**INTRODUCTION**

Medication errors account for a large number (28%) of adverse drug events (ADEs) and can be prevented. About 50% of these adverse effects are due to inappropriate\footnote{Beheshti University of Medical Sciences, 3 Department of Pharmacology and Toxicology, School of Pharmacy, Shahid Beheshti University of Medical Sciences, 4 Chronic Respiratory Disease Research Center (CRDRC), NRITLD, Masih Daneshvari Hospital, Tehran, Iran.} dosing especially in patients with renal failure.

**Objective:** To determine the impact of short message alerting on physicians’ drug dosing of patients with decreased renal function.

**Methods:** Eighteen physicians accepted to enroll in the study. Their patients who received at least one of the six selected drugs were selected for evaluation. The physicians with an estimated glomerular filtration rate of 50 ml/minute or lower were randomly divided into two groups of case and control. An alert was sent to the physician in charge of the intervention (case) group. Physicians’ reactions were recorded as “dose adjustment”, “discontinuation of medication” or “none” and were compared in both groups. The reaction time of physicians before and after receiving alerts was recorded as well.

**Results:** One hundred and thirty seven patients entered the study. The study results showed a significant difference in overall changes between the two groups (\(*** P <0.001\)). The rate of dose adjustment increased significantly after sending alerts to physicians (\(*** P <0.001\)). However, there was no significant difference regarding discontinuation of medication between groups (\(P= 0.76\)). On the other hand, prompt reaction of physicians (0-6 hours after receiving short message) significantly increased after intervention (\(* P <0.05\)). Nevertheless, physicians’ reaction time in 6-24 hours and 24-48 hours was not changed significantly after intervention.

**Conclusion:** The results of this study show that informing physicians about the renal function of the patients leads to appropriate dosing.

**Keywords:** Acute Kidney Injury, Chronic Kidney Disease, Dosage adjustment, Creatinine clearance, SMS, Alerting system.

**MATERIALS AND METHODS**

**Setting**

This study was performed from August 2012 to June 2013 at Masih Daneshvari Hospital, a 446-bed teaching affiliate of Shahid Beheshti University of Medical Sciences in Tehran, Iran. The hospital consists 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**

The study was a single center, randomized, single-blind, crossover study to evaluate the reactions of physicians to short message alerts in clinical setting. Twenty nine physicians including attending and fellow physicians were asked to participate in the study. Eighteen physicians including 16 attendings and 2 fellow physicians agreed to receive short text message alerts if their patients’ renal function was decreased. However to prevent observer induced bias, the physicians were not aware of the exact purpose of the study. Initially, in the permission letter sent to the physicians it was stated...
that the project was a part of pharmacy healthcare improvement program. Physicians in each ward were then randomly selected and put in one of the intervention and no intervention groups. The data was then analyzed using demographics and the physicians remained anonymous. Six medications including ciprofloxacin (IV), vancomycin (IV), amikacin (IV), ranitidine (IV), ranitidine (PO) and digoxin (PO) were selected for this study. This selection was based on our previous study [14] which indicated commonly prescribed drugs with high rates of inappropriate dosing based on renal function. The inclusion criteria consisted of patients of the participating physicians with an estimated glomerular filtration rate (eGFR) less than 50 ml/min/1.73 m². Also, the patients should have received at least one of our studied medications inappropriately based on their renal function to be included in our study. Furthermore, patients undergoing dialysis or discharged from the hospital before our evaluation were excluded from the study. Demographic and laboratory data were then retrieved from the charts. Serum creatinine was checked daily for these patients and creatinine clearance (or GFR) was estimated using the appropriate equation on daily basis. Cockcroft & Gault formula was used in our study to calculate estimated GFR because of the fact that most of the dose adjustment guidelines in renal impairment are based on this formula. Since our hospital beds are not equipped with scales, for critically ill patients whose actual body weights were not available, we calculated ideal body weight (IBW) based on existing formulas by measuring the height of the patient. 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 guidelines. The appropriate dosage data for each drug in different GFR ranges were collected from five different references [1, 6, 16, 17, 18, 19]. Required dosage adjustments were based on the level of kidney function impairment which was divided into three categories (eGFR<10 ml/min/1.73 m²; eGFR 10 to 50 ml/min/1.73 m²; eGFR >50 ml/min/1.73 m²).

The final guideline was obtained by choosing the widest acceptable dosage range in different GFRs. We used correction factor as a tool to remove between session variations (the number of observations for each medication was different). All available data are equally weighted using correction factor. Correction factor expresses the number of opportunities for errors for each prescribed medication. It is calculated by multiplying the number of observations by the number of opportunities for errors. In other words, corrected percentage of error for each selected drug was calculated by using the number of errors divided by factor correction multiplied by 100. Patients with an estimated GFR lower than 50 ml/min/1.73 m² who were prescribed at least one of the 6 target medications that required dose adjustment, were monitored for 24 hours and if no adjustment was applied by physician during the 24-hour period, a short message alert was sent to the responsible physician as a reminder of the patient’s impaired renal function. Patients were observed for 48 hours after sending alerts. Any change in prescribed drugs including dose adjustment or discontinuation of medication was recorded.

