Renal adjustment of antibiotics in elderly inpatients: A retrospective cohort study

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Abstract

Introduction: The world is seen a rapidly growing of elderly population and with age comes a natural reduction in glomerular filtration rate (GFR). This subgroup of patients is at high risk to develop adverse effects caused by antibiotics that need renal adjustment. The risk is higher when these patients are hospitalized for several reasons including other concomitant clinical conditions and the use of more restricted antibiotics like the aminoglycosides. **Objective:** The objective of the study was to describe the prevalence of elderly patients that received unadjusted doses of antibiotic for their estimated GFR (eGFR). **Methods:** A retrospective observational study that included all patients with 65 years or older admitted to a tertiary Brazilian hospital from January 2014 to July 2014. All of them should have a course of antibiotics for an active infection. We excluded all dialysis patients as well as all those who received antibiotic just as prophylaxis before a surgical procedure. The eGFR was calculated by Chronic Kidney Disease Epidemiology Collaboration equation using the first serum creatinine dosed during hospitalization. The antimicrobial dosage recorded was get from the 2nd day of treatment to avoid the loading dose. **Results:** We screened 6066 inpatients from which 285 were match the inclusion criteria. The mean age was 74.8 ± 7.3 years (minimum 65, maximum 104), 48.8% were women and 46.3% had health insurance. About 55.8% were patients from clinical wards and 44.2% from surgical wards. About 49% (n = 140) had GFR < 60 ml/min. Over recommended doses were prescribed for 37.2% (n = 106). There was no difference in the comparison between clinical (37.7%) and surgical (36.5%) specialties. All patients with severe reduction in eGFR (< 45 ml/min) received overdoses of nephrotoxic antibiotics. **Conclusion:** Elderly patients are unnecessarily exposed to high doses of antibiotics. The use of absolute values of creatinine rather than formulas to estimate GFR is likely the cause behind our concerning findings. Initiatives to increase the awareness of renal adjustments of antibiotics are necessary.

Key words: Antibiotic. Aging. Renal toxicity.

Ajuste renal de antibióticos en pacientes ancianos hospitalizados: un estudio de cohorte retrospectivo

Resumen

Introducción: En el mundo se ve un rápido crecimiento de la población de edad avanzada, y con la edad viene una reducción natural en la tasa de filtrado glomerular (TFG). Este subgrupo de pacientes tiene un alto riesgo de desarrollar efectos adversos causados por antibióticos que necesitan ajuste renal. El riesgo es mayor cuando estos pacientes son

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Date of reception: 17-01-2018

Date of acceptance: 04-02-2020

DOI: 10.24875/NEFRO.20000018

Available online: 03-04-2020

Nefro Latinoam. 2020;17:19-24

www.nefrologialatinoamericana.com

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hospitalizados por varias razones, incluyendo otras condiciones clínicas concomitantes y el uso de antibióticos más restringidos como los aminoglucósidos. **Objetivo:** Describir la prevalencia de pacientes ancianos que recibieron dosis no ajustadas de antibióticos para su tasa de filtrado glomerular estimada (TFGe). **Métodos:** Estudio observacional retrospectivo que incluyó a todos los pacientes de 65 años o más ingresados en un hospital brasileño terciario desde enero de 2014 hasta julio de 2014. El criterio de inclusión es tener un curso de antibióticos para una infección activa. Se excluyó a todos los pacientes de diálisis, así como a todos los que solo recibieron antibióticos como profilaxis antes de un procedimiento quirúrgico. La TFGe se calculó mediante la ecuación CKD-EPI, utilizando la primera creatinina sérica dosificada durante la hospitalización. La dosis antimicrobiana registrada se obtuvo a partir del segundo día de tratamiento para evitar la dosis de carga. **Resultados:** Fueran seleccionados 6,066 pacientes hospitalizados, de los cuales, 285 coincidieron con los criterios de inclusión. La edad media fue de 74.8 ± 7.3 años (mínimo 65, máximo 104), el 48.8% eran mujeres y el 46.3% tenían seguro de salud. Aproximadamente el 55.8% eran pacientes de clínicas y el 44.2% de salas quirúrgicas. Alrededor del 49% ($n = 140$) tenía TFG < 60 ml/min. Sobredosis recomendadas se prescribieron para el 37.2% ($n = 106$). No hubo diferencias en la comparación entre especialidades clínicas (37.7%) y quirúrgicas (36.5%). Todos los pacientes con reducción severa en la TFGe (< 45 ml/min) recibieron sobredosis de antibióticos nefrotóxicos. **Conclusión:** Los pacientes ancianos están innecesariamente expuestos a altas dosis de antibióticos. El uso de valores absolutos de creatinina en lugar de fórmulas para estimar la TFG es probablemente la causa detrás de nuestros hallazgos relativos. Se necesitan iniciativas para aumentar la conciencia sobre los ajustes renales de los antibióticos.

