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Nephrotoxicity in reports of suspected adverse drug events: Descriptive study of data reported to the VigiMed system in 2019

Nefrotoxicidade em notificações de suspeita de eventos adversos a medicamento: estudo descritivo de dados reportados ao sistema VigiMed em 2019

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ABSTRACT

Introduction: Nephrotoxicity is a frequent adverse event during medication use, especially in the hospital environment. Its occurrence may occur for reasons inherent to the drug and/or the individual. The main drugs associated with this complication are non-steroidal anti-inflammatory drugs, antimicrobials, antineoplastics, lithium, immunosuppressants, antivirals. In Brazil, the notification of the occurrence of adverse events is reported to the VigiMed system; through notifications it is possible to both monitor the use of medicines and plan health actions. **Objective:** To describe the therapeutic groups reported as suspected drug-related adverse events received in 2019 by the national pharmacovigilance system in Brazil. **Method:** Cross-sectional, descriptive, retrospective study made through information from adverse drug event notifications related to nephrotoxicity reported to VigiMed in the period from 01/01/2019 to 12/31/2019. Drugs were classified by the Anatomical Therapeutic Chemical classification system up to the fifth level. **Results:** 146 notifications reporting nephrotoxicity, with 79 different drugs reported. There was a prevalence of systemic anti-infective agents (group J), 97 (51.05%), mainly antibacterials for systemic use (J01), 70 (36.80%) and antimycotics for systemic use (J02), 18 (9.97%). They were followed by antineoplastic agents and immunomodulators (group L), 30 (16.31%), mainly antineoplastic agents (L01), 23 (12.10%), and the group Various, with contrast (V08), 19 (10.00%). The most frequent medications were Vancomycin, 19, followed by Amphotericin B, 16, and Piperacillin + Tazobactam and Ioexol. **Conclusions:** The most frequent therapeutic groups in notifications of suspected drug-related adverse events were antibacterials for systemic use, anticancer agents, antimycotics for systemic use and contrast agents.

KEYWORDS: Pharmacovigilance; Adverse Event; Acute Kidney Injury

RESUMO

Introdução: A nefrotoxicidade é um evento adverso frequente durante o uso de medicamentos, principalmente no ambiente hospitalar. Sua ocorrência pode decorrer por razões inerentes ao fármaco e/ou ao indivíduo. Os principais medicamentos associados a essa complicação são: anti-inflamatórios não esteroidais, antimicrobianos, antineoplásicos, lítio, imunossupressores e antivirais. No Brasil, a notificação da ocorrência de eventos adversos é feita pelo sistema VigiMed. Por meio das notificações, é possível acompanhar o uso dos medicamentos e planejar ações de saúde. **Objetivo:** Descrever os grupamentos terapêuticos notificados como suspeita de evento adverso relacionado a medicamento recebidos em 2019 pelo sistema nacional de farmacovigilância do Brasil. **Método:** Estudo transversal, descritivo, retrospectivo feito por meio das informações das notificações de evento adverso a medicamento relacionadas à nefrotoxicidade feitas ao VigiMed no período de 01/01/2019 a 31/12/2019. Os medicamentos foram classificados

pelo sistema de classificação anatômico químico terapêutico (ATC) até o quinto nível. **Resultados:** Houve 146 notificações com relato de nefrotoxicidade, com 79 medicamentos diferentes relatados. Houve prevalência dos agentes anti-infecciosos sistêmicos (grupo J), 97 (51,05%), principalmente os antibacterianos de uso sistêmico (J01), 70 (36,80%); os antimicóticos para uso sistêmico (J02), 18 (9,97%); seguido dos agentes antineoplásicos e imunomoduladores (grupo L), 30 (16,31%), principalmente os agentes antineoplásicos (L01), 23 (12,10%) e o grupo Vários, com contraste (V08), 19 (10,00%). Os medicamentos mais frequentes foram: vancomicina (19), seguido de anfotericina B (16) e piperacilina + tazobactam e loexol. **Conclusões:** Os grupos terapêuticos mais frequentes nas notificações de suspeita de evento adverso relacionados a medicamentos foram os antibacterianos de uso sistêmico, os agentes antineoplásicos, os antimicóticos de uso sistêmico e os contrastes.

PALAVRAS-CHAVE: Farmacovigilância; Evento Adverso; Lesão Renal Aguda

INTRODUCTION

Nephrotoxicity is characterized as a frequent adverse event (AE) as a result of drug use, especially in hospitalized critically ill patients[1]. This adverse drug reaction may occur for reasons inherent to the drug and/or the individual; in the first one, some drugs can be nephrotoxic and present a high risk of causing kidney damage due to their chemical structure, pharmacokinetics, dose used, medication errors, or synergistic effect between drugs[2,3].

