Farm Hosp. 2009;**33(3):**147-54

Farmacia
HOSPITALARIA

www.elsevier.es/farmhosp

ORIGINAL ARTICLE

Assessment of a pharmaceutical interventional programme in patients on medications with renal risk☆

L. Álvarez Arroyo,[a,*] E. Climent Grana,[a] N. Bosacoma Ros,[a] S. Roca Meroño,[b] M. Perdiguero Gil,[b] J.P. Ordovás Baines,[a] and J. Sánchez Payá[c]

[a]*Servicio de Farmacia, Hospital General Universitario de Alicante, Alicante, Spain*
[b]*Servicio de Nefrología, Hospital General Universitario de Alicante, Alicante, Spain*
[c]*Servicio de Medicina Preventiva, Hospital General Universitario de Alicante, Alicante, Spain*

Received July 31, 2008; accepted March 19, 2009

KEYWORDS
Renal disease;
Pharmaceutical care;
Medications with renal risk;
Dosage adjustment;
Compliance

Abstract
Objective: To compare the adaptation of medical prescriptions according to the dosage guides in patients with renal disease, before and after applying a pharmaceutical intervention programme. The secondary objectives were to prepare a guide to dosing in renal disease and to measure the prevalence of prescription of drugs with renal risk.
Method: Non-randomised, experimental interventional study (before/after) conducted in a general hospital with 800 beds, including hospitalised patients, over the age of 18, with kidney disease and drugs with renal risk prescribed in their pharmaco-therapeutic profile. The study was designed to be carried out in 2 descriptive cross-cutting phases (control group) and a prospective interventional cohort study (intervention group). The primary variable was the percentage non-adaptation according to the stage of renal disease.
Results: The study included 185 patients, 88 in the control group and 97 in the intervention group. In the intervention group, the prevalence of non-compliance before and after the intervention was 18.7% and 2.1%, representing a statistically significant reduction in non-adaptation of the dose. The costs saved with the pharmaceutical intervention programme were 1939.63 euro over 2 months, the average saving per medication intervened amounting to 62.57 euro (95%CI, 23.99-101.14 euro; *P*=.02).
Conclusions: The results of the study indicate that the application of a pharmaceutical care model based on the prospective validation of drugs with renal risk, very significantly improved the adaptation of dosing regimens in kidney disease.

☆The preliminary data from this study was presented to the 52nd Congress of the Spanish Society of Hospital Pharmacy held in Tenerife in September of 2007 as a poster: "*Cumplimiento de las pautas posológicas en pacientes con enfermedad renal: estudio de prevalencia*" (Compliance of dosage guidelines in patients with kidney disease: prevalence study).

*Corresponding author.
E-mail address: lauraalvarez6@yahoo.es (L. Álvarez Arroyo).

PALABRAS CLAVE
Enfermedad renal;
Atención farmacéutica;
Medicamentos con riesgo renal;
Ajuste posológico;
Cumplimiento

Evaluación de un programa de intervención farmacéutica en pacientes con medicamentos de riesgo renal

Resumen
Objetivo: Comparar la adecuación de las prescripciones médicas según las guías de dosificación, en pacientes con enfermedad renal, antes y después de aplicar un programa de intervención farmacéutica. Los objetivos secundarios fueron la elaboración de una guía de dosificación en enfermedad renal y medir la prevalencia de prescripción de fármacos con riesgo renal.
Método: Estudio experimental de intervención no aleatorizado (antes/después) realizado en un hospital general de 800 camas, que incluyó a pacientes ingresados, mayores de 18 años, con enfermedad renal y medicamentos con riesgo renal prescritos en su perfil farmacoterapéutico. El estudio se diseñó para realizarlo en dos fases: un corte transversal descriptivo (grupo control) y un estudio de intervención de cohortes prospectivo (grupo de intervención). La variable principal fue el porcentaje de inadecuación posológica según el grado de enfermedad renal.
Resultados: El estudio incluyó a 185 pacientes, 88 en el grupo control y 97 en el de intervención. En el grupo de intervención la prevalencia de incumplimiento antes y después de la intervención fue del 18,7 y el 2,1%, lo que supone una reducción estadísticamente significativa en la inadecuación posológica. El coste evitado con el programa de intervención farmacéutica fue de 1.939,63 euros en 2 meses; la media por cada medicamento en el que se intervino fue de 62,57 euros (intervalo de confianza del 95 %, 23,99-101,14 euros; p = 0,02).
Conclusiones: Los resultados del estudio indican que la aplicación de un modelo de atención farmacéutica, basado en la validación prospectiva de los medicamentos con riesgo renal, mejora de forma muy significativa la adecuación de las pautas posológicas en enfermos renales.

