

Impact of a Renal Drug Dosing Service on Dose Adjustment in Hospitalized Patients with Chronic Kidney Disease

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Appropriate drug selection and dosing for patients with chronic kidney disease (CKD) is important to avoid unwanted drug effects and to ensure optimal patient outcomes. Efforts to reduce dosing errors can lower the rate of adverse drug events (ADEs), reduce costs, and improve the overall delivery of health care.^{1,2} Patients with renal impairment often show pharmacokinetic parameters (eg, drug absorption, distribution, protein binding, biotransformation, renal excretion) that are different from those of patients with normal renal function. Many medications and their metabolites are eliminated via the kidneys; thus, adequate renal function is important to avoid toxicity.^{3,4} Patients can also show an altered pharmacodynamic response to a given drug due to the physiological and biochemical changes associated with progressive renal insufficiency.⁵

Drug-related problems are common in patients with renal insufficiency and in those undergoing hemodialysis. These patients are at higher risk since they need complex therapeutic regimens that require frequent monitoring and dosage adjustments. In addition, they usually have other comorbidities, including diabetes mel-

BACKGROUND: Appropriate drug selection and dosing for patients with chronic kidney disease (CKD) is important to avoid unwanted drug effects and ensure optimal patient outcomes.

OBJECTIVE: To assess the rate of inappropriate dosing in patients with CKD in a nephrology unit and to evaluate the impact on dose adjustment, adverse drug events (ADEs), and drug cost of having a pharmacist accompany a team of physicians on their rounds.

METHODS: This was a comparative study with a preintervention and post-intervention design. The preintervention phase served as the control; it was prospective and observational only and was conducted from the beginning of February to the end of May 2007. The second phase (intervention phase) was conducted from the beginning of March to the end of June 2008. Two random samples of 300 patients with an estimated creatinine clearance less than or equal to 50 mL/min were included. During the intervention phase, a clinical pharmacist made rounds with the nephrology unit team and gave dosing adjustment recommendations when needed. A collection of reliable and up-to-date drug information references that are commonly used globally were used during the intervention.

RESULTS: In the preintervention group, drug dosage adjustment or avoidance, based on renal function, was necessary in 607 of 2814 (21.6%) prescriptions. Of these, 322 (53.0%) did not comply with guidelines. In the intervention group, adjustment was necessary for 640 of 2981 (21.5%) prescriptions. The pharmacist made 388 recommendations related to dosing adjustment, 212 (54.6%) of which were accepted by physicians. Clinicians' noncompliance with dosing guidelines decreased to 176 (27.5%) ($p < 0.001$). In the preintervention group, 64 (21.3%) patients had a suspected ADE, with a total of 73 events. In the intervention group, this number was significantly lower with 49 events in 48 (16.0%) patients ($p < 0.05$). The intervention resulted in drug cost savings of \$2250 US.

CONCLUSIONS: A renal drug dosing service for patients hospitalized with CKD can increase the proportion of drug dosing that is adjusted to take into account renal function. This can save drug costs and may prevent ADEs.

KEY WORDS: chronic kidney disease, dose adjustment, renal drug dosing service.

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litus, hypertension, coronary artery disease, and infection.^{3,5,6} Inappropriate use of drugs can increase ADEs, which can lead to excessively long hospital stays, an excessive burden on the healthcare system, and increased costs.^{1,2,7-9} Many ADEs cannot be avoided, but some are caused by errors in management and are therefore preventable. The median preventability rate of ADEs in hospitals has been found to be 35.2% (range 18.7–73.2%),¹⁰ and many of these preventable events are dose-related.^{10,11}

Dosing errors are some of the most important drug-related problems in patients with CKD.^{2,6,12,13} Proper dosing can maximize therapeutic efficacy, minimize toxicity, and decrease the workload for nurses. It can also have an economic impact, resulting in the elimination of costs associated with drug-related toxicity and savings in terms of drug costs.^{2,14} However, the importance of dosage adjustment in patients with renal impairment is often underestimated.¹⁵⁻¹⁷

Studies from different countries have indicated that dosing errors and toxicity are common in patients with renal impairment.^{2,16-19} A review that assessed clinicians' compliance with dosing guidelines in CKD patients reported noncompliance rates ranging from 19.0% to 67.0%.² Most of the dosing errors occur when physicians order drugs, and most are due to lack of knowledge about the drug or lack of information about the patient.^{20,21} How to address this problem to improve the quality of health care delivered to patients remains unclear. Two strategies have been suggested to assist practitioners in monitoring and adjusting drug therapy in patients: the use of pharmacy-managed dosing services and computerized dosing programs.^{2,22}

Studies have shown benefits for using computer support to determine optimal drug doses.^{15,23,24} Despite the advantages of such systems, a major financial barrier prevents widespread adoption. Another major difficulty arises from the need to make the system available at the bedside of each hospitalized patient. In our hospitals, prescriptions for hospitalized patients are still paper-based, so the best option is the use of a clinical pharmacy dosing service. Many studies and reports have recognized that pharmacists are an essential resource for safe medication use, that participation of pharmacists in clinical rounds promotes safe use of medications, and that collaboration among pharmacists, nephrologists, and patients is important.^{21,22,25,26}

The aim of this study was to assess the rate of inappropriate dosing in hospitalized patients with CKD and to implement and evaluate the impact of having a pharmacist accompany a team of physicians on clinical rounds in a nephrology unit. Factors evaluated included dose adjustment according to renal function, ADEs, and savings in drug cost.