Different drugs used routinely from different therapeutic groups, whether sold under prescription or over-the-counter, are described with nephrotoxic potential. Among these are non-steroidal anti-inflammatory drugs, antimicrobials (mainly aminoglycosides, vancomycin, and amphotericin B), antineoplastics, lithium, immunosuppressants, and antivirals[4,5].

In this scenario, due to constant exposure to drugs, pharmacovigilance is evidenced as an important counterpoint to detect, evaluate, and prevent drug-related AEs, such as drug-induced nephrotoxicity[6]. Therefore, it is necessary to notify the AEs to a pharmacovigilance system. In Brazil, VigiMed, a drug-related AE notification system, established in 2018, is responsible for receiving, analyzing, and disseminating notification data[7].

When reports are received by VigiMed, the terms described in the AE are classified according to the Medical Dictionary for Regulatory Activities - MedDRA, which is used to standardize medical terms in the regulatory scope[8]. Reports can be classified into five hierarchical levels. The highest is the System Organ Classes - SOC, which provides the broadest concept for data recovery. The fourth level, the preferred term - PT, is a distinct descriptor (single medical concept) to classify the data described in the AE notification[8].

Therefore, with the newly established system, little is known about the reports received. By analyzing and understanding them, the health system acquires support for its actions by encouraging pharmacovigilance actions. In this sense, this study aimed to describe the drugs and their therapeutic groups reported as suspected drug-related AEs received in 2019 by the national pharmacovigilance system in Brazil (VigiMed).

METHOD

This is a cross-sectional, descriptive, retrospective study of drug-related AE notifications related to nephrotoxicity performed in the VigiMed system. The information collected referred to the period from January 1, 2019, to December 31, 2019, with collection through the data available in the pharmacovigilance reports section of the website: https://www.gov.br/anvisa/pt-br/acessoainformacao/dadosabertos/informacoesanaliticas/notificacoes-defarmacovigilancia.

As inclusion criteria, terms denoting nephrotoxicity were selected and, as exclusion criteria, those denoting chronic kidney injury, as well as those in which the drug was not identified, were eliminated. Thus, the terms selected in the filter were: “comprometimento renal” (kidney impairment), “depuração de creatinina aumentada” (increased creatinine clearance), ”distúrbio tubular renal” (kidney tubular disorder), ”hemorragia renal” (kidney hemorrhage), “insuficiência renal” (kidney failure), ”lesão renal” (kidney injury), “lesão renal aguda” (acute kidney injury), ”necrose tubular renal” (kidney tubular necrosis), “creatininemia aumentada” (increased creatininemia), “creatininemia anormal” (abnormal creatininemia), “creatinina no sangue aumentada” (increased blood creatinine), “nefrite” (nephritis), “nefrite túbulo intersticial” (tubulointerstitial nephritis), “nefropatia” (nephropathy), “nefropatia tóxica” (toxic nephropathy), “proteinúria” (proteinuria), “taxa de filtração glomerular diminuída” (decreased glomerular filtration rate), “distúrbio renal” (kidney disorder), “teste de função renal anormal” (abnormal kidney function test).

In addition to general information from the reports, information was collected from AEs to medication according to MedDRA.

Data processing

The listed drugs were classified according to the Anatomical Chemical Therapeutical - ATC classification, up to the fifth level, available at: https://www.whocc.no/atc_ddd_index/.

Then the data were tabulated in Microsoft Excel software and analyzed in SPSS software, version 25, with description of absolute and relative frequency.

RESULTS

A total of 146 reports of nephrotoxicity were found, with 79 different drugs reported. A drug was excluded because it did not contain the name in the list. In the frequency analysis, 190 drugs were observed in the total of reports.

Reports classified according to the Medical Dictionary for Regulatory Activities (MedDRA)

The reports found associated with nephrotoxicity, when classified according to MedDRA, presented mostly, at the first level, SOC, kidney and urinary disorders, with 108 cases. According to the PT, the most frequent reports were increased blood creatinine, with 31 cases, and kidney failure and toxic nephropathy, with 26 cases (Table 1).

Drugs reported according to the Anatomical Therapeutic Chemical (ATC) classification

Drugs that act as systemic anti-infectives (group J) were reported 97 times (51.05%), mainly antibacterials for systemic use (J01), 70 times (36.80%), and antimycotics for systemic use (J02), 18 times (9.97%). Added to these, the notification of antineoplastic agents and immunomodulators (L group) is highlighted, 30 times (16.31%), in this group, mainly antineoplastic agents (L01), 23 times (12.10%). Another frequent therapeutic group was present in the "several" contrast group (V08) present 19 times (10.00%) (Table 2).