At the same time the physicians in no intervention group did not receive any alert. Due to ethical issues the physicians in control group received a short message alert 48 hours after GFR drop if they did not make any adjustment. In the second phase of the study, we did a crossover between intervention and no intervention physician groups. Expected reactions from physicians both in intervention and no intervention groups was divided into three categories: 1) drug dose adjustment 2) drug discontinuation 3) no action.

Reaction time of physicians was defined as time elapsed from the moment that alert was sent until we detected a reaction from the physician. Review of the orders was performed 6, 24, and 48 hours after sending the text message. Statistical analysis was performed using Graph pad Prism 5.0.

RESULTS

A total of 152 patients were evaluated. After excluding 15 patients who were discharged or underwent dialysis, further evaluation was done for 137 patients. Mean age ± SD was 66.41 ± 13.51 years and male: female ratio was 90:47. Mean serum creatinine ± SD was 2.08 ± 1.25. Mean estimated GFR ± SD of patients was 32.99 ± 11.42. One hundred and twenty five patients had the eGFR range of 10-50 ml/min/1.73 m², while 12 patients eGFR was less than 10 ml/min. Among 645 observations of the studied medications, renal dose adjustment was required for 239 (37.05%) cases. Ciprofloxacin (IV) had the highest rate of inappropriate dosing among six medications with 64 (26.78%) cases while ranitidine (PO) had the lowest rate of inappropriate dosing with 20 (8.36%) cases. Vancomycin, ranitidine (IV), amikacin (IV), and digoxin (PO) had the inappropriate dosing rates of 25.52%, 19.24%, 10.80% and 9.20% respectively.

Fifty four (39.4%) patients required dose adjustment for only one drug in their prescription, 64 (46.71%) patients required dose adjustment for 2 drugs and 19 (13.86%) patients required dose adjustment for 3 drugs according to their renal function. One hundred and nineteen inappropriate dosing out of 239 prescriptions was found in internal ward, while 58, 26, 25 and 11 cases were recorded in medical ICU, infectious diseases ward, surgical ICU and cardiac ward respectively. Regarding the specialty of physicians, 5 intensive care unit physicians, 9 internists, 2 infectious disease specialists and 2 cardiologists participated in our study. During the study period, 102 short message alerts were sent to the physicians. Sixty eight alerts were sent to the physicians in the intervention group. Thirty four alerts were sent to the physicians in intervention group during the first phase of the study while remaining 34 alerts were sent to the physicians during the second phase of study after doing crossover between physicians. Fifty three alerts (77.94%) of 68 sent alerts led to a change in patients’ medications as dose adjustment or discontinuation. Reaction time of physicians was categorized into 0-6 (quick reaction time), 6-24 (moderate reaction time) and 24-48 hour (delayed reaction time) intervals. Eleven changes out of 53 (20.75%) were applied during the first six hours after sending short message alert, 30 (56.60%) changes were applied in 6-24 hour time period and 12 (22.64%) changes occurred within 24-48 hour time period. Physicians were divided in two groups. Group A included the physicians who received alerts during the first phase of the investigation while group B physicians started to receive alerts after cross-over. The overall reaction of physicians (including dose adjustment and discontinuation of medication)

### Table 1: Inappropriate dosage adjustment for the studied drugs with and without correction factor

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of observations</th>
<th>Number of errors</th>
<th>Number of errors after applying correction factor</th>
<th>Percentage of errors without correction factor</th>
<th>Percentage of errors after applying correction factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin (IV)</td>
<td>159</td>
<td>64</td>
<td>40.25</td>
<td>26.78</td>
<td>18.29</td>
</tr>
<tr>
<td>Vancomycin(IV)</td>
<td>114</td>
<td>61</td>
<td>53.50</td>
<td>25.52</td>
<td>24.31</td>
</tr>
<tr>
<td>Ranitidine (PO)</td>
<td>73</td>
<td>20</td>
<td>27.39</td>
<td>8.36</td>
<td>12.44</td>
</tr>
<tr>
<td>Ranitidine (IV)</td>
<td>89</td>
<td>46</td>
<td>51.68</td>
<td>19.24</td>
<td>23.48</td>
</tr>
<tr>
<td>Amikacin(IV)</td>
<td>90</td>
<td>26</td>
<td>28.88</td>
<td>10.87</td>
<td>13.12</td>
</tr>
<tr>
<td>Digoxin(PO)</td>
<td>120</td>
<td>22</td>
<td>18.33</td>
<td>9.20</td>
<td>8.33</td>
</tr>
<tr>
<td>Total</td>
<td>645</td>
<td>239</td>
<td>220.03</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

significant increase after the short message intervention, regardless of the group of the study (*** P < 0.001). More detailed analysis indicated that only drug dose adjustment based on reduced renal function significantly increased after sending alerts (*** P < 0.001). However, there was not a significant change when discontinuation of medication in intervention and non-intervention groups was considered (P=0.76). A comparison showed that the overall changes did not differ significantly between group A and group B during no-intervention stage (P= 0.46).