Introduction

Chronic kidney disease (CKD) is an important world-wide problem for public health due to its high incidence, the concomitant cardiovascular mortality, and the economic costs that it generates.

The available epidemiologic data for CKD comes mostly from patients that start substitutive treatment with dialysis or kidney transplants,[1] and epidemiologic information for the earlier stages of CKD is scarce. In the NHANES III study carried out in the United States on the general population, the total prevalence of CKD was 11%[2]

In Spain, the prevalence of CKD is unknown, however, according to different epidemiologic studies, it varies between 7.5%and 18.4% Results from the pilot stage carried out in Galicia have recently been obtained, from the EPIRCE[3] study (Epidemiological Study on Kidney Failure in Spain), where the prevalence was 12.7% In the hospital environment in Spain, the ERPHOS study (Chronic Kidney Kisease in Hospitalised Patients) is being carried out, but results are not yet available.

Kidney disease (KD) is relatively common in hospitalised patients and it entails an increase in mortality and morbidity related to hospitalisation.[4] Patients with acute or chronic KD are more frequently hospitalised than those patients that do not suffer from KD, due to the KD in itself as well as its effects on other pathological processes.

The adjustment of the dosage of drugs to the individual characteristics of each patient helps to maximise the therapeutic effectiveness and minimise the adverse effects related with medications. This dose adjustment is especially important in CKD as many drugs (antibiotics, digoxin, lithium..) or their metabolites, are eliminated through the kidneys, and can accumulate and cause adverse effects or an increase in the morbidity and mortality, which generates additional unnecessary sanitary expenses.

Dosage guidelines have been published for drugs that are susceptible to dose adjustments in patients with kidney disease to support medical prescriptions.[5]

Previous studies carried out in hospitals found non-compliance rates with the various dosage guides in kidney failure of 19%-67%; the criteria of defining CKD and the medications used in different studies[6-11] are also variables.

The principal objective of this study was to compare the adjustment of medical prescriptions according to the dosage guides in patients with kidney disease, before and after implementing a pharmaceutical intervention programme. The secondary objectives were the elaboration of a dosage guide for kidney disease and to measure the prevalence of the prescription of drugs with renal risk in said patients.

Method

The study was a non-randomised experimental interventional study (before/after) conducted in a general university hospital with 800 beds, with medical, surgical, critical, and emergency services.

Design

The study was conducted in 3 periods:

1. Elaboration of the dosage guide for kidney failure medications. A multidisciplinary team, formed by a pharmacist and a nephrologist, carried out a bibliographic review of all of the medications included in the pharmaco-therapeutical guide (PTG) of the hospital that were susceptible for dose adjustment in CKD. A computer application was designed in Access (with the following fields: principle active ingredient, dosage schedule for normal renal function and for kidney failure with different intervals depending on creatinine clearance (ClCr): 60-30 mL/min, 30-10 mL/min, <10 mL/min, haemodialysis, and peritoneal dialysis.
2. Descriptive transversal study. The patients selected in this period formed the control group. This group included all patients with glomerular filtration rates (GFR) <60 mL/min/1.73 m^2, calculated from the creatinine-serum (Cr) data provided by the laboratory department using the abbreviated Modification of Diet in Renal Disease (MDRD) formula: $186 \times Cr^{-1.154} \times age^{-0.203} \times 0.742$ (for women) and/or 1.210 (for Afro-Americans). The pharmaco-therapeutic profile of these patients was analysed and the dosage of the prescribed medications was crossed with the need to adjust in kidney failure with the recommendations given by the GDMIR through SQL consultations using a computer application designed ad hoc. The dose prescribed, the dose required according to the degree of CKD, and the level of compliance of the GDMIR were recorded for all patients.
3. Prospective intervention cohort study. The patients included in this phase formed the intervention group and, the same methodology was used for selection as that used for the control group. Pharmaceutical intervention was carried out for all patients in which some medication with an inadequate dose was found concerning the level of renal function. All of the interventions carried out and the level of acceptance were recorded.