Palabras claves: Antibiótico. Envejecimiento. Toxicidad renal.

Introduction

The world is seen a rapidly growing of elderly population and with it a great challenge for the health system arises the burden of chronic kidney disease (CKD). As any other organ, the kidney is also affected within the aging process losing function in a small but progressive rate. In addition, the prevalence of diabetes and hypertension, the main causes of CKD, also increases with age contributing to a higher prevalence of CKD¹⁻³. This reduction in the glomerular filtration rate (GFR) is not easily perceived when absolute values of creatinine are used to evaluate kidney function.

The use of specific formulas, specifically the CKD Epidemiology Collaboration (CKD-EPI) and the modification of diet in renal disease, may help to overcome the disadvantage of the absolute values of creatinine⁴. However, the majority of laboratories in Brazil provide only the absolute value of creatinine with a range of values, supposed to be normal, for males and females. This approach frequently misclassifies the real renal function of older patients, exposing them to a high risk of adverse effects from several drugs that require adjustment for the renal clearance. Hence, the risk of an adverse effect is more frequent in hospitalized older patients given the higher exposure to nephrotoxic drugs in this setting^{1,3}. Nevertheless, no study of our knowledge analyzed what is the prevalence of older patients receiving overdoses of antibiotics by incorrect adjustment for the renal function.

Therefore, our aim was to evaluate the prevalence of older patients hospitalized in a tertiary hospital from the south region of Brazil that received intravenous antibiotics properly adjusted for estimated GFR (eGFR).

Methods

This is a retrospective study performed in a tertiary hospital located in south region of Brazil. We screened all patients admitted from January to July 2014 and selected those with age of > 65 years. Then, we excluded those on chronic dialysis; patients that did not use any antibiotic or that used antibiotic only for prophylaxis in a surgical procedure.

The eGFR was calculated by CKD-EPI equation using patient's first serum creatinine during hospitalization. Patients were then stratified in six groups as follows: Group I – GFR > 90 ml/min/1.73 m², Group II – GFR between 60 and 90 ml/min/1.73 m² including; Group III – GFR 45-60 ml/min/1.73 m² including; Group IV – GFR 30-45 ml/min/1.73 m² including; Group V – GFR 15-30 ml/min/1.73 m² including; and Group VI – GFR < 15 ml/min/1.73 m².

Regarding the dosage of antibiotics, we considered only the second dose administered to patients with active infections to avoid the loading dose of some antibiotics that sometimes are similar to the full dose. Table 1 depicts the doses we used for each antibiotic according to eGFR. In our study, we considered as nephrotoxic the following antibiotics: aminoglycosides,

Table 1. Doses considered appropriate for prescribing in the study according to different ranges of glomerular filtration rates

Antibiotic	Clearance (mL min/1.73m ²)	Dosing
Amikacin	> 60	5-7.5 mg/Kg/dose 8/8 h
	40-60	5-7.5 mg/Kg/dose 12/12 h
	20-40	5-7.5 mg/Kg/dose 24/24 h
	< 20	Loading dose and adjustment according to serum levels
Amoxicilin	> 30	250-500 mg 8/8h or 500-750 mg 12/12h
	10-30	250-500 mg 12/12h
	< 10	250-500 mg 24/24h
Ampicilin	> 50	6/6 h
	10-50	Each 6-12h
	< 10	12-24 h
Ampicilin/sulbactam	> 30	1.5-3 g 6/6 h
	15-29	1.5-3 g 12/12 h
	< 15	1.5-3 g 24/24 h
Cefazolin	≥ 35	1-1.5 g 8/8 h
	11-34	1-1.5 g 12/12 h
Cefepime	> 60	500 mg 12/12 h or 1 g 12/12 h or 2 g 12/12 h or 2 g 8/8 h
	30-60	500 mg 24/24 h or 1 g 24/24 h or 2 g 24/24 h or 2 g 12/12 h
	11-29	500 mg 24/24 h, 500 mg 24/24 h, 1 g 24/24 h or 2 g 24/24 h
	< 11	250 mg 24/24 h, 250 mg 24/24 h, 500 mg 24/24 h or 1 g 24/24 h
	< 10	1-1.5 g 18-24 h
Ciprofloxacin	> 50	500 mg 12/12 h or 400 mg 12/12 h
	30-50	250-500 mg 12/12 h
	< 30	500 mg 24/24 h or 200-400 mg 18-24 h
Clarithromicin	< 30	50% of loading dose
Gentamicin (conventional)	> 60 (conventional)	1-2.5 mg/kg/dose 8/8 h
	> 60 (1x/day)	4-7 mg/kg/dose 24/24 h
	40-60	1-2.5 mg/kg/dose 12/12 h
	20-40	1-2.5 mg/kg/dose 24/24 h
	< 20	Loading dose and adjustment according to serum levels
Meropenem	> 50	1.5-6 g divided each 8 h
	30-50	20-40 mg/kg 12/12 h
	10-30	10-20 mg 12/12 h
	< 10	10-20 mg/kg 24/24 h
Piperacilin/Tazobactan	> 40	3.375 g 6/6 h or 4.5 g 6-8 h
	20-40	2.25-3.375 6/6 h
	< 20	2.25 g 6-8 h