To our knowledge, no similar study has yet been performed in Malaysia. Moreover, no similar studies done in other countries have been conducted in a nephrology unit in which most hospitalized patients have stage 5 CKD and whose dosing is therefore complicated by dialysis.

Methods

SETTING

This study was conducted in the nephrology unit at Penang General Hospital, Penang, Malaysia. The 35-bed nephrology unit provides care to patients from all over Penang State. The unit is highly crowded, and most of the time, extra beds are needed, as the number of patients exceeds 35. Patients are mainly those who have CKD and develop other medical problems that require hospitalization, such as vascular access problems, fluid overload, infections, uremic symptoms, septicemia, and cardiovascular problems. Historically, the medical team in the unit included a pharmacist. The pharmacist's role was to take medication histories, provide therapeutic drug monitoring based on serum concentrations (ie, vancomycin, gentamicin, amikacin, digoxin), and discharge counseling. Pharmacists did not participate on rounds.

DESIGN

The study was interventional, with a preintervention versus postintervention design (historical control) to evaluate the impact of an inpatient collaborative clinical pharmacy renal dosing service on dosage adjustment in patients with CKD. The study protocol was reviewed and approved by the Penang Hospital Research Ethics Committee. In each phase, a random sample of 300 patients was chosen. This number was approximately 50% of the admitted patients who met the inclusion criteria. To avoid bias, a random number generator was used to select patients according to their admission numbers. CKD patients were included in the study if they were older than 18 years and had an estimated creatinine clearance (CrCl) less than or equal to 50 mL/min at admission. Patients with acute renal failure were excluded.

For inclusion criteria and dosing purposes, the Cockcroft-Gault equation was used.

$$\text{If male: CrCl} = \frac{(140 - \text{age}) \times \text{weight}}{72 \times \text{SCr}}$$

$$\text{If female: CrCl} = \frac{(140 - \text{age}) \times \text{weight}}{72 \times \text{SCr}} \times 0.85$$

where CrCl is expressed in milliliters per minute, age in years, weight in kilograms, and serum creatinine (SCr) in milligrams per deciliter.

Despite the limitations of this equation, it is the most appropriate method for determining drug dosage based on kidney function in a clinical setting.^{27,28} Since most of the patients in the sample were on dialysis, there was no need to calculate CrCl for dosing purposes. Doses for CrCl less than 10 mL/min were used unless the guidelines stated a different recommendation.²⁹ The abbreviated 4-variable

Modification of Diet in Renal Disease Study equation was used to determine the stage of CKD based on the classification of the Kidney Disease Outcomes Quality Initiative of the National Kidney Foundation.³⁰

The preintervention phase served as the control; it was prospective and observational only and was conducted from the beginning of February to the end of May 2007. The physicians were not aware of their involvement in the study in this phase. The second phase (intervention phase) was conducted from the beginning of March to the end of June 2008. The intervention was performed by a clinical pharmacist (MSc in clinical pharmacy) who had acquired suitable training in internal medicine. In the ward, the daily medical rounds started around 0900 hours every day. This allowed the pharmacist to review patients' medical records and medical sheets from 0800 to 0900 hours and to write notes. The clinical pharmacist joined the daily rounds with the medical team, usually from 0900 to 1200 hours, and made recommendations to adjust medications that were prescribed in excess or less than the recommended doses based on CrCl.

In designing the intervention for the second phase of the study, we could not refer to any standard guidelines on dosage adjustment for patients with renal impairment. Sources differ significantly in their recommendations for dosage adjustment, and some guidelines are qualitative and unclear.^{29,31} To overcome this problem, a pocket-size handbook was prepared for use by the clinical pharmacist during rounds. The medications in the formularies of our hospital were reviewed for dosing recommendations specific for patients showing renal impairment or undergoing dialysis. A collection of reliable and up-to-date international drug information references were used, including the *American Hospital Formulary Service Drug Information*, *Martindale: the Complete Drug Reference*, the *British National Formulary*, the *Drug Information Handbook*, *Drug Prescribing in Renal Failure*, *2007 Dialysis of Drugs*, and the *Physician's Desk Reference*. The recommendations in the prepared handbook were reviewed and approved by a professor of clinical pharmacy and a senior consultant nephrologist before the intervention phase was started.

