuberculosis and Lung Diseases (IUATLD) and the reference center for TB educational and research programs in the country.

Design
One hundred and forty two patients were recruited in the study. Patients’ files were studied on random basis during hospital stay and patients with elevated serum creatinine (above 1.1 mg/dl) were selected for further analysis. The inclusion criteria consisted of 1) age older than 16, 2) GFR less than 50 ml/min/1.73 m2 at admission or during hospital stay and 3) patients who were prescribed at least one drug needing dosage adjustment. Furthermore, patients undergoing dialysis were excluded from the study. Demographic and laboratory data were then retrieved. Patients were categorized in AKI, CKD and undefined groups according to duration of elevated serum creatinine (at least 3 months to be considered as CKD), medical records, previous admissions, laboratory data and nephrology consultation. Moreover, AKI and CKD patients were further categorized according to RIFLE and K/DOQI recommendations, respectively.13-Creatinine clearance or GFR were estimated using the appropriate equation on daily basis and according to patient’s group. Modification of Diet in Renal Disease (MDRD) and Jelliffe formula were used for CKD and AKI patients with weight record (ICU beds were not equipped with scales), respectively.14-15 In cases where no weight record was available, the MDRD formula was used to estimate GFR. Medications needing dose adjustment in kidney dysfunction and potential nephrotoxic drugs were assessed along with estimated creatinine clearance or GFR on daily basis and when data were available. Dosages, dosing intervals and dose adjustments of the studied drugs were investigated based on the calculated creatinine clearance. These were then evaluated using the dose adjustment guideline.21 In order to eliminate between-session variations, factor corrections were calculated and the actual percentage of incorrect dose adjustments were obtained for each drug. Factor correction was calculated by multiplying the number of observed errors (incorrect dosage) by number of opportunities for error.22 In addition, contraindicated drugs in renal...
dysfunction were detected. Among studied drugs, spironolactone, glyburide, metformin, phenobarbital and phenazopyridine were either contraindicated in severe renal insufficiency or required further dose adjustment in heart failure or liver disease as recommended by the guideline. (UpToDate 19.2).⁴³

RESULTS
A total of 142 patients were evaluated. Most patients (85.9%) were hospitalized in general internal and infectious disease wards. At least four serum creatinine data were available for 115 patients. Mean age ± SD was 62.7±16.4 years and male:female ratio was 86:56. Mean serum creatinine ± SD was 2.3± 2.0 mg/dl. Patients' demographic data is summarized in Table 1. After excluding 11 patients who underwent dialysis, the remaining 131 patients were categorized in AKI, CKD and undetermined groups (due to insufficient data available) with 44, 75 and 12 patients in each group, respectively and according to nephrologist's consultation and available guidelines.⁴⁻⁵ Among 830 evaluated orders, dose adjustment was required for 193 (23.2%) of cases. These adjustments were correct in 88 (45.5%) orders and overlooked in 105 (54.4%) orders. Ranitidine, digoxin (PO) and midazolam were the most inappropriately dosed drugs, being incorrect in 79.5%, 73.5% and 28.5% of cases, respectively. After calculating factor corrections, atenolol, metformin and digoxin (IV) had the most incorrect dosage with 49.0 (100%), 48.2 (98.3%) and 42.8 (87.3%) incorrect dosage, respectively (Table 2). Furthermore, 81% of patients needed dose adjustment for at least one prescribed drug. Nineteen contraindicated orders were also detected. These orders included spironolactone, glyburide, metformin and phenazopyridine being contraindicated in 47.6%, 83.3%, 66.6% and 100% of cases, respectively.