Study population

Patients admitted to the hospital during the study period, over 18-years-old, with kidney disease, defined as GFR<60 mL/min/1.73 m^2 (classification of the KDOQI guides),[12] being treated with medications that need adjusting for CKD.

Patients admitted to critical and emergency units were not included in the study as no computerised medical prescriptions were available for these departments. Also, the creatinine-serum, a value used to calculate the glomerular filtration to select and stratify patients, may be affected in these critical patients due to malnutrition and could add confusion to the study.

Pharmaceutical intervention

The pharmacist, with the help of the computerised application, identified the patients with kidney disease that were susceptible for intervention. The clinical records of the patients were reviewed, which revealed their diagnosis, co-morbidities, evolution, and motive for the prescription of the different drugs. This is especially important in the case of antibiotics, given that, according to the type and severity of the infection, the doses are variable and they are also variable in kidney failure. After this pharmaceutical evaluation, the intervention consisted in giving recommendations to modify the doses, the dosage intervals or both in the inadequate prescriptions according to the degree of CKD. The recommendation was done orally to the prescribing physician and/or in writing in a report included in the clinical records of the patients.

The acceptance of the recommendations was defined as the modification and/or suspension of the treatment in a period of 24 h after the recommendation was given.

Also, follow-up was carried out on all patients included in the study until their discharge from the hospital or death to detect possible variations in the clinical situation, renal function and the need for new interventions.

Sample size and type

— Descriptive study: a transversal cut was done for a day of hospitalisation including all of the patients that met the previously mentioned criteria
— Prospective cohort intervention study: the sample size needed was calculated regarding the results obtained in the descriptive study; a consecutive sampling was done until the needed sample size was reached. Given that the first phase of incompliance of the dose schedules was 22.5% and assuming an alpha error of 5% and a statistical power of 90%, the needed sample size to demonstrate a decrease in the rate of incompliance of 50% and 75% would be 214 and 81 medications. Given that a loss of 10% is assumed, a sample size of 160 medications or, equally, 80 patients. The duration of this phase was 2 months

Study variables

— Dose adjustment (%): correctly adjusted drugs according to the degree of CKD related to the total amount of prescribed drugs
— Economic cost (euros): calculated as the difference between the true cost of treatment (cost to acquire drugs) and the cost without intervention, in the case that this happened; this is the pharmaco-economic impact of the intervention programme
— Other variables: age (years), sex, GFR (mL/min/1.73 m^2), CKD stage (stage 3: GFR, 59-30 mL/min/1.73 m^2; stage 4: GFR, 29-15 mL/min/1.73 m^2; stage 5: GFR <15 mL/min/1.73 m^2); co-morbidities (hypertension, diabetes, dyslipidaemia, cardiovascular disease); and clinical service

Statistical analysis

The standard deviation and mean were used for the quantitative variables and relative frequencies were used for the qualitative variables. To find the differences in the compliance of the control group and the intervention group, the χ^2 test was used, while the McNemar test was used to compare the compliance before and after in the intervention

group for paired data. To compare economic costs, the Student *t* test was used for paired data.

The statistical significance for the contrast tests was $P<.05$.