The purpose of this strategy was to save the clinicians time during clinical rounds and provide them with evidence-based recommendations so that appropriate dosing decisions could be made. Prescription of a medication was rated as inappropriate and a recommendation to adjust was given to the prescriber when the dosage prescribed was greater or lower than the recommendations in the drug information references that we used or when the drug was contraindicated. Dosages that agreed with recommendations from any of the previously mentioned drug information references were considered correct.

An ADE was defined as "an injury resulting from the use of a drug."^{32,33} To assess the causal relationship between the suspected drug and the event, the Naranjo algorithm³⁴ was used. For clinical laboratory tests, any value below or above the normal range used by the hospital pathology laboratory with a possible causality to a medication using Naranjo's causality assessment was considered an ADE. Events were classified as preventable and non-preventable. Preventable ADEs were those that could have been avoided by appropriate drug selection or management. Preventability was determined on the basis of the physician's presumed knowledge at the time of drug prescribing. The physician's decision was correct if insufficient information was available. If an event was preventable, the type of error was specified.³⁵ To evaluate the seriousness of ADEs, we used the Food and Drug Administration's definition of serious ADEs, which are those that "result in death, a life-threatening condition, initial or extended hospitalization, persistent or significant disability, cancer, and congenital abnormalities." Adverse drug events that did not meet this definition but still required treatment were defined as significant. Finally, events that did not require treatment were defined as mild or insignificant.^{32,33}

Cost savings or additions were calculated from the difference between the cost of the regimen (number of doses/day \times number of days \times cost of unit dose) initially prescribed by the physician and the cost of the regimen after the intervention of the pharmacist. The costs of medications on file in the hospital pharmacy were used.

A standardized form specially designed for the study was used for data collection. Data were collected from the patients' medical records and charts and included age, sex, race, weight, medical history and comorbidities, diagnostic tests, dialysis information, drug therapy (strength, frequency, duration), ADEs, and dosage appropriateness during hospitalization.

Data analysis was performed using the Statistical Package for the Social Sciences version 15 (SPSS Inc., Chicago, IL). Continuous variables were expressed as the mean \pm SD. Discrete variables were expressed as counts and percentages. A χ^2 test was used to compare categorical data between the 2 groups. The Mann-Whitney rank sum test was used for continuous variables that were not normally distributed. Two-sided p values less than 0.05 were considered statistically significant.

Results

Baseline characteristics of the patients are shown in Table 1. There were no significant differences between the preintervention and intervention groups in terms of age, sex, weight, dialysis, comorbidities, or number of medications taken during the study. Most of the patients had stage 5 CKD and were on dialysis.

In the preintervention group, drug dosage adjustment or avoidance based on renal function was necessary for 607 of 2814 (21.6%) prescriptions. Of these, 285 (47.0%) complied with dosing guidelines and 322 (53.0%) did not. In the intervention group, dosage adjustment or avoidance based on renal function was necessary for 640 of 2981 (21.5%) prescriptions. With the collaborative renal drug dosing service, 464 (72.5%) of the prescriptions were adjusted according to recommendations. Deviations from recommended doses decreased to 176 (27.5%) prescriptions of the drugs studied ($p < 0.001$), as shown in Figure 1.

Of 388 pharmacist recommendations during the intervention phase, the prescribers accepted a total of 212 (54.6%). Drugs often prescribed inappropriately for patients with renal impairment (ie, prescribed at doses or frequencies higher than recommended or prescribed when contraindicated) included antibacterials such as ampicillin/sulbactam, ceftazidime, amoxicillin/clavulanic acid, and amikacin; ranitidine; metoclopramide; angiotensin-converting enzyme (ACE) inhibitors; tramadol; atenolol; chlorothiazide; and allopurinol. The dosages were always too high and never too low. Table 2 shows a comparison between the preintervention and intervention groups.

Of the 300 patients in the preintervention group, 64 (21.3%) had a suspected ADE, for a total of 73 events (Table 3). This number was significantly lower in the inter-

vention group, which had 49 events in 48 (16.0%) patients ($p < 0.05$). When the preventability of events was evaluated, 25 events were possibly preventable in the preintervention group versus 12 in the intervention group. The major cause of preventable events was inappropriate dose, which resulted in 14 preventable events in the preintervention group and 5 in the intervention group. The drug classes most frequently involved in ADEs were antibacterials, drugs for diabetes mellitus, diuretics, mineral supplements, and antithrombotic agents. Regarding the seriousness of events, in the preintervention group, 20 (27.4%) ADEs were serious, 42 (57.5%) were significant, and 11 (15.1%) were insignificant. In the intervention group, 5 (10.2%) were serious, 36 (73.5%) were significant, and 8 (16.3%) were insignificant. Serious ADEs included symptomatic electrolyte disturbances, severe hypotension, severe hypoglycemia, neutropenia, intestinal bleeding, and respiratory depression. Examples of significant ADEs included mild hypoglycemia, mild electrolyte disturbances, mild hypotension, myalgia, diarrhea, vomiting, and epigastric pain that required therapeutic interventions. Insignificant events included hypoglycemia, electrolyte disturbances, diarrhea, nausea, and vomiting that were abnormal or bothersome but required no treatment.