Table 1: Demographic data of the patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± S.D. (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>62.7 ± 16.4 (23-87)</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>56.0 (39.0)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>2.3 ± 2.0 (1.0-16.0)</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>34.4 ± 11.0 (10.5-49.9)</td>
</tr>
<tr>
<td>≥30, n (%)</td>
<td>82 (58.8%)</td>
</tr>
<tr>
<td>15-30, n (%)</td>
<td>43 (30.6%)</td>
</tr>
<tr>
<td>&lt;15, n (%)</td>
<td>17 (10.5%)</td>
</tr>
</tbody>
</table>

Table 2: Inappropriate dosage adjustment for the studied drugs

<table>
<thead>
<tr>
<th>Drug (Route of Administration)</th>
<th>Number of Orders</th>
<th>Inappropriate Dosage, n (% of Total)</th>
<th>Factor Correction</th>
<th>Corrected Inappropriate Dosage, n (% of Total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranitidine (IV)</td>
<td>49</td>
<td>39 (37.1)</td>
<td>1</td>
<td>39 (11.5)</td>
</tr>
<tr>
<td>Digeoxin (PO)</td>
<td>31</td>
<td>23 (21.9)</td>
<td>1.5</td>
<td>36 (10.6)</td>
</tr>
<tr>
<td>Midazolam (IV)</td>
<td>28</td>
<td>8 (7.6)</td>
<td>1.7</td>
<td>14 (4.1)</td>
</tr>
<tr>
<td>Morphine (IV)</td>
<td>21</td>
<td>1 (0.9)</td>
<td>2.3</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Spironolactone (PO)</td>
<td>21</td>
<td>0 (0)</td>
<td>2.3</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Digeoxin (IV)</td>
<td>16</td>
<td>14 (13.3)</td>
<td>3.0</td>
<td>42 (12.4)</td>
</tr>
<tr>
<td>Metoclopramide (PO)</td>
<td>8</td>
<td>6 (5.7)</td>
<td>6.1</td>
<td>36 (10.6)</td>
</tr>
<tr>
<td>Glyburide (PO)</td>
<td>6</td>
<td>5 (4.7)</td>
<td>8.1</td>
<td>40 (11.8)</td>
</tr>
<tr>
<td>Ranitidine (PO)</td>
<td>6</td>
<td>4 (3.8)</td>
<td>8.1</td>
<td>32 (9.4)</td>
</tr>
<tr>
<td>Metformin (PO)</td>
<td>3</td>
<td>3 (2.8)</td>
<td>16.3</td>
<td>48 (14.2)</td>
</tr>
<tr>
<td>Atenolol (PO)</td>
<td>2</td>
<td>2 (1.9)</td>
<td>24.5</td>
<td>49 (14.4)</td>
</tr>
<tr>
<td>Phenobarbital (PO)</td>
<td>1</td>
<td>0 (0.9)</td>
<td>49</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Phenazopyridine (PO)</td>
<td>1</td>
<td>0 (0.9)</td>
<td>49</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>193</td>
<td>105 (100)</td>
<td>172.9</td>
<td>338 (100)</td>
</tr>
</tbody>
</table>

DISCUSSION
Drug dose adjustment is a strategy that should be followed in order to individualize drug therapy and improve patient safety.⁶ In the present study we evaluated 830 orders written for 142 patients in which 193 orders required dose adjustment according to patients' renal function. The 105 (54.4%) overlooked dosages necessitate the use of a drug dosing system involving pharmacist intervention.

Although estimated Gomerular Filtration Rate (eGFR) using the four-variable MDRD equation is now routinely reported by many available guidelines, there remains uncertainty as which method of estimation (creatinine clearance vs. eGFR) or equation should be used for drug dose adjustment.⁶ Among commonly-used equations for estimating GFR, certain equations are preferred in different patient populations as suggested by a number of studies.⁶⁻¹² In critically ill patients with AKI, Modified Jelliffe formula is preferred over other equations since it underestimates GFR by only 2%, however, in our study Jelliffe equation was used for these patients (overestimating GFR by 10%) since we did not have access to height data for critically ill patients in the ICU to calculate Ideal Body Weight (IBW). We realize that in AKI patients with fluctuating serum creatinine levels, modified Jelliffe formula is a better estimate of renal function as it adjusts creatinine for fluid balance.⁶ On the other hand, it was shown in another study that MDRD formula gives a more accurate estimate of GFR in patients with CKD and therefore it was used for estimating creatinine clearance in CKD and patients with no weight record available. We recommend automatic report of eGFR by all hospital laboratories as a tool to further facilitate recognition and dosage adjustment for renal failure patients.