Results

Demographic characteristics

During the descriptive period, 577 admitted patients were identified of which 421 had been prescribed some drug with renal risk, and, among them, 20.9%(88 patients, control group) had kidney disease at different stages (13.1%, stage 3; 4.5%, stage 4; and 3.3%, stage 5). The study included a total of 185 patients, 88 in the control group and 97 in the intervention group, whose demographic and base characteristics are shown in Table 1. Both groups were similar regarding age, distribution of sexes, creatinine, average hospital stay and co-morbidities, or renal risk factors (diabetes, cardiovascular diseases, hypertension, dyslipidaemia, anaemia). However, the patients of the intervention group had lower GFR and, therefore, a greater deterioration of renal function.

Table 1 Demographic data and basic characteristics

Variable	Control group (n=88)	Intervention group (n=97)	*P*[a]
Women	41 (46.6)	34 (45.1)	
Men	47 (53.4)	63 (64.9)	.11
Age, mean (SD), y	72.73 (15.11)	72.28 (14.1)	.835
Creatinine, mg/dL	2.93 (2.66)	2.83 (1.68)	.767
GFR, mL/min/1.73 m^2	33.38 (16.73)	28.33 (12.25)	.021
Stay, d	20 (17.97)	16.96 (13.91)	.183
Kidney failure stage			.106
Stage 3	55 (62.5)	50 (51.5)	
Stage 4	14 (15.9)	28 (28.9)	
Stage 5	19 (21.6)	19.6 (19)	
Diabetes mellitus	34 (38.6)	34 (35.1)	.613
Cardiovascular disease	47 (53.4)	56 (57.7)	.554
Hypertension	70 (79.5)	73 (75.3)	.486
Dyslipidaemia	29 (33)	41 (42.3)	.192
Anaemia	36 (40.9)	38 (39.2)	.117
CKF	61 (69.3)	70 (72.2)	.67

CKF indicates chronic kidney failure; GFR, glomerular diltration rate.
The data express n (%) or the average (standard deviation).
[a]The statistical significance has been determined using the Student *t* test to compare the averages and the χ^2 to compare proportions.

Table 2 Difference between the proportion of inadequate dosage between period 1 (control) and 2 (before intervention)

	Period 1 (n=169)	Period 2 (n=187)	Statistical significance[a]
Inadequate dosage, n (%)	38 (22.5)	35 (18.7)	Difference, 3.7%; SS, 4.3; 95%CI, −4.6 to 12.2; *P*=.483

Drugs that require dose adjustments for KD

The number of drugs with renal risk prescribed to the control group was 169 and to the intervention group, 187. In the control group, the prevalence of incompliance in the dosage of drugs with renal risk was 22.5%, and in the intervention group before carrying out the pharmaceutical intervention was 18.7%, with a difference of 3.8%, without statistical significance (Table 2). After the pharmaceutical intervention, the prevalence of incompliance was 2.1%, which implied a significant reduction in the inadequate dosage (Table 3).

This reduction in the incompliance is observed by stages of the kidney disease (Table 4), which is significant in stages 3 and 4.

The pharmaco-therapeutic group that was prescribed inadequate drugs with greater frequency in the intervention group was the antibiotic group (Figure 1) and, within said group, levofloxacin was the drug that required a greater number of interventions (Figure 2).

Pharmaceutical interventions

The level of acceptance of the pharmaceutical intervention by the prescribing physicians was 88.6%(95%confidence interval, 73.3–96.8). The number and type are shown in Table 5.

Economic costs

The economic impact of the pharmaceutical intervention programme (Table 6) was calculated as the cost avoided; this is the difference between the true cost of the treatment correctly adjusted to renal function and the cost that would have been necessary if the intervention was not carried out. The average cost avoided for each drug in the intervention group was 62.57 (105.16) Euros ($P=.02$).

Discussion

One of the principle causes of the high prevalence of kidney disease in hospitalised patients is due to a greater average age than the general population. In our population, 1 of every 5 patients that was hospitalised had kidney disease. This prevalence of kidney disease (20.9%)[13] is similar to the 17%found in the Falconnier et al[6] study and to the 25%of another study recently published.[7]

However, this contradicts the 5%prevalence found in the Cantu et al[8] study. This low frequency, compared with out population, is probably due to the stricter definition of Kidney Disease that these authors used (creatinine clearance <40 mL/min) and the younger age of the population with kidney disease (64 [15] years).