The intervention of a collaborative dosing scheme resulted in drug cost savings of Malaysian Ringgit (RM) 7760 (\$2250 US). Given that the study lasted 4 months and the sample represented approximately 50% of the patients who were admitted to the nephrology unit, the possible savings for all patients in 1 year can be estimated to be around RM 46,560 (\$13,500 US). In fact, some of the drugs prescribed in this study were expensive, and dosage adjustment led to substantial savings. These included imipenem/cilastatin, meropenem, piperacillin/tazobactam, cefepime, ampicillin/sulbactam, and fluconazole.

Discussion

The available literature indicates that improvements in compliance with renal dosing guidelines are needed in all patient care settings. Several studies have indicated that dosing errors and the risk of toxicity are common among patients with renal impairment.^{2,15-19,22} In this study, noncompliance with dosing guidelines was observed in 322 (53.0%) prescriptions in the preintervention group. When a pharmacist collaborated in clinical rounds, however, the number of dosages prescribed that were higher than those recommended by medical books and the number of prescrip-

Table 1. Patient Demographic and Clinical Characteristics

Characteristic	Preintervention	Intervention	p Value
Sex, n (%)			0.220 ^a
male	168 (56.0)	153 (51.0)	
female	132 (44.0)	147 (49.0)	
Ethnic group, n (%)			0.016 ^a
Chinese	153 (51.0)	120 (40.0)	
Malay	97 (32.3)	134 (44.7)	
Indian	48 (16.0)	45 (15.0)	
other	2 (0.7)	1 (0.3)	
Age, mean \pm SD	55.56 \pm 14.15	55.30 \pm 14.37	0.781 ^b
Weight, mean \pm SD	59.20 \pm 10.81	58.84 \pm 11.77	0.853 ^b
Stage of CKD, n (%)			0.044 ^a
5	266 (88.7)	281 (93.7)	
4	23 (7.7)	16 (5.3)	
3	11 (3.7)	3 (1.0)	
Dialysis, n (%)			0.679 ^a
none	56 (18.7)	55 (18.3)	
hemodialysis	163 (54.3)	154 (51.3)	
peritoneal	35 (11.7)	45 (15.0)	
in-hospital only	46 (15.3)	46 (15.3)	
Drugs used in hospital (n), mean \pm SD	9.38 \pm 3.63	9.94 \pm 3.78	0.064 ^b
CKD = chronic kidney disease.			
^a χ^2 test.			
^b Mann-Whitney test.			

tions for contraindicated drugs decreased to 176 (27.5%) ($p < 0.001$). Compared with other studies that evaluated the dosage adjustment according to renal function in inpatient settings, the rate of inappropriate dosages in this study before the intervention (53.0%) was higher than that reported by Salomon et al.¹⁷ from France, whose rate was 34.0% of inappropriate dosages, and that by Pillans et al.¹⁶ from Australia, who found doses to be inappropriately

high in 42.2% of admission prescriptions for drugs that required adjustment. However, it was lower than that reported by Falconnier et al.²² from Switzerland, where doses were not adjusted to individual renal function in 67.0% of renally eliminated drugs before the pharmacist intervention, and by Sweileh et al.¹⁸ from Palestine, where medication dosing errors reached 73.6%. The rate after the intervention (27.5%) was lower than that in all other studies ex-

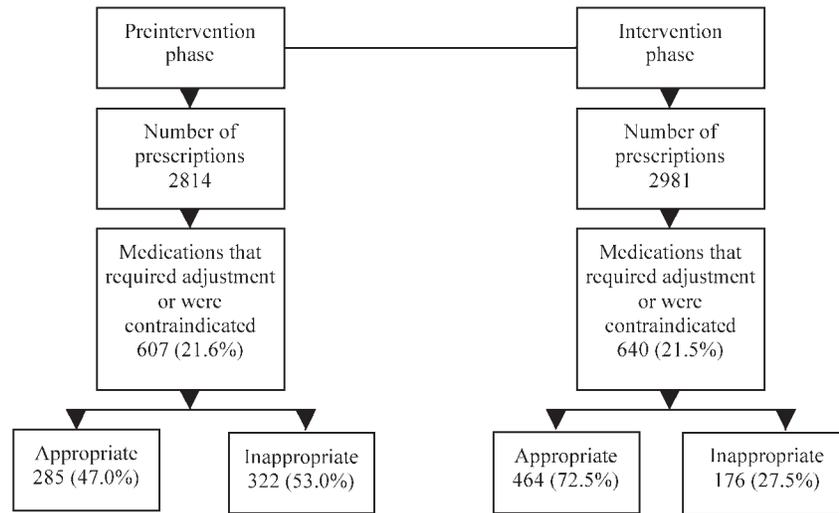


Figure 1. Main results of dose appropriateness.