DISCUSSION

Considerable attention has been drawn to electronic alerting systems in clinical setup as a means of reducing prescription and medication errors. We implemented short message alerting system for informing physicians about the renal function of the patients. The intervention by sending short message alerts was associated with a significant increase in rate of drug dose adjustment based on impaired renal function. However, there was not a significant difference between intervention and control group in discontinuation of drugs which shows that physicians mostly tended to adjust the doses rather than ceasing the medication. In one study Sellier et al [3] implemented an alerting system for adjusting drug doses for inpatients with renal insufficiency. The intervention led to a significant decrease in inappropriate dosages from 67% to 54%. Similarly, Oppenheim et al implemented an alert system displaying the correct dosage of a drug when a wrong dosage was selected by a physician and half of the orders were adjusted in response to alerts [20]. In these two previous studies, the exact dosage was suggested to the physician, whereas we only provided the eGFR values to the physicians, asking them to check their patient’s status. Previous studies showed that there is a significant difference between responses of residents and senior physicians to alerts. Residents tended to improve their performance in prescribing drugs whereas senior physicians tended to make more errors [3]. What makes our study different from this aspect is that all included physicians in our study were attending and fellow physicians. Results from our study showed that all of the dose adjustments after sending alerts were within the acceptable range of dose. There can be two reasons for this: 1) knowledge of the participated physicians about dose adjustment in renal failure 2) choosing the widest acceptable renal dose range for studied drugs. Although all physicians were aware of the study, the exact purpose of the study was unknown to them. In this way we prevented observer induced bias in the study. Time of corrective actions in renal impairment is of a great clinical importance. Several studies have shown that early detection of renal failure has positive prognostic outcomes and reduces the rate of mortality [21]. In our study, quick reaction of physicians (response during the first six hours after sending message) considerably increased which was statistically significant, indicating that physicians in intervention group took a quicker action compared to non-intervention group. Physicians’ early reaction (during 0-6 hours after sending alerts) significantly increased after receiving short message alerts (P < 0.05). However there was not a significant difference in moderate (6-24 hours) and delayed (24-48 hours) reaction times between intervention and non-intervention groups (P = 0.63 and 0.09 respectively). The results also indicated that ICU physicians tended to respond to the alerts quicker than physicians in other studied wards.

<table>
<thead>
<tr>
<th>Table 2: Reaction time of physicians in studied wards</th>
</tr>
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<tbody>
<tr>
<td>Ward</td>
</tr>
<tr>
<td>----------------------------</td>
</tr>
<tr>
<td>ICU</td>
</tr>
<tr>
<td>Internal</td>
</tr>
<tr>
<td>Infectious diseases</td>
</tr>
<tr>
<td>Cardiology</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

Because of various interfering factors in discontinuation of a drug, its clinical value may not be as important as drug dose adjustment in renal failure since other factors such as inadequate clinical response, development of side effects or unavailability of a drug may result in discontinuation. This may be the reason of non-significant difference in discontinuation of medication in both group A and group B. Non-significant difference between no-intervention periods of group A and group B may be resulted from a potential dependence of the physicians to receive short messages to make changes.

This study was subject to several limitations. First, the intervention was conducted in only one hospital with limited number of patients and physicians. Second, lack of a consistent renal dosing guideline was a problem, having the potential to change therapeutic outcomes. According to a study by Fahimi et. al using different dosing guidelines results in an inconsistency in decision about dose adjustment [21].

It should be taken into consideration that for some medications like vancomycin, taking blood concentration levels is not routinely performed in our hospital, so we had to rely on the dosing guidelines gathered from available resources. Concomitant illnesses such as hypothyroidism, hepatic impairment and chronic heart failure have the potential to interfere with the existing renal impairment and should be scrutinized in detail to understand their impact on renal dosing. Moreover, one limitation of the study was that we were not certain if the alert was received or seen by the physician or not. On the other hand, there are different GFR estimation equations which could be used to calculate creatinine clearance. Among commonly-used equations for estimating GFR, certain equations are preferred in different patient populations as suggested by previous studies (14). We mainly used Cockcroft & Gault equation in our study since most of renal dosing guidelines are based on this equation. Patients with no weight record were evaluated with IBW calculation. Moreover, the relation between the demographic qualities of physicians [specialty, gender, work experience] and the rate of responses to alerts can be a subject for future studies.

CONFLICT OF INTERESTS

Declared None

ACKNOWLEDGMENTS

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This study was done as a Pharm D thesis.

REFERENCES

5. Kohli HS, Bhaskaran MC, Muthukumar T, Thennarasu K, Sud K, Jha V, et al. Treatment-related acute renal failure in the...