Table 3 Period 2: difference between the proportion of inadequate dosage after the pharmaceutical intervention between periods and in period 2 (before/ after)

Period 1 (control) compared to period 2 after intervention	Period 1 (n=169)	Period 2 (n=187)	Statistical test[a]
Inadequate dosage, n (%)	38 (22.5)	4 (2.1)	χ^2, 35; *P*<.001; RR=0.095; 95%CI, 0.03-0.26; RRR=90.5%
Period 2 (before and after), 187 drugs	Before	After	Statistical test[b]
Inadequate dosage, n (%)	35 (18.7)	4 (2.1)	χ^2, 29; *P*<.001; difference, 16.6%; SS, 2.72; 95%CI, 11.2-21.9

[a]Distribution of independent groups, 2×2 table, statistical test of the χ^2, and exact test of Fisher.
[b]Non-parametric distribution, paired groups, McNemar's statistical test.

Table 4 Statistical comparison of the degree of inadequate dosage in period 2 (before after) and its distribution according to the stage of chronic kidney disease

Period 2 (before and after intervention) 187 drugs	Stage	Before	After	*P*
Inadequate dosage, n (%)	3 (n=100)	11 (11)		<.001
	4 (n=47)	19 (40.4)	2 (4.3)	<.001
	5 (n=40)	5 (12.5)	2 (5)	.428

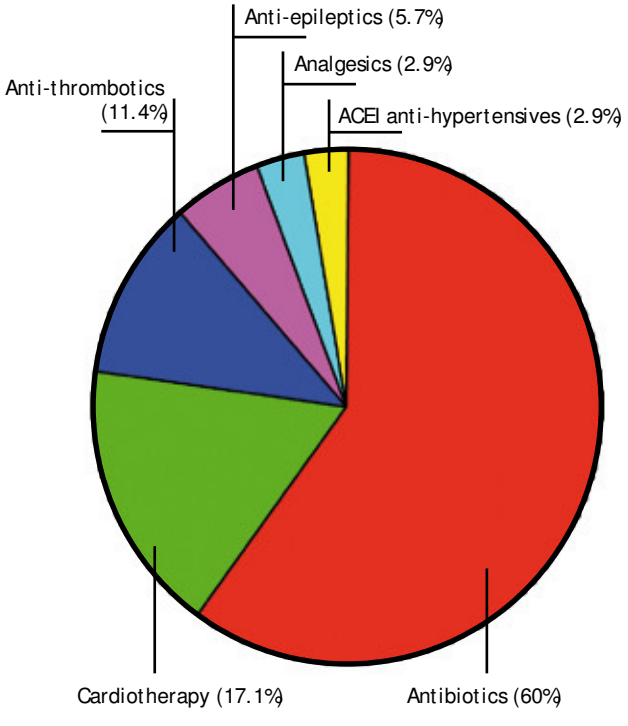

Figure 1 Distribution by percentages in the intervention group according to the pharmacological class (n=35). ACEI indicates inhibitors of the angiotensin converting enzyme.

