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Use of antibiotics by hospitalized elderly and changes in serum creatinine

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Abstract

The rapid growth of the elderly population, associated with longer life expectancy, is associated with a higher prevalence of chronic non-communicable diseases, such as those of the cardiovascular, renal system and neoplasms. A large portion of these pathologies require hospitalization and their conditions require the use of antibiotics (ATB), whose indiscriminate use can lead to Acute Kidney Injury (AKI), which has serum creatinine as one of its markers. Therefore, the present study aimed to evaluate changes in serum creatinine of hospitalized elderly people submitted to antibiotic therapy in a university hospital. This was a cross-sectional study in which patients over 60 years old were identified during a period of 6 months and who used ATB, as well as had their serum creatinine measured. The variables age, gender, length of hospital stays and use of ATB were considered, as well as serum creatinine values before and after antibiotic therapy. A total of 796 patients participated in the study, 51.4% (409) of whom were male. Ages ranged from 60 to 109 years, with an average of 74.9 (± 9.6). It was identified that length of stay and use of ATB are variables that interfere with the increase in creatinine due to antibiotic therapy, which was observed in 75.5% of the patients. This leads to the reflection about a possible indiscriminate prescription of antimicrobials and their correlation to AKI.

Keywords: Aged; Anti-Bacterial Agents; Prescriptions; Creatinine; Renal Insufficiency.

INTRODUCTION

Population aging is a phenomenon on a global scale predicted by the World Health Organization (WHO). In this phenomenon, the rapid growth of the elderly population has an important impact on health systems due to the greater need to use services. In this context, there is an increase in chronic and acute health problems in this population subgroup, which may predispose patients to a higher consumption of drugs, including antibiotics (ATB)[1-2].

Regarding ATBs, these are used in about 40% of hospitalized patients for therapeutic and prophylactic purposes[3]. Despite their benefits,

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these drugs, when used indiscriminately, can be harmful to the health of the individual and the community, such as, for example, favoring the emergence of resistant bacteria[4].

Among the main negative consequences of using ATB, we highlight Acute Kidney Injury (AKI), in which the loss of organ function is reflected through serum creatinine levels, in addition to other clinical and laboratory parameters[5]. Among the biomarkers available for the identification of AKI, the wide applicability and use of creatinine in clinical practice stands out, as it is a quantitative parameter of kidney function established in the literature, in addition to its low cost[4].

It is understood that the complications related to kidney functioning resulting from the use of ATB are even more significant in the elderly, when considering the polypharmacy to which they are usually subjected, as well as the physiological changes inherent to senescence[6]. This shows a greater need for monitoring and implementing strategies to prevent possible harm resulting from the use of these drugs in this population profile[7].

Given this context, the present study aimed to assess changes in serum creatinine of hospitalized elderly people undergoing antibiotic therapy in a university hospital.

METHODOLOGY

This was a cross-sectional study, with data collected from January 1st to July 31st, 2014, through which elderly patients on ATB had their respective serum creatinine values identified before and during antibiotic therapy. The study was developed in a large university hospital, inserted in the municipal health network of Belo Horizonte, Minas Gerais.

Through generating reports from the institution's computerized system, all patients over 60 years of age who were hospitalized during the study period, who took ATBs and who underwent serum creatinine measurement exams were identified.

The reports contained records from the hospital's clinical analysis laboratory and from the electronic medical records. The data were recorded in the Microsoft Excel 97-2003® program for compilation, followed by univariate statistical analysis.

The following variables were considered: age, gender, length of hospital stay, time of using ATB, ATB in use and the values of measured serum creatinine before and after initiating the ATB treatment. In order to identify the variation in creatinine, it was decided to use the highest serum measurement value after the beginning of the use of ATB and compare it to the measurement value of creatinine 24 hours before the start of use.

Initially, a database with 1247 patients was obtained. Of these, 451 were considered ineligible for having only one creatinine test, making the comparison proposed by the study unfeasible.

From this analysis, the groups of patients were subdivided according to the increase in creatinine identified, considering significant variations every 0.2 mg/dL. Student's t test for independent samples was used to perform statistical analysis when comparing two groups of patients regarding continuous variables. The Chi-squared test was used to assess the association between two categorical variables. All results were considered significant for a probability of significance less than 5% ($p<0.05$), with a 95% confidence in the conclusions presented. In this study, the descriptive measures Percentage, Median (Md), Mean and Standard Deviation (SD) were presented to describe the results of the studied variables.

This project was approved by the ethics committee of the study institution and received opinion number 1.057.180.