Choosing the best drug dosing guideline for dose adjustment is another problem having the potential to change therapeutic outcome as shown in several studies.²⁰⁻²⁷ Reasons for noncompliance with guidelines could be due to: prescribers' lack of awareness, unwillingness to adjust dosage because of inconsistent guideline recommendations and patient's unstable renal function. Identifying each of these factors and implementing a system for their improvement such as pharmacist intervention and computerized alert systems is recommended. Computerized Physician Order Entry (CPOE) and Clinical Decision Support Systems (CDSS) have been tested but the results are variable though some show significant decrease in medication errors and improvement in prescriber's ordering behavior and compliance with guidelines.²⁰⁻²⁰ A recent systematic review by Tawadrous, et al.,¹² also revealed promising results using computerized or manual CDSS in kidney drug prescribing. On the other hand, presence of a pharmacist as a full member of the patient care team has been shown to significantly reduce medication errors at prescribing stage.²⁰ Pharmacists can also offer their expertise in choosing the safest and most efficacious dose for each patient. On the other hand, presence of a pharmacist as a full member of the patient care team has been shown to significantly reduce medication errors at prescribing stage.²⁰ Pharmacists can also offer their expertise in choosing the safest and most efficacious dose for each patient.

Routine educational programs and updates (in the form of presentations or educational booklets) for physicians and residents and also developing a comprehensive, easy to use dosing guideline in the hospital can further facilitate drug dose adjustment.

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The table shown lists the inappropriately dosed drugs, specifically highlighting Ranitidine, Digeoxin, Midazolam, and others, with their respective numbers and percentages. It also notes the factor correction and the corrected inappropriate dosage percentage. The DISCUSSION section delves into the strategies and considerations for drug dose adjustment, emphasizing the importance of individualization and the role of guidelines in improving patient safety and therapeutic outcomes. The text also discusses the challenges and benefits of using computerized systems like CPOE and CDSS, as well as the role of pharmacists in this process.
In addition, using factor correction helped us further interpret the results of the study to determine if the prescribed medications had the same chance of prescription frequency and by avoiding between-session variations. Ramitidine (prescribed 49 times) can no longer be considered the most inappropriately-adjusted drug (Table 2). Using this method, atenolol was the most unadjusted drug (ordered 21 times where in both cases the dose was not adjusted). We recognize the results of the present study unique to our observed data and setting, however, these results are consistent with the results of our previous study on antibiotic dosage adjustment and other studies where a relatively high percentage of incorrect dose adjustments were reported.5,9,26

According to our study, guideline recommendations on contraindicated drugs were also variable. For instance, spironolactone dosage (ordered 21 times) was correct in all 21 cases where a relatively high percentage of incorrect dose adjustments were reported.6,7,26

According to the present study, 23.2% of orders written for patients with renal insufficiency (either computerized or direct pharmacist intervention). Further, finding a correlation between patient’s age, worsening of renal function or underlying diseases with incorrect drug dosing behavior and also recognizing medications more prone to dosing errors can guide clinical pharmacists in providing optimal pharmaceutical care for this patient population; however, these were not the objectives of our study.

CONCLUSION

According to the present study, 23.2% of orders written for patients with varying degrees of renal impairment required dosage adjustment but were performed in only 45.5% of these cases. A solution to this problem could be the implementation of a computerized alert system at the ordering stage and/or clinical pharmacists’ intervention. However, further research is necessary to demonstrate the effectiveness of such interventions. We recommend continuous presence of clinical pharmacists at physician rounds to review all medications as an effective solution in reducing medication errors and overall improvement in pharmaceutical care.

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REFERENCES

22. Basow DS (Ed), UpToDate, Waltham, MA, 2011.
27. Kaushal R, Shoiania KJ, Bates DW. Effects of computerized physician order entry and clinical decision support systems on...