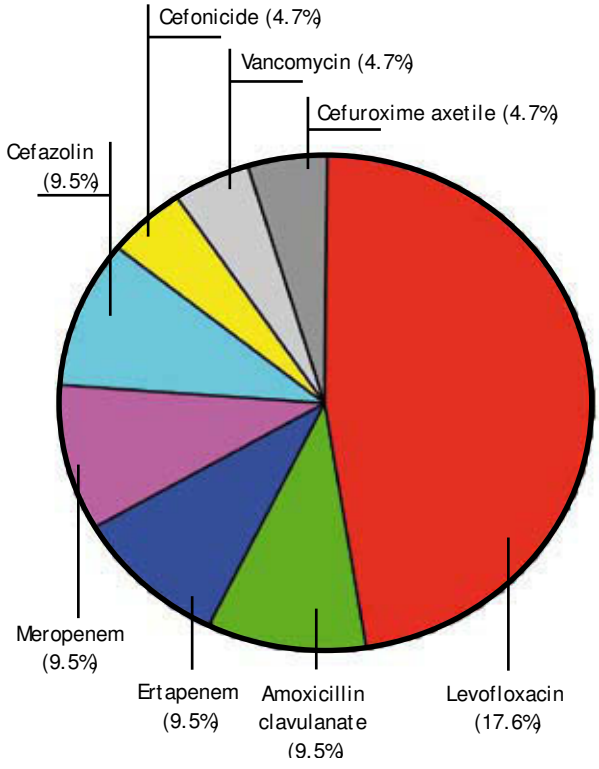

Figure 2 Distribution by percentages in the intervention group according to the drugs of group J (anti-infectious and antibiotics) (n=21).

Table 5 Distribution by percentages of the diverse interventions to optimise dosage in the intervention group (n=35)

Intervention	Drugs, n (%)	95%CI
Dose adjustment	22 (62.9)	44.9-78.5
Modify dose interval	10 (28.6)	14.6-46.3
Dose and interval	3 (8.6)	1.8-23.1

In our study, drugs with renal risk were prescribed inadequately in an important percentage of patients, however, after the pharmaceutical intervention, the incompliance of the GDMIR was reduced to 2.5%, compared with 22.5% of the control group. Long et al[9] recently carried out a systematic review of literature to determine the level of compliance with the dosage guides in CKD in hospitalised, chronic and ambulatory patients. The 4 studies analysed, carried out in hospitals, revealed incompliance rates of the dosage guides for CKD varying between 19%-67%; the criteria of defining CKD in the different studies is also a variable.

In the Falconier et al[6] study, carried out in an internal medicine department of a university hospital with 870 beds, the doses were inadequate in 67% of the patients in the retrospective control group and were reduced by 19% during the prospective intervention period.

In another recent study, the inadequate dosage of drugs with renal risk was 73.58%; and, 77.5% of these were prescribed during the hospital stay.[10]

Our results are similar to those from Salomon et al,[11] which reveal an incompliance rate of 20%, but they did not carry out interventions.

When trying to improve adequate dosage in patients with CKD, some authors have designed computer programmes that provide support to prescribers. This is the case of the study by Chertow et al,[4] where the physician is alerted at the moment of prescribing by the programme during the intervention period, and adequate dosage in CKD is improved, however, in spite of this tool, 49% of the doses continued to be inadequate. One of the limitations of these programs is that they do not take into account the reason the drug is prescribed, for example, antibiotics for severe infections, that require higher doses, and they also do not detect changes in renal function.

The pharmaco-therapeutic group that required the greatest number of interventions, similar to other studies,[14] was the group of the antibiotics. This result is probably due to the fact that this is the group with more principle active ingredients that require adjustment for kidney failure.

In our case, the elevated acceptance of the recommendations (88.6%), was probably because the oral and written reports were combined. Also, each patient was individually evaluated taking into account the reason for prescribing the drug, as well as the severity of the infection in the cases when antibiotics were used. The elevated percentage of dosage adjustment could also be due to the fact that this study only intervened on drugs where information in scientific literature is available from specific recommendations on dosage for kidney failure. The drugs that must be used with precaution with kidney disease were excluded. In other studies, the recommendations were accepted in 63.9%, 74% and 75%[14-16] of the cases, but no previous data is available regarding the implementation of a computer programme.

In the period of control, the proportion of inadequate dosage is lower than that obtained in other studies,[9] which could be due to the fact that the environment where the study was carried out, a general hospital that has a nephrology department. Therefore, greater compliance is expected with the dosage guides if the prescription is done by a nephrologist, given that they are specialists that are highly aware of the need to adjust medications to the degree of kidney disease.