RESULTS

A total of 796 patients were included in the study, 51.4% (409) were male and 48.6% (387) female. The ages ranged from 60 to 109 years, with an average of 74.9 (± 9.6); where 34.8% (277) aged 60 to 69 years, 32% (255) 70 to 79 years, 26.5 % (211) 80 to 89 years old and 6.7% (53) over 90 years old.

Of the total number of patients included in the study, 601 (75.5%) had an increase in creatinine, of which 321 (53.4%) were male. The mean age was 74.7 years (± 9.6; Md = 74.0) and the average length of stay, in days, was 26.1 (± 28.2; Md = 18.0). The mean duration of antibiotic therapy in this group was 19.8 days (± 22.7; Md = 13.0).

A total of 195 (24.5%) patients maintained normal levels of creatinine, 88 (21.5%) of whom were male. The mean age was 75.6 (± 9.7; Md = 75.0), with an average hospital stay of 13.2 days (± 11.1; Md = 10.0). The mean time of antibiotic therapy in these patients was 8.9 days (± 9.5; Md = 6.0).

Of the total number of patients included in the study, 189 (23.7%) patients received five or more antibiotics with different formulations, 92 (11.5%) received four, 143 (18%) received three, 225 (28.3%) received two, and 147 (18.5%) received only one.

Table 1 shows the prevalence of the number of ATB reportedly used, by class.

When analyzing the increase of creatinine according to the variables gender, age, length of stay and time of use of ATB, it was identified that length of stay in days and time of use of ATB are variables that interfered in the increase of creatinine due to the use of ATB ($p<0.05$) (table 2).

When analyzing the variation in the measurement of creatinine per patient, it was found that the majority of patients had an oscillation between 2.01 and 3.00, as seen in the table below. (Table 3)

Table 4 shows the mean creatinine increase considering the type of ATB used.

Table 1 – Frequency of ATB used in the study period considering grouping by pharmacological classification:

Pharmacological class	Prevalence	
	n	%
Penicillin + β-lactamase inhibitors	644	81
3rd generation cephalosporins	363	45.6
Imidazoles	266	33.4
Quinolones	224	28.7
Glycopeptides	182	22.9
Macrolides	173	21.7
Carbapanemics	168	21.1
Aminoglycosides	154	19.4
Polypeptides	134	16.8
4th generation cephalosporins	103	12.9
1st generation cephalosporins	98	12.4
Penicillins	82	10.4
Sulphonamides	44	5.6
Lincosamides	36	4.5
Oxazolidinones	18	2.3
Nitrofurans	6	0.8
Tetracyclines	5	0.6

Table 2 – Characterization of patients according to gender, age, length of stay and duration of antibiotic use

Characteristic	Creatinine increase		p
	No (n = 195)	Yes (n = 601)	
Gender			
Female	107 (27.6%)	280 (72,4%)	0.044*
Male	88 (21.5%)	321 (78,5%)	
Age (years)	75.6 ± 9.7	74,7 ± 9,6	0.278**
	Md = 75.0	Md = 74,0	
Length of hospital stay (days)	13.2 ± 11.1	26,1 ± 28,2	< 0.001**
	Md = 10.0	Md = 18,0	
Antibiotic time (days)	8.9 ± 9.5	19,8 ± 22,7	< 0.001**
	Md = 6.0	Md = 13,0	

Note: Md (Median); the probability of significance refers to the Chi-squared test (*) and the Student's t test (**)

Table 3 – Prevalence of patients who presented variation in creatinine during the use of ATB.

Variation ranges in creatinine identified before and after using ATB (mg/dL)	Prevalence of patients who presented the variation	
	n	%
Up to 0.20	32	5.3
0.21 to 0.40	54	9.0
0.41 to 0.60	51	8.5
0.61 to 0.80	34	5.6
0.81 to 1.00	37	6.2
1.01 to 1.20	30	5.0
1.21 to 1.40	30	5.0
1.41 to 1.60	31	5.2
1.61 to 1.80	17	2.8
1.81 to 2.00	29	4.8
2.01 to 3.00	100	16.6
3.01 to 4.00	68	11.3
4.01 to 5.00	37	6.2
Above 5.00	51	8.5
Total	**601**	**100.0**