Table 2. Impact of Clinical Pharmacy Service on Dosage Adjustment and Avoidance of Contraindicated Drugs

Drug	Preintervention Group		Intervention Group		p Value ^a
	Total	Inappropriate, n (%)	Total	Inappropriate, n (%)	
Drugs that required dosage adjustment or were contraindicated	607	322 (53.0)	640	176 (27.5)	<0.001
Antibacterials	233	63 (27.0)	270	32 (11.9)	<0.001
ampicillin/sulbactam					
ceftazidime					
amoxicillin/clavulanate					
vancomycin					
piperacillin/tazobactam					
cefuroxime					
amikacin					
Cardiovascular	142	87 (61.3)	110	49 (44.6)	<0.001
perindopril					
atenolol					
spironolactone					
chlorothiazide					
captopril					
digoxin					
Gastrointestinal	157	118 (75.2)	176	62 (35.2)	<0.001
ranitidine					
metoclopramide					
Other	75	54 (72.0)	84	33 (39.3)	<0.001
tramadol					
allopurinol					
acyclovir					
colchicine					
tranexamic acid					
gabapentin					

^a χ^2 test.

cept the one by Falconnier et al.,²² in which the pharmacist intervention decreased the rate to 19.0%. The previous studies differed in the level of CrCl used for inclusion criteria, the guidelines used, and the hospital units included, which limits the ability to compare the percentages of inappropriate dosages. However, it is reasonable to say that the problem is international in scope. Most of the previous studies were descriptive, with no interventions to try to improve the situation.¹⁶⁻¹⁹ A limited number of studies tried to implement interventions to overcome the problem.

Several studies have suggested that clinical pharmacists be included as multidisciplinary healthcare providers in the management of CKD.^{2,22,36,37} Pharmacists have had a dramatic impact in decreasing drug-related problems in ambulatory hemodialysis patients and transplant patients.³⁶⁻⁴⁰ Regarding dosing services, we were unable to find previous studies that focused specifically on patients in a nephrology unit. The patients in this study were hospitalized in the nephrology unit, and most were on dialysis, with many complications, making the task of the physician more difficult. In agreement with our results, studies from other units have shown a positive impact of pharmacist interventions. Falconnier et al.²² studied the impact on dosage adjustment of a list of targeted drugs from immediate feedback by a clinical pharmacist at an internal medicine unit concurrent with prescribing during medical rounds. In the control group, doses were adjusted to individual renal function in only 23 (33%) renally eliminated drugs. In the

intervention group, 155 (81%) were corrected. They also decreased the cost of renally eliminated drugs. Drugs often prescribed in high dosages in their study included digoxin, amoxicillin, ciprofloxacin, flucloxacillin, norfloxacin, atenolol, sotalol, enalapril, ranitidine, fluconazole, and acyclovir. In a study by Moffett et al.,⁴¹ pharmacist recommendations were responsible for 96% of medication adjustments for renal dysfunction in a pediatric cardiac intensive care unit, and the recommendations were accepted and appropriate all of the time.

In our study, the pharmacist made 388 recommendations related to dosing adjustment, 212 (54.6%) of which were accepted by physicians. This acceptance rate is considered low if compared with other studies that include pharmacists' interventions. Acceptance of pharmacists' recommendations varies among studies. In the US, acceptance rates range from 76%³⁷ to 99%.^{42,43} In Malaysia, clinical pharmacy is a new, developing field and some prescribers might not be familiar with pharmacist intervention.

The number of preventable ADEs was lower in the intervention phase, with 12 events compared with 25 in the preintervention group. Preventable events due to inappropriate doses decreased from 14 to 5 events. The results agree with those of many other studies, which support the hypothesis that participation of pharmacists in clinical rounds lowers the frequency of ADEs.^{6,11,21,26}

The intervention in this study resulted in cost savings of approximately \$2250 US. The possible savings for all patients in the ward in one year can be estimated to be around \$13,500 US. These drug acquisition costs represent only part of the total possible savings. Savings in administrative costs, such as materials and nursing time, and savings from avoidance of ADEs were not calculated. Yet we can conclude that pharmacist intervention can save money. This finding is similar to those of other studies aiming to optimize drug and antibiotic dosing in patients with renal impairment.^{14,22,37} Recommendations for drug dosing adjustments are part of the clinical pharmacist's daily responsibilities and do not require additional staff support at our institution.

One limitation of this study is that any laboratory value outside the normal range with a possible causality to a medication, determined by using Naranjo's causality assessment, was considered an ADE. This may have led to an overestimation of ADEs. In fact, we used this definition because electrolyte disturbances were very common in these patients; these were possible ADEs in many cases (eg, hypokalemia with diuretics, hyperkalemia with ACE inhibitors or potassium supplements), in addition to hypoglycemia with insulin. In many cases, these abnormalities required medical treatment. If the abnormality in the laboratory value required no treatment, this was considered an insignificant ADE.