The pharmaceutical intervention programme was efficient, with economic savings of a total of 1939.63 euros in a 2 month period, that is, the direct cost avoided, by adjusting doses in these patients, would be 2.6 euros per drug and day of treatment. The magnitude of savings is probably greater, given that the costs have been calculated exclusively as the costs to acquire the drugs and the costs for the health professionals involved was not included (for example, time that nurses used administering drugs) nor the costs related with the potential adverse effects that would be produced as a consequence of not correctly adjusting the doses. One of the limitations of the study is that no follow-up has been carried out regarding the side effects in patients in order to calculate if the reduction in the inadequate dosage also produces a decrease in them.

One of the strong points of the study is that follow-up is carried out on all of the patients once they are included in the study and this is very important given that renal function can vary, meaning that when the dose of a drug is adjusted, we could be under-dosing the patients if their renal function later improves. The study by Cantu et al,[8] with 169 patients with kidney disease, detected an improvement in 29% of the patients.

In our study, to estimate the renal function, the glomerular filtration rate (GFR) was used, calculated from the abbreviated MDRD equation,[17] while in other previous studies, the Cockcrof-Gault equation (C-G)[18] was used. The

Table 6 Comparison of costs (costs avoided) in the intervention group (n=35)

Cost of drugs	True cost, euros	Average (SD)	Difference of costs (cost avoided, euros)
Cost without intervention, euros	3037.93	97.99 (158.1)	62.56 (95%CI, 23.99-101.14 euros);
Coste real, euros	1098.3	35.43 (62.66)	*P*=.02

CI indicates confidence interval; SD, standard deviation.

greatest inconvenience of the C-G equation radiates in that the exact body weight of the patients is not always known, and therefore the National Kidney Foundation K/DOQI[12] established the MDRD as a recommended method to estimate renal function.

Blix et al,[7] in a recently published study, also used the MDRD and, also, in a subgroup of patients of which they possessed the weight, they calculate the GFR using both formulas, without finding differences in the magnitude of patients with CKD.

However, the application of the MDRD equation could be an important limitation of the study, taking into account a study[19] published recently where both formulas were compared for the dosage of antibiotics and they found differences in 25% of the patients. Although the clinical significance is unknown for these results, given that the majority of recommendations for adjustment of dosage of drugs with renal risk have been taken from studies that applied the C-G formula as the method to calculate the creatinine clearance, currently, the generalised use of the MDRD cannot be recommended until more studies are carried out.

Nonetheless, the MDRD should be applied for screening and selection of patients and the C-G formula should be reserved for the selections of the dosage schedule that is more appropriate for the patients.

In the evaluation of the treatment, moderate Kidney failure (GFR 60-90 mL/min/1.73 m^2) is considered normal renal function, given that it does not affect the metabolism and the elimination of drugs in a clinically significant manner.

Other authors and ourselves[6,7,14,20-22] we have considered a GFR<50-60 mL/min/1.73 m^2 to identify patients with kidney disease that require dosage adjustments.

The results of this study indicate that renal dysfunction in a considerable number of patients is not considered in medical prescriptions, which leads to excessive and avoidable costs, as well as a risk of adverse effects. Also, these pharmaceutical intervention programmes are well accepted by the prescribing physicians and they improve dosage adjustment, for which they should be used in clinical practice.

Our analysis in patients with kidney disease shows the importance of the interdisciplinary collaboration of the pharmacist and the nephrologist in the therapeutic optimisation of the patient with CKD, that may be very helpful to the team that cares for the patient and to improve the quality of care provided.

More studies are needed so that they could also measure the adverse effects to demonstrate if the improvement in the dosage adjustment (intermediate result) corresponds with health results, as well as the development of working tools and computer applications that help in the clinical practice of prescribing, together with educational programmes.

Acknowledgments

To Ángel Esteban, from the Clinical Analysis Department of the Hospital General of Alicante, for his logistical collaboration to obtain laboratory data, indispensable to carry out this study.