Table 4 – Identification of creatinine increase considering the ATB administered

ATB specification	Mean creatinine increase (mg/dL) ± SD	ATB specification	Mean creatinine increase (mg/dL) ± SD	ATB specification	Mean creatinine increase (mg/dL) ± SD
Amoxicillin 1g + Clavulanic acid 0.2 g (EV)	2.3 ± 2.1	Vancomycin 500mg (EV)	3.2 ± 2.1	Piperacillin 4g + Tazobactam 500mg (EV)	2.9 ± 2.3
Metronidazole 5mg / mL (EV)	2.5 ± 2.0	Meropenem 1g (EV)	3.1 ± 2.1	Amoxicillin 500mg + Clavulanic acid 125mg (VO)	2.1 ± 2.1
Ceftriaxone 1g (EV)	2.4 ± 1.9	Ceftazidime 1g	2.4 ± 2.1	Polymyxin B 500,000 IU (IM)	3.5 ± 2.1
Cefepime 1g (EV)	2.7 ± 2.2	Clarithromycin 500mg (VO)	2.2 ± 1.7	Cefazolin 1g (EV)	2.9 ± 2.5
Amikacin 250mg / mL (IM, EV)	3.3 ± 2.0	Ciprofloxacin 2mg / mL (IM, EV)	2.6 ± 2.3	Clarithromycin 500mg (EV)	3.1 ± 2.7

to be continued...

... continuation table 4.

ATB specification	Mean creatinine increase (mg/dL) ± SD	ATB specification	Mean creatinine increase (mg/dL) ± SD	ATB specification	Mean creatinine increase (mg/dL) ± SD
Ciprofloxacino 500mg (VO)	2.2 ± 2.2	Metronidazole 250mg (VO)	2.9 ± 1.8	Oxacillin 500mg (EV)	2.4 ± 1.1
Gentamicin 40mg / mL (IM, EV)	2.9 ± 2.0	Levofloxacin 5mg / mL (EV)	2.0 ± 1.4	Ampicillin 1g + Sulbactan 500mg	3.5 ± 2.8
Clindamycin 150mg / mL	3.0 ± 2.5	Levofloxacin 500mg (VO)	2.3 ± 2.4	Norfloxacin 400mg (VO)	1.5 ± 1.3
Amoxicillin 50mg / mL + Clavulanic acid 12.5mg / mL (VO)	2.4 ± 2.5	Silver Sulfadiazine 1% (Topic)	3.0 ± 2.2	Ampicillin 1g (EV)	2.7 ± 1.4
Linezolid 2mg / mL (EV)	4.3 ± 2.6	Teicoplanin 400mg (IM, EV)	3.5 ± 2.0	Sulfamethoxazole 400mg + Trimethoprim 80mg (VO)	2.2 ± 0.7
Ciprofloxacin 0.35% (Eye drops)	1.4 ± 1.2	Cefotaxime 1g (EV)	3.3 ± 2.1	Amoxicillin 500mg (VO)	3.8 ± 4.0
Azithromycin 500mg (EV)	3.0 ± 1.9	Teicoplanin 200mg (IM, EV)	2.6 ± 2.0	Clindamycin 300mg (VO)	1.3 ± ---
Sulfamethoxazole 80mg + Trimethoprim 16mg (EV)	6.1 ± 1.3	Nitrofurantoin 100mg (VO)	3.9 ± 3.5	Doxycycline 100mg (VO)	1.2 ± ---
Azithromycin 500mg (VO)	2.4 ± 0.5	Rifampicin 300mg (VO)	3.8 ± 1.8	Amoxicillin 50mg / mL	3.8 ± 4.0
Sulfadiazine 500mg (VO)	3.9 ± 4.9	Benzyl benzylpenicillin 1,200,000 IU (IM)	4.6 ± -	Cephalexin 500mg (VO)	1.3 ± ---
Benzylpenicillin potassium 5,000,000 IU (IM, EV)	3.3 ± ---	Metronidazole 100mg / g Topical	4.3 ± ---	Polymyxin and colistimethate sodium 1,000,000 IU (IM)	1.2 ± ---

O que significa EV, VO, IM??

DISCUSSION

The average length of stay was 23 days, which is higher when compared to the averages found in other studies, which ranged from 6 to 118.9. This difference may be associated with the variation in the complexity of the hospitals under study. However, the average number of days of treatment with ATB in the present study was 17 days, which is similar to that observed in other studies[3,10,11].

It is noteworthy that the majority of patients (81.5%) used more than one ATB. Despite this fact being commonly identified in the literature12,13, when considering the population subgroup under study, it is considered important for

professionals responsible for providing care to have knowledge of drug interactions and potential adverse effects of drugs in use[1,14,15].

Regarding creatinine, there is a controversial discussion in the literature about its role as a biomarker. Unlike cardiology, in which troponin is considered a classic marker of acute myocardial infarction (AMI), in nephrology there is a deficit of such a sensitive and specific biomarker for AKI[16,17]. However, creatinine is still seen as an important parameter for the assessment of kidney function loss, which is intrinsic to AKI[18]. Therefore, creatinine imposes itself as a reliable biomarker for kidney distress, in a context of clinical practice[19,20], mainly because it is an easy test, requires a quick execution and is low cost[2,19]. It is noteworthy that other more specific methods, such as kidney biopsies, are not viable and present a greater risk of iatrogenesis.