Table 3. Comparison of Adverse Drug Events

Parameter	Preintervention n (%)	Intervention n (%)
Preventability		
preventable	25 (34.2)	12 (24.5)
unpreventable	48 (65.8)	37 (75.5)
Causality^a		
highly probable	26 (35.6)	13 (26.5)
probable	26 (35.6)	17 (34.7)
possible	21 (28.8)	19 (38.8)
Seriousness		
serious	20 (27.4)	5 (10.2)
significant	42 (57.5)	36 (73.5)
insignificant	11 (15.1)	8 (16.3)
Main drug classes related to ADEs		
antibacterials	26 (35.6)	7 (14.3)
drugs used in diabetes	18 (24.7)	8 (16.3)
diuretics	5 (6.8)	10 (20.4)
mineral supplements	8 (11.0)	5 (10.2)
antithrombotic agents	3 (4.1)	4 (8.20)
TOTAL	73 (100.0)	49 (100.0)
ADEs = adverse drug events.		
^a Naranjo rating.		

The pharmacoeconomic impact of the intervention is probably underestimated in this study, as we included savings in drug costs only. Also, we did not examine the clinical significance of clinicians' noncompliance with dosing guidelines. Theoretically, excessive doses are expected to subject patients to toxicity and ADEs.

We conclude that a renal drug dosing service provided by a clinical pharmacist for patients hospitalized with CKD can increase the proportion of drugs adjusted to renal function. This could reduce drug costs and prevent ADEs. Thus, this study argues for including pharmacists in multidisciplinary teams in nephrology units.

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References

1. Classen DC, Pestotnik SL, Evans RS, Lloyd JF, Burke JP. Adverse drug events in hospitalized patients: excessive length of stay, extra cost, and attributable mortality. *JAMA* 1997;227:301-6.
2. Long CL, Raebel MA, Price DW, Magid DJ. Compliance with dosing guidelines in patients with chronic kidney disease. *Ann Pharmacother* 2004;38:853-8. Epub 30 Mar 2004. DOI 10.1345/aph.1D399
3. Kappel J, Calissi P. Safe drug prescribing for patients with renal insufficiency. *Can Med Assoc J* 2002;166:473-7.
4. Swan SK, Bennett WM. Drug dosing guidelines in patients with renal failure. *West J Med* 1992;156:633-8.
5. Gabardi S, Abramson S. Drug dosing in chronic kidney disease. *Med Clin North Am* 2005;89:649-87.
6. Manley HJ, Cannella CA, Bailie GR, Pater WL. Medication-related problems in ambulatory hemodialysis patients: a pooled analysis. *Am J Kidney Dis* 2005;46:669-80.
7. Bonk ME, Krown H, Matuszewski K, Oinonen M. Potentially inappropriate medications in hospitalized senior patients. *Am J Health Syst Pharm* 2006;63:1161-5.
8. Fattinger K, Roos M, Vergères P. Epidemiology of drug exposure and adverse drug reactions in two Swiss departments of internal medicine. *Br J Clin Pharmacol* 2000;49:158-67.
9. Fijn R, Van den Bemt PM, Chow M, et al. Hospital prescribing errors: epidemiological assessment of predictors. *Br J Clin Pharmacol* 2002;53:326-31.
10. Kanjanarat P, Winterstein AG, Johns TE, Hatton RC, Gonzalez-Rothi R. Nature of preventable ADEs in hospitals: a literature review. *Am J Health Syst Pharm* 2002;60:1750-9.
11. Rommers MK, Teepe-Twiss IM, Guchelaar HG. Preventing adverse drug events in hospital practice: an overview. *Pharmacoepidemiol Drug Saf* 2007;16:1129-35.
12. Blix HS, Viktil KK, Moger TA, Reikvam A. Use of renal risk drugs in hospitalized patients with impaired renal function—an underestimated problem. *Nephrol Dial Transplant* 2006;21:3164-71.
13. Manley HJ, Drayer DK, Muther RS. Medication-related problem type and appearance rate in ambulatory hemodialysis patients. *BMC Nephrol* 2003;4:10.
14. Preston SL, Briceland LL, Lomaestro BM, Lesar TS, Bailie GR, Drusano GL. Dosing adjustment of 10 antimicrobials for patients with renal impairment. *Ann Pharmacother* 1995;29:1202-7.
15. Chertow GM, Lee J, Kumperman GJ, et al. Guided medication dosing for inpatients with renal insufficiency. *JAMA* 2001;286:2839-44.
16. Pillans PI, Landsberg PG, Fleming AM, Fanning M, Sturtevant MJ. Evaluation of dosage adjustment in patients with renal impairment. *Intern Med J* 2003;33:10-3.
17. Salomon L, Deray G, Jaudon MC, et al. Medication misuse in hospitalized patients with renal impairment. *Int J Qual Health Care* 2003;15:331-5.
18. Sweileh WM, Janem SA, Sawalha AF, et al. Medication dosing errors in hospitalized patients with renal impairment: a study in Palestine. *Pharmacoepidemiol Drug Saf* 2007;16:908-12.
19. VanDijk EA, Drabbe NR, Kruijtbosch M, Smet PAD. Drug dosage adjustments according to renal function at hospital discharge. *Ann Pharmacother* 2006;40:1254-60. Epub 27 Jun 2006. DOI 10.1345/aph.1G742
20. Leape LL, Bates DW, Cullen DJ, et al. System analysis of adverse drug events. *JAMA* 1995;274:35-43.
21. Kucukarslan SN, Peters M, Mlynarek MM, Nafziger DA. Pharmacists on rounding teams reduce preventable adverse drug events in hospital general medicine units. *Arch Intern Med* 2003;163:2014-8.
22. 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;16:369-75.
23. Galanter WL, Didomenico RJ, Polikaitis A. A trial of automated decision support alerts for contraindicated medications using computerized physician order entry. *J Am Med Inform Assoc* 2005;12:269-74.
24. Walton R, Dovey S, Harvey E, Freemantle N. Computer support for determining drug dose: systematic review and meta analysis. *Br Med J* 1999;318:984-90.
25. Kaboli PJ, Hoth AB, McClimon BJ, Schnipper JL. Clinical pharmacists and inpatient medical care: a systematic review. *Arch Intern Med* 2006;166:955-64.
26. Leape LL, Cullen DJ, Clapp MD, et al. Pharmacist participation on physician rounds and adverse drug events in the intensive care unit. *JAMA* 1999;282:267-70.
27. Spruill WJ, Wade WE, Cobb HH. Estimating glomerular filtration rate with a modification of diet in renal disease equation: implications for pharmacy. *Am J Health Syst Pharm* 2007;64:652-60.
28. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function—measured and estimated glomerular filtration rate. *N Engl J Med* 2006;354:2473-83.
29. Ashley C, Morlidge C. Introduction to renal therapeutics. London: Pharmaceutical Press, 2008.
30. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;39(2 suppl 1):S1-266.
31. 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. *Br Med J* 2005;331:263-6.
32. Nebeker JR, Barach P, Samore MH. Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. *Ann Intern Med* 2004;140:795-801.
33. Nebeker JR, Hurdle JF, Hoffman JM, Roth B, Weir CR, Samore MH. Developing a taxonomy for research in adverse drug events: potholes and signposts. *J Am Med Inform Assoc* 2002;9(suppl):S80-5.
34. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30:239-45.
35. Gandhi TK, Weingart SN, Borus J, et al. Adverse drug events in ambulatory care. *N Engl J Med* 2003;348:1556-64.
36. Joy MS, DeHart RM, Gilmartin C, et al. Clinical pharmacists as multidisciplinary health care providers in the management of CKD: a joint opinion by the Nephrology and Ambulatory Care Practice and Research Networks of the American College of Clinical Pharmacy. *Am J Kidney Dis* 2005;45:1105-18.