(Continues)

Table 1. Doses considered appropriate for prescribing in the study according to different ranges of glomerular filtration rates (*Continued*)

Antibiotic	Clearance (mL min/1.73m ²)	Dosing
Polymyxin	> 80	15000-25000 UI/kg/dia 4-6 h
	30-80	25000 UI/kg 12/12 h and then 10-15000 UI each 12/12 h
	< 30	25000 UI/kg 12/12 h and then 10-15000 UI each 2-3 days
Sulfamethoxazole/trimethoprim	> 30	800/160 mg 12/12 h
	≤ 30	800/160 mg 24/24 h
Vancomycin	> 90	30-60 mg/kg/dose 8-12 h
	50-90	15-20 mg/kg/dose 8-1 h
	20-49	15-20 mg/kg/dose 24/24 h
	< 20	According to vancomycin serum level

Figure 1. Prevalence of inadequate prescribed doses according to chronic kidney disease stage.

polymyxin, and vancomycin. The Research and Ethics Committee of the institution approved the study.

Statistical analysis

Continuous variables were expressed as mean $\pm$ standard deviation or median and interquartile range depending on the distribution of the variable. Categorical variables were expressed as frequency and percentage. Results were presented as the percentage of patients using an antibiotic dose above the range recommended for their eGFR. Finally, to explore the identification of potential risk factors for our outcome, we used logistic regression. All analyses were done with STATA 14.0 software.

Results

We screened 6066 patients between January and June 2014. After we applied the exclusion criteria, we identified 285 patients above 65 years old who used intravenous antimicrobial for an active bacterial infection during the period of hospitalization (Fig. 1). The mean age of the population included in the study was 74.8 ± 7.3 years (minimum 65, maximum 104), women were 48.8% of the population and 46.3% had health insurance. Regarding medical specialty, 55.8% were from clinical and 44.2% from surgical specialties at the time of hospitalization. Table 2 shows summarize data for comparison between gender and medical specialties, whether the patient was treated by the public or private health system.

Table 2. Odds ratio for the risk to receive inadequate antibiotic doses

	Odds ratio	Confidence interval 95%	p-value
Non-nephrotoxic drugs			
Health insurance (no)	2.04	1.05-4.0	0.03
Gender (female)	0.71	0.38-1.34	0.29
Specialty (clinical)	1.21	0.64-2.29	0.55
Nephrotoxic drugs			
Health insurance (no)	1.66	0.66-4.16	0.28
Gender (female)	0.93	0.37-2.29	0.87
Specialty (clinical)	0.98	0.40-2.40	0.96
Overall			
Health insurance (no)	1.45	0.89-2.35	0.13
Gender (female)	0.71	0.44-1.15	0.16
Specialty (clinical)	1.05	0.65-1.71	0.83

Considering the CKD stage, 15.8% (n = 45) were on Stage I, 35.1% (n = 100) on Stage II, 16.1% (n = 46) on Stage IIIa, 14.7% (n = 42) Stage IIIb, 11.9% (n = 34) Stage IV, and 6.3% (n = 18) on Stage V but not yet on dialysis. Doses above the recommended for the eGFR were prescribed to 37.2% (n = 106) of all patients and were more frequent in patients from the public health system (41.2% vs. 32.6%) and in males (41.1% vs. 33.1%). There was no difference in the comparison between clinical (37.7%) and surgical (36.5%) specialties.