The present study evaluated that the increase in serum creatinine levels may reflect the pattern of nephrotoxicity of the ATB used, and data from the literature describe that 40 to 50% of these drugs have this adverse effect[22].

Among the cephalosporins, the first-generation drugs stand out with a greater nephrotoxic characteristic, and, comparatively, the other generations have less potential for kidney injury[13]. Despite this, the third generation cephalosporins found in this study were related to abnormal serum creatinine values, indicating a pattern of loss of kidney function. Despite the literature pointing out that the interruption of antibiotic therapy may be associated with the recovery of kidney function[22-25], the loss of kidney function during the use of ATB may be associated with the worsening of clinical conditions; especially in a more fragile population subgroup, such as the elderly .

With regard to the use of meropenem and piperacillin associated with tazobactam, it is possible to note that, despite their reportedly low nephrotoxicity26, such drugs were responsible for high creatinine values. The combination of piperacillin and tazobactam has characteristics of low kidney toxicity among the penicillin group. However, periodic examinations are recommended to assess kidney functions in long-term treatments[7].

Among the glycopeptides, this study highlights the use of vancomycin. Its elimination is exclusively by the renal route, and nephrotoxicity can vary between 5 to 35%. The nephrotoxicity of this pharmacological class is one of the limitations of its use, and it is recommended to assess the risk-benefit at the time of prescription[27].

Concerning polymyxins, these have a mechanism of action and bactericidal potential that is different from other ATBs used in the current scenario of Brazilian clinical practice, which reduces the likelihood of cross-resistance and favors its use for infections with multi-resistant bacteria. In this study, only the use of polymyxin B was demonstrated, which has a higher bactericidal potential than polymyxin E, but also has a greater nephrotoxic potential[28].

Although serum creatinine is not a direct marker of kidney function, it is understood that an increase in its levels may be indicative of a possible kidney injury caused by antibiotic therapy[24,29]. A considerable percentage of elderly people (75.5%) identified an increase in creatinine after the use of ATB, which indicates an overload of kidney function in these patients. Studies report that simple serum markers such as creatinine are especially attractive for measurements of Glomerular Filtration Rates (GFR)[30].

Some authors report that serum creatinine levels are not sensitive markers of real kidney function in chronic kidney disease, and the result found in serum creatinine must be corrected through the use of formulas that take into account the individual's own characteristics to be properly interpreted. The use of equations developed specifically for the estimation of creatinine clearance (Cockcroft-Gault) or GFR and Modification of Diet in Renal Disease (MDRD) has been advocated by many authors, and some even consider that they offer results

as good as, if not better than, the measurement of renal creatinine clearance30,31. However, as the weight and body surface of the patients under study were not obtained, it was not possible to calculate the creatinine clearance by using the formulas mentioned, which is a limitation of this study. Another limitation was the failure to identify the other medications in use, and assessing the possibility that these could also cause kidney damage.

The considerable number of elderly people excluded from the study (451) for not having more than one serum creatinine dosage value refers to the need for implementing protocols for monitoring kidney function of the elderly who use ATB in the hospital under study using this biomarker. This data also reflects the strengthening of pharmacovigilance actions that can track and prevent AKI cases from the use of ATB in the elderly.

As the average length of hospital stay and use of ATB are variables that can interfere with the occurrence of changes in serum creatinine, it is understood that practices related to the rational use of ATB, which prevent prescriptions of ATB for excessive time, can contribute to the safety of patients. It is also emphasized that the occurrence of AKI itself is a factor that can contribute to the increase in the length of hospital stay, which can trigger the risk of new hospital infections, higher consumption of ATB and new cases of AKI. Actions related to the promotion of safe hospital discharge can also contribute to shorter hospital stays, fewer infections and lesser need for ATB use.

It is suggested that strategies of continuous surveillance on the prescriptions of ATB be implemented for the elderly population in the hospital studied, so that the prevention of kidney damage would be a reality.

CONCLUSION

Of the 796 patients evaluated, 601 showed a greater increase in serum creatinine after the use of ATB, of which the aminoglycosides, polypeptides and glycopeptides were the main drugs responsible for such alterations; specifically highlighting the drugs gentamicin, polymyxin, amikacin and vancomycin.

The changes in serum creatinine in hospitalized elderly people who used ATB are a reality in the institution studied. Moreover, the length of hospital stay and time of ATB use are variables related to changes in serum creatinine.

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