37. Manley HJ, Carroll CA. The clinical and economic impact of pharmaceutical care in end-stage renal disease patients. *Semin Dial* 2002;15:45-9.
38. Kaplan B, Shimp LA, Mason NA, Ascione FJ. Chronic hemodialysis patients. Part II: reducing drug-related problems through application of the focused drug therapy review program. *Ann Pharmacother* 1994;28:320-4.
39. Wang HY, Chan AL, Chen MT, Liao CH. Effect of pharmaceutical care intervention by clinical pharmacists in renal transplant clinics. *Transplant Proc* 2008;40:2319-23.
40. Grabe DW, Low CL, Bailie GR, Eisele G. Evaluation of drug-related problems in an outpatient hemodialysis unit and the impact of a clinical pharmacist. *Clin Nephrol* 1997;47:117-21.
41. Moffett BS, Mott AR, Nelson DP, Gurwitsch KD. Medication dosing and renal insufficiency in a pediatric cardiac intensive care unit: impact of pharmacist consultation. *Pediatr Cardiol* 2008;29:744-8.
42. Leape LL, Cullen DJ, Clapp MD, et al. Pharmacist participation on physician rounds and adverse drug events in the intensive care unit. *JAMA* 1999;282:267-70.
43. Gandhi PJ, Smith BS, Tataronis GR, Maas B. Impact of a pharmacist on drug costs in a coronary care unit. *Am J Health Syst Pharm* 2001;58:497-503.

Impacto de un Programa de Dosificación en el Ajuste de Dosis en Pacientes Hospitalizados con Enfermedad Crónica del Riñón en Malasia

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EXTRACTO

TRASFONDO: La selección y dosificación adecuadas de medicamentos para pacientes con enfermedad crónica del riñón (CKD) es importante para evitar efectos no deseados y asegurar resultados óptimos en los pacientes.

OBJETIVO: Evaluar el índice de dosificación inapropiada en pacientes con CKD en una unidad de nefrología y evaluar el impacto de un farmacéutico en el ajuste en dosis de medicamentos, eventos de reacciones adversas (ADEs) y costo en medicamentos, al realizar rondas con el equipo de médicos.