Drugs in reports

The most frequent drugs reported in VigiMed with suspected AE of nephrotoxicity were: vancomycin, 19 cases; followed by amphotericin B, 16 cases; and piperacillin + tazobactam and Iohexol, both with nine cases each (Table 3).

Table 1. Frequency of suspected adverse event according to the Medical Dictionary for Regulatory Activities (MedDRA) classification in VigiMed reports. Brazil, 2019.

Adverse event according to MedDRA classification	n
Systemic group (SOC)	
Kidney and urinary disorders	108
Investigation	39
Preferred term (PT)	
Increased blood creatinine	31
Kidney insufficiency	26
Toxic nephropathy	26
Kidney impairment	20
Acute kidney injury	11
Increased creatinemia	9
Kidney injury	4
Toxic nephropathy	3
Proteinuria	3
Kidney tubular disorder	3
Nephritis	2
Abnormal creatininemia	1
Kidney creatinine clearence	1
Kidney creatinine clearence	1
Kidney hemorrhage	1
Kidney tubular necrosis	1
Oliguria	1
Glomerular filtration rate	1

Source: pharmacovigilance reports (Brazilian National Health Surveillance Agency/VigiMed).
MedDRA: Medical Dictionary for Regulatory Activities; SOC: systemic group; PT: preferred term.

DISCUSSION

Among the therapeutic groups, antibacterials are described as potential nephrotoxic agents. Studies associate its use with this adverse effect, this is justified by its interaction with kidney tissues[9]. In this group of drugs, vancomin stands out, an antibacterial drug of the glycopeptide class used in hospitals to treat infections caused by Gram-positive bacteria[2], with emphasis on *Staphylococcus aureus* resistant to methicillin (MRSA).

Nephrotoxicity occurs mainly when administered doses are higher than necessary, this is accentuated when there is no control of serum concentrations, through therapeutic monitoring[10]. In support of these data, in a meta-analysis of 15 studies, the prevalence of vancomycin-associated acute kidney injury was observed, ranging from 5% to 43%[11].

The development of this adverse effect associated with vancomycin can be explained by its clearance, which is a phase of pharmacokinetics in which the process of elimination of the drug and its metabolites occurs, since it occurs mainly through the kidneys[12]. As for the effector mechanisms in this tissue injury process, the available information is still inconclusive, however, in experimental studies, evidence of apoptosis induced by the accumulation of the drug in the proximal tubular epithelial cells and of tubular ischemia due to oxidative stress were observed[13].

In addition, individuals with changes in renal function are more susceptible to damage resulting from the use of vancomycin, especially those with critical illness, those affected by burns, as well as those on renal replacement therapy and the elderly[10,14,15]. This is mainly due to the decrease in drug excretion and accumulation in the tissues, with a consequent increase in the probability of the occurrence of nephrotoxicity[3].

The second most frequent drug in the reports was amphotericin B. This drug is used in several systemic infections by fungi, and also in the treatment of some cases of leishmaniasis[16]. There are three types of formulations available on the market: deoxycholate (also called conventional), liposomal, and lipid complex; with the main difference between them in the nephrotoxicity

Table 2. Frequency of drugs in reports of suspected adverse events in the VigiMed system, classified according to the Anatomical Therapeutic Chemical (ATC) classification, in two levels. Brazil, 2019.

Level 1	n (%)	Level 2	n (%)
J	97 (51.05)	J01 - Antibacterials for systemic use	70 (36.80)
		J02 - Antimycotics for systemic use	18 (9.47)
		J04 - Antimycobacterials	1 (0.53)
		J05 - Antivirals for systemic use	8 (4.21)
L	31 (16.31)	L01 - Antineoplastic agents	23 (12.10)
		L02 - Endocrine therapy	1 (0.53)
		L04 - immunosuppressants	7 (3.68)
V	22 (11.57)	V03 - All other therapeutic products	2 (1.05)
		V06 -Nutrients in general	1 (0.53)
		V08 - Contrast	19 (10.00)
C	18 (9.47)	C01 - Cardiac therapy	1 (0.53)
		C02 - Antihypertensives	1 (0.53)
		C03 - Diuretics	8 (4.21)
		C07 - Beta blocking agents	2 (1.05)
		C09 - Agents that act on the renin-angiotensin system	6 (3.15)
B	6 (3.16)	B01 - Antithrombotic agents	4 (2.10)
		B05 - Blood substitutes and infusion solutions	2 (1.05)
P	5 (2.63)	P011 - Antiprotozoal	5 (2.63)
N	5 (2.63)	N01 - Anesthetics	1 (0.53)
		N02 - Analgesics	2 (1.05)
		N03 - Antiepileptics	1 (0.53)
		N05 - Psycholeptics	1 (0.53)
A	2 (1.06)	A06 - Constipation drugs	1 (0.53)
		A11 - Vitamines	1 (0.53)
M	3 (1.58)	M01 - Anti-inflammatory and anti-rheumatic products	1 (0.53)
		M04 - Anti-gout preparations	1 (0.53)
		M05 - Drugs for treating bone disease	1 (0.53)
R	1 (0.53)	R06 - Antihistamines for systemic use	1 (0.53)
Total	**190 (100.00)**		**190 (100.00)**

