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Research Article

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.[5] The incidence of ADRs is closely associated with number of medications used, patient's age and other underlying diseases.[6] 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.[7] 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.[2] Furthermore, the length of hospital stay, associated costs and mortality rate increases with each adverse drug event.[8] It is also established that a considerable number of drug-related hospital admissions are preventable and dose-related.[7] 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] 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.[12] While drug dosage adjustment alerts have been implemented in a number of studies[13-14], 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 Daneshvari 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 m^2 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.[3,4] 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.[19-20] 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)[23].

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.[3,4]. 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 (Table2). 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

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

Table 2: Inappropriate dosage adjustment for the studied drugs

Drug (Route of Administration)	Number of Orders	Inappropriate Dosage, n (% of Total)	Factor Correction*	Corrected Inappropriate Dosage, n (% of Total)
Ranitidine (IV)	49	39 (37.1)	1	39 (11.5)
Digoxin (PO)	31	23 (21.9)	1.5	36 (10.6)
Midazolam (IV)	28	8 (7.6)	1.7	14 (4.1)
Morphine (IV)	21	1 (0.9)	2.3	2 (0.5)
Spironolactone (PO)	21	0 (0)	2.3	0 (0.0)
Digoxin (IV)	16	14 (13.3)	3.0	42 (12.4)
Metoclopramide (PO)	8	6 (5.7)	6.1	36 (10.6)
Glyburide (PO)	6	5 (4.7)	8.1	40 (11.8)
Ranitidine (PO)	6	4 (3.8)	8.1	32 (9.4)
Metformin (PO)	3	3 (2.8)	16.3	48 (14.2)
Atenelol (PO)	2	2 (1.9)	24.5	49 (14.4)
Phenobarbital (PO)	1	0 (0.9)	49	0 (0.0)
Phenazopyridine (PO)	1	0 (0.9)	49	0 (0.0)
Total	193	105 (100)	172.9	338 (100)

Number of observations multiplied by number of opportunities for errors.

DISCUSSION

Drug dose adjustment is a strategy that should be followed in order to individualize drug therapy and improve patient safety.[9] 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 Glomerular Filtration Rate (eGFR) using the four-variable MDRD equation is now routinely reported by many hospital laboratories as a tool for staging CKD, there remains uncertainty as which method of estimation (creatinine clearance vs. eGFR) or equation should be used for drug dose adjustment.[24] Among commonly-used equations for estimating GFR, certain equations are preferred in different patient populations as suggested by a number of studies.[4,25] 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.[24] On the other hand, it was shown in another study[4] 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.[26-27] Reasons for noncompliance with guidelines could be due to: prescribers' lack of awareness, unwillingness to adjust dosage because of inconsistent guideline dose 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.[28-30] A recent systematic review by Tawadrous, et al,[31] also revealed promising results using computerized or manual CDSSs 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.[16] Pharmacists can also offer their expertise in choosing the safest and most efficacious drug to prevent ADRs and help promote the rational use of drugs.[32] Moreover, information provided by the pharmacists through their drug information services can further assist clinicians regarding drug dose adjustment.[33] Moreover, whether inappropriate drug dose adjustment is correlated to factors such as physician's specialty, patient's age or severity of renal insufficiency can be assessed but these were not the objectives of our study.

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.

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. Ranitidine (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 2 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.[7,8,26]

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 (100%) according to APhA[21] guideline, however with respect to UpToDate[23], 10 of these orders were contraindicated (where patient's creatinine clearance was below 30 ml/min), leading to a further rise in potassium level in a patient with renal insufficiency. Metformin was also contraindicated in 47.6% of cases, increasing the risk of lactic acidosis especially in renal failure patients with concomitant respiratory disease or severe infection.[4] Recognizing contraindicated and nephrotoxic drugs prior to ordering and consensus regarding which guideline to follow is highly recommended.

As a result, an intervention would be necessary in cases of contraindicated or incorrect orders in patients with renal insufficiency, (either computerized or direct pharmacist intervention). Further, finding a correlation between patients' 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