METODOLOGÍA: El estudio consistió de una fase de pre-intervención (grupo control) y una fase de intervención. Dos muestras aleatorias de 300 pacientes con una depuración estimada de creatinina ≤ 50 mL/minutos fueron incluidos. Durante la fase de pre-intervención se realizó observación prospectiva durante un período de 4 meses. Durante la fase de intervención, un farmacéutico clínico realizó rondas junto al equipo de la unidad de nefrología y recomendó ajustes en dosis cuando era necesario. Se preparó un manual de bolsillo para realizar las recomendaciones, utilizando referencias actualizadas y confiables.

RESULTADOS: Durante la fase de pre-intervención 607 (21.6%) órdenes de un total de 2814 requerían ajuste en dosis o cambio en medicamento, basado en la función renal del paciente. De éstas, 322 (53%) no cumplieron con las guías de dosificación para pacientes con CKD que recomiendan las referencias. Durante la fase de intervención 640 (21.5%) órdenes de un total de 2981 requerían ajuste en dosis. El farmacéutico realizó 388 recomendaciones relacionadas con ajuste en dosis, de las cuales 212 (54.6%) fueron aceptadas por los médicos. El incumplimiento de los médicos con las guías de dosificación disminuyó a 176 (27.5%, $p < 0.001$) órdenes de los medicamentos estudiados. Durante la fase de pre-

intervención 64 (21.3%) pacientes tuvieron sospecha de un ADE para un total de 73 eventos. En el grupo de las intervenciones este número fue significativamente menor (49 eventos en 48 [16.0%] pacientes, $p < 0.05$). Las intervenciones resultaron en una economía de \$2250.

CONCLUSIONES: Un programa de dosificación de medicamentos para pacientes hospitalizados con CKD puede aumentar la proporción de ajuste en dosis de medicamentos al tomar en consideración la función renal. Esto puede resultar en economía en costos de medicamentos y puede prevenir ADEs.

Traducido por Astrid J García-Ortiz

Impact des Interventions d'un Pharmacien Clinicien auprès de Patients Souffrant d'Insuffisance Rénale Chronique Hospitalisés dans une Unité de Néphrologie en Malaisie

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RÉSUMÉ

INTRODUCTION: Le choix et la posologie d'un médicament chez les patients atteints d'insuffisance rénale chronique sont particulièrement importants pour optimiser les effets thérapeutiques tout en minimisant les effets indésirables.

OBJECTIF: Estimer la fréquence à laquelle des dosages inadéquats sont prescrits aux patients souffrant d'insuffisance rénale chronique dans une unité de soins de néphrologie et évaluer l'impact de la présence d'un pharmacien au sein de l'équipe soignante sur l'ajustement des doses, les effets secondaires, et les coûts.

DEVIS EXPÉRIMENTAL: Il s'agit d'une étude comparant la situation durant l'intervention du pharmacien à celle précédant son intervention. Deux échantillons de 300 patients ayant une clairance à la créatinine estimée à ≤ 50 mL/minute ont été inclus. Au cours de la phase d'intervention, un pharmacien clinicien accompagnait l'équipe médicale dans sa tournée des patients hospitalisés à l'unité de soins de néphrologie et donnait des recommandations, lorsque nécessaire, quant à l'ajustement des doses de médicaments. Une compilation des sources de référence les plus récentes était à la disposition du pharmacien pour ses interventions.

RÉSULTATS: Dans le groupe pré-intervention, un ajustement de la dose ou encore l'arrêt complet du médicament à cause de la fonction rénale a été nécessaire pour 607 des 2814 (21.6%) prescriptions. Dans 322 (53.0%) cas, la prescription était en contradiction avec les guides thérapeutiques existants. Dans le groupe ayant bénéficié de l'intervention du pharmacien, l'ajustement a été nécessaire pour 640 des 2981 (21.5%) prescriptions. Le pharmacien effectua 388 recommandations concernant la dose et 212 (54.6%) furent acceptées par le médecin. La non observance par les cliniciens des guides thérapeutiques n'a été constaté que dans 176 (27.5%) cas, une diminution significative par rapport au groupe pré-intervention ($p < 0.001$). Dans le groupe pré-intervention, 64 (21.3%) des patients souffrent d'un effet secondaire, pour un total de 73 événements. Dans le groupe avec intervention, ce nombre était significativement plus bas: 49 événements chez 48 (16.0%) patients ($p < 0.05$). L'intervention du pharmacien s'est soldé par des économies se chiffrant, en termes de médicaments seulement, à 2250 USD.

CONCLUSIONS: La présence d'un pharmacien dans l'équipe de néphrologie permet de mieux ajuster les doses de médicaments chez les patients souffrant d'insuffisance rénale chronique, et ainsi réduire le nombre d'effets secondaires et les coûts.

Traduit par Suzanne Laplante