Source: pharmacovigilance reports (Brazilian National Health Surveillance Agency/VigiMed).
Notes: Level 1: Major anatomical group; level 2: Therapeutic group. J: Anti-infectives for systemic use; L: Antineoplastic and immunomodulatory agents; V: Various; C: Cardiovascular system; B: Blood and blood-forming organs; Q: Anti-parasitic, insecticide, and repellent products; N: Nervous system; A: Alimentary tract and metabolism; M: Musculoskeletal system; R: Respiratory system.

profile, with the first formulation being the most associated with this adverse effect[17].

At this juncture, the mechanism of nephrotoxicity is not fully understood, however it has been proposed that there is an important role in the association between tubular injury and kidney vasoconstriction when amphotericin B is being used[17].

Another therapeutic subgroup of anti-infectives for systemic use also present in the results, aminoglycosides, are known for their nephrotoxic effect[18]. Acute kidney injury occurs due to acute tubular necrosis, with an increase in the concentration of serum creatinine, with the main representatives being neomycin, followed by tobramycin and gentamicin, then amikacin and, finally, streptomycin, on a scale from highest to lowest risk of nephrotoxicity. This is due to the affinity profile with proximal tubule cells[18].

Similar to anti-infectives, the antineoplastic group, the second therapeutic group with the highest number of AE reports, are also drugs with a known profile of nephrotoxicity[19]. The effect on the renal system is justified by the constant contact during its use, given that the kidneys carry out most of the process of eliminating many of these drugs and their metabolites[19].

Table 3. Most frequent drugs in reports of suspected adverse events of nephrotoxicity in VigiMed. Brazil, 2019.

Drug (ATC code)	n
Vancomycin (J01XA01)	19
Amphotericin B (J02AA01)	16
Piperacillin + Tazobactam (J01CR05)	9
Iohexol (V08AB02)	9
Polymyxin B (J01XB02)	8
Tacrolimus (L04AD02)	7
Furosemide (C03CA01)	6
Amikacin (J01GB06)	6
Acyclovir (J05AB01)	6
Ceftriaxone (J01DD04)	4
Cisplatin (L01XA01)	4
Meglumine antimoniate (P01CB01)	4
Iobitridol (V08AB11)	4
Iopromide (V08AB05)	4
Total	**106**

Source: pharmacovigilance reports (Brazilian National Health Surveillance Agency/VigiMed).
Note: 14 drugs were listed, those with a frequency equal to or greater than 4. ATC: Anatomical Therapeutic Chemical.

Thus, kidney impairment can result in a delay in the metabolism of antineoplastic agents, consequently, excretion is reduced and there is increased toxicity[19]. Cisplatin, one of the drugs in this group present in the study, is used in several protocols in combination with other drugs, which also have a nephrotoxic profile[20].

In sequence, the contrasts, drugs used for diagnosis, also have a known nephrotoxic profile. Data regarding the understanding of this adverse effect come from evidence of acute tubular necrosis in experiments in animal models[21,22].

However, although the notifications contain information on AE-related drugs, it is neither possible nor advisable to make inferences about the safety of these drugs[7]. This is due to the need to analyze this information by the national pharmacovigilance service, through validation, in order to plan and implement prevention actions[27]. Therefore, even though many of the therapeutic groups and drugs present in this study are known agents with nephrotoxic potential, it cannot be said that they should not be used, nor that they are unsafe.

Compared to similar studies carried out in other countries, in which there is a search for information on AE notifications related to medication, in a study carried out in France[23], the anatomical groups were presented more frequently (level 1 ATC): C (cardiovascular system), followed by J (anti-infectives for systemic use), V (various) and L (antineoplastic and immunomodulatory agents). The study carried out by Pierson-Marchandise et al.[24], also in France, observed that, when separated by the therapeutic group (level 2 ATC), there was a higher frequency of antibacterials for systemic use (J01), followed by diuretics (C03), inhibitors of the renin-angiotensin system (C09), and antineoplastic agents (L01). This information is similar to that of this study, with the J01 group presenting the highest number of notifications with nephrotoxicity information.

However, the data from these studies differ in the size of the data universe, that is, of the reports, since they were carried out with greater temporal cuts. This difference can lead to the largest number of notifications and, consequently, the difference between their numbers, which makes them different when compared. Another point that may