1. Giles PD, Fitzmaurice DA. Formula estimation of glomerular filtration rate: have we gone wrong? BMJ 2007; 334: 1198-1200.
2. Yahaya H, Al-Ramahi RJ, Abd Aziz N, Ghazali R. Drug use and dosing in chronic kidney disease. Ann Acad Med Singapore 2009; 38(12): 1095-1103.
3. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Available at:
4. http://www.kidney.org/professionals/KDOQI/guidelines_ckd/toc.htm. (Accessed- Aug.3, 2011).
5. Venkataraman R, Kellum JA. Defining acute renal failure: the RIFLE criteria. J Intensive Care Med 2007; 22(4): 187-193.
6. Munar MY, Singh H. Drug dosing adjustments in patients with chronic kidney disease. Am Fam Physician 2007; 75(10): 1487-1496.
7. Kappel J, Calissi P. Nephrology: 3. Safe drug prescribing for patients with renal insufficiency. CMAJ. 2002; 166(4): 473-477. Hudson JQ, Nyman HA. Use of estimated glomerular filtration rate for drug dosing in the chronic kidney disease patient. Curr Opin Nephrol Hypertens 2011; 20(5): 482-491.
8. Bates DW, Spell N, Cullen DJ, et al. The costs of adverse drug events in hospitalized patients. Adverse Drug Events Prevention Study Group. JAMA 1997; 277(4): 307-311.
9. Falconnier AD, Haefeli WE, Schoenenberger RA, Surber C, Martin-Facklam M. Drug dosage in patients with renal failure optimized by immediate concurrent feedback. J Gen Intern Med 2001; 16(6): 369–375.
10. Van Dijk EA, Drabbe NRG, Kruijtbosch M, De Smet PAGM. Drug dosage adjustments according to renal function at hospital discharge. Ann Pharmacother 2006; 40(7): 1254-1260.
11. Hartmann B, Czock D, Keller F. Drug therapy in patients with chronic renal failure. Dtsch Arztebl Int 2010; 107(37): 647-655.
12. Long CL, Raebel MA, Price DW, Magid DJ. Compliance with dosing guidelines in patients with chronic kidney disease. Ann Pharmacother 2004; 38: 853-858.
13. Bhardwaja B, Carroll NM, Raebel MA, et al. Improving Prescribing Safety in patients with renal insufficiency in the ambulatory setting. The drug renal alert pharmacy (DRAP) program. Pharmacotherapy 2011; 31(4): 346-356.
14. Sellier E, Colombet I, Sabatier B, et al. Effect of alerts for drug dosage adjustment in inpatients with renal insufficiency. J Am Med Inform Assoc. 2009; 16(2): 203-210.
15. Hassan Y, Al-Ramahi RJ, Aziz NA, Ghazali R. Impact of a renal dosing service on dose adjustment in hospitalized patients with chronic kidney disease. Ann Pharmacother 2009; 43(10): 1598-1605.
16. Kucukarslan SN, Peters M, Mlynarek M, Nafziger DA. Pharmacists on rounding teams reduce preventable adverse drug events in hospital general medicine units. Arch Intern Med 2003; 163: 2014-2018.
17. Leape LL, Cullen DJ, Clapp MD, et al. Pharmacist participation on physician rounds and adverse drug events in the intensive care unit. JAMA 1999; 282: 267-270.
18. Gandhi PG, Smith BS, Tataronis GR, Mass B. Impact of a pharmacist on drug costs in a coronary care unit. Am J Health Syst Pharm 2001; 58: 497-503.
19. Levey AS, Bosch JP, Breyer Lewis J, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999; 130(6): 461-470.
20. Jelliffe RW. Estimation of creatinine clearance when urine cannot be collected. Lancet. 1971; 297: 975-976.
21. Lacy CF, Armstrong LL, Goldman MP, Lance LL. Drug information handbook. A comprehensive resource for all clinicians and healthcare professionals. 18th ed. Philadelphia (PA): Lexi-Comp, 2009.
22. Ruijter JM, Thygesen HH, Schoneveld OJLM, Das AT, Berkhout B, Lamers WH. Factor correction as a tool to eliminate between-session variation in replicate experiments: application to molecular biology and retrovirology. Retrovirology. 2006; 3: 2-10.
23. Basow DS (Ed), UpToDate, Waltham, MA, 2011.
24. Dowling TC, Matzke GR, Murphy JE, Burckart GJ. Evaluation of renal drug dosing: Prescribing information and clinical pharmacist approaches. Pharmacotherapy 2010; 30(8): 776-786.
25. Bouchard J, Macedo E, Soroko S, Chertow GM, Himmelfarb J, Ikizler TA, et al. Comparison of methods for estimating glomerular filtration rate in critically ill patients with acute kidney injury. Nephrol Dial Transplant. 2010; 25(1): 102-107.
26. Vidal L, Shavit M, Fraser A, Paul M, Leibovici L. Systematic comparison of four sources of drug information regarding adjustment of dose for renal function. BMJ. 2005; 331: 263-266.
27. Fahimi F, Emami S, Rashid Farokhi F. The rate of antibiotic dosage adjustment in renal dysfunction. IJPR; Feb 2012, (In Press).
28. Kaushal R, Shojania KJ, Bates DW. Effects of computerized physician order entry and clinical decision support systems on

medication safety: a systematic review. Arch Intern Med 2003; 163(12): 1409-1416.

29. Rommers MK, Teepe-Twiss IM, Guchelaar HJ. A computerized adverse drug event alerting system using clinical rules: a retrospective and prospective comparison with conventional medication surveillance in the Netherlands. Drug Saf. 2011; 34(3): 233-242.
30. Durieux P, Nizard R, Ravaud P, Mounier N, Lepage E. A clinical decision support system for prevention of venous thromboembolism: effect on physician behavior. JAMA. 2000; 283(21): 2816-2821.
31. Tawadrous D, Sharriff SZ, Haynes RB, Iansavichus AV, Jain AK, Garg AX. Use of clinical decision support systems for kidney-related drug prescribing: a systematic review. Am J Kidney Dis. 2011; 58(6): 903-914.
32. Shill MC, Das AK. Medication Practices in Bangladesh-----roles of pharmacists at current circumstances. Int J Pharm Pharm Sci. 2011; 3(4): 5-8.
33. Rajanandh MG, Varghese R, Ramasamy C. Assessment of drug information services in a south Indian tertiary care hospital in Kanchipuram district. Int J Pharm Pharm Sci. 2011; 3(3): 273-276.