References

1. Stengel B, Billon S, van Dijk PCV, Pager KJ, Dekker FW, Simpson K. On behalf of the ERA-EDTA Registry Committee. Trends in the incidente of renal replacement therapy for end stage Kidney Disease in Europe, 1990-1999. Nephrol Dial Transplant. 2003;18:1824-33.
2. Coresh J, Astor BC, Greeene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adults US population: Third National Health and Nutrition Examination Survey. Am J Kidney Dis. 2003;41:1-12.
3. Otero A, Gayoso P, Garcia F, de Francisco AL; EPIRCE study group. Epidemiology of Chronic kidney disease in the Galician population: results of the pilot Spanish EPIRCE study. Kidney Int Suppl. 2005;99:S16-9.
4. Chertow GM, Lee J, Kuperman GJ, Burdick E, Horsky J, Seger DL, et al. Guided medication dosing for inpatients with renal insufficiency. JAMA. 2001;286:2839-44.
5. Munar MY, Singh H. Drug dosing adjustments in patients with chronic kidney disease. Am Fam physician. 2007;75:1487-96.
6. Falconier 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.
7. 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;11:3164-71.
8. Cantu TG, Ellerbeck EF, Yun SW, Castine SD, Kornhauser DM. Drug prescribing for patients with changing renal function. Am J Hosp Pharm. 1992;49:2944-8.
9. Long CL, Raebel MA, Price DW, Magid DJ. Compliance with dosing guidelines in patients with cronic kidney disease. Ann Pharmacother. 2004;38:853-8.
10. Sweileh WM, Janem SA, Sawalha AF, Abu-Taha AS, Zyoud SH, Sabri IA, et al. Medication dosing errors in hospitalized patients with renal impairment: a study in Palestine. Pharmacoepidemiol Drug Saf. 2007;16:908-12.
11. Salomon L, Deray G, Jaundon MC, Chebaiser C, Bossi P, Launay-Vacher V, et al. Medication misuse in hospitalized patients with renal impairment. Int J Qual Health Care. 2003;15:331-5.
12. National Kidney Foundation K/DOQI. Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. Am J Kidney Dis. 2002;39 Suppl 1:S1-266.
13. Álvarez Arroyo L, Climent Grana E, Roca Meroño S, Perdiguero Gil M, Bosacoma Ros N, Ordovas Baines JP. Cumplimiento de las pautas posológicas en pacientes con enfermedad renal: studio de prevalencia. Farm Hosp. 2007;31 Ext 1:31.
14. Fernández-Díaz E, Goikolea-Ugarte FJ, Domingo-Echaburu S, Domínguez-Menéndez JA, Balzola-Regout B, Yurrebaso-Ibarretxe MJ. Implantación de un programa de ajuste posológico en pacientes con función renal disminuida. Aten Farm. 2007;9:102-6.
15. Goldberg DE, Baardsgaard G, Johnson MT, Jolowsky CM, Sheperd M, Peterson CD. Computer-based program for identifying medication orders requiring dosage modification based on renal function. Am J Hosp Pharm. 1991;48:1965-9.
16. McMullin ST, Reichley RM, Kahn MG, Dunagan WC, Bailey TC. Automated system for identifying potential dosage problems at a large university hospital. Am J Health-Sys Pharm. 1997;54: 545-9.
17. Levey AS, Greene T, Kusek JW, Beck GJ. A simplified equation to predict glomerular filtration rate from serum creatinine. J Am Soc Nephrol. 2000;11:A0828.
18. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31-41.

19. Wargo KA, Eiland EH III, Hamm W, English TM, Phillipe HM. Comparison of the modification of diet in Kidney Disease and Cockcroft-Gault equations for antimicrobial dosage adjustments. Ann Pharmacother. 2006;40:1248-53.
20. Papaioannou A, Clarke JA, Campbell G, Bedard M. Assessment of adherence to renal dosing guidelines in long-term care facilities. J Am Geriatr Soc. 2000;48:1470-3.
21. Yap C, Dunham D, Thompson J, Baker D. Medication dosing errors for patients with renal insufficiency in ambulatory care. Jt Comm J Qual Patient Saf. 2005;31:514-21.
22. Nash IS, Rojas M, Hebert P, Marrone SR, Colgan C, Fisher LA, et al. Reducing excessive medication administration in hospitalized adults with renal dysfunction. Am J Med Qual. 2005;20:64-9.