The probability of receiving inadequate dose for the renal function was higher for nephrotoxic drugs. Among patients exposed to nephrotoxic antibiotics, all patients from Groups IV, V, and VI received doses above the recommended. For non-nephrotoxic drugs, the percentage of patients with over recommended doses was for Groups II 3.1%, IIIa 8.8%, IIIb 42.4%, IV 66.7%, and V 85.7% (Fig. 1).

Discussion

This is the first study of our knowledge to describe the prevalence of hospitalized elderly patients receiving unadjusted doses of intravenous antibiotics for all stages of CKD based on eGFR. Our findings suggest an alarming high prevalence of inadequate doses of antibiotics that increase as eGFR decline.

Life expectancy is rapidly increasing worldwide as a consequence of several factors including socioeconomic development and the improvement in the understanding and treatment of several diseases including non-communicable chronic pathologies that are the main causes of CKD, namely, hypertension and diabetes^{5,6}. In addition, the aging process *per se* is associated with a

reduction in the number of nephrons contributing to a reduction in the GFR^{7,8}. Despite the debate about whether the later condition should be considered physiological or pathological, the reduction in the GFR does not change the fact that we should always be careful when administering medications to older patients^{2,3}.

The prevalence of CKD worldwide in the general population is estimated to already have passed 10%⁹. However, given the natural decrease in the GFR, we observe with aging, the prevalence of CKD is higher in older patients. The previous reports found a prevalence of eGFR < 60 ml/min in almost 60% of patients aged 75 or older¹⁰. Such numbers are expected to be even greater in older patients that need hospitalization if we considered that the prevalence of diabetes and hypertension is likely greater in this subgroup of patients. In our study, an eGFR < 60 ml/min was present in almost three of every four patients. Since we were not able to get access to ambulatory levels of creatinine previous to the admission and/or the presence of proteinuria in this population, the real prevalence of CKD is not known^{6,11}.

Inadequate doses of oral antibiotics for patients > 70 years were reported to occur in almost 50% of patients treated as outpatients in a Canadian cohort of 2871 patients¹². Our expectations when designing the study were not different, but such high prevalence was beyond our initial thoughts. Adjustments for eGFR were practically inexistent for patients with moderate-to-severe kidney dysfunction that received nephrotoxic drugs. Of note, during the study period, the hospital did not have routine serum levels monitoring for any antibiotic.

We then investigated whether our findings occurred equally between patients with and without health insurance. This is because it is believed that the care delivered to patients on the public health system could differ from the private system in several aspects. Overall, there were no significant differences in the adjustment of antibiotics between patients from public and private systems. Nevertheless, in a subanalysis, we found that the doses of non-nephrotoxic drugs were more likely to be prescribed above the recommended for patients of the public health system. It is difficult to interpret the underlying reasons for this difference, but could be related to an undesirable reality of many public hospitals, which is the overload of work with too many patients per doctor. Unfortunately, our study was not designed and able to capture details that could have helped to clarify this finding.

Finally, we also looked at possible differences between clinical specialties given that both the

exposure to critic septic patients and the focus on their practices differ considerably and could have some influence in the pattern of prescription. Nevertheless, the pattern of antibiotic prescription to the elderly was homogeneous across clinical and surgical medical specialties. Hence, despite the great importance in estimating GFR in current clinical practice and the wide and accessible availability of technology to use current validated formulas for the calculation of eGFR, there is not acceptable justification for the high incidence of inadequate prescribed doses of antibiotic in older patients with CKD. Initiatives aiming to increase the use of eGFR in hospitals, including laboratories providing the eGFR rather than absolute levels of creatinine alone, may reduce the frequency of adverse effects associated with inadequate doses of medications.

Our study has some limitations, which includes all those related any retrospective study. In addition, it is a single-center study, which can compromise external validation. We estimated rather than measured GFR using the CKD-EPI equation that, despite have been recommended by the KDIGO to estimate the GFR, has not been validated to older patients. At last, we cannot exclude that some patients could have been admitted with some degree of acute kidney injury and in that case, the real GFR was even lower. In contrast, our study also has strong points which include (a) the large sample size that reflects the reality of a large public hospital from a developing country and (b) it identifies the important and seldom reported problem of inadequate drug prescription for older CKD patients, contributing to increase the awareness and development of strategies to tackle this issue.

Conclusion

Hospitalized elderly patients are highly exposed to receive inadequate doses of antibiotics probably because eGFR has been still neglected in some centers.

Conflicts of interest

Thyago P. de Moraes received speaker honorarium from Baxter and travel grants from Baxter, Astrazeneca,

and Genzyme. The other authors have no conflicts of interest to declare.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the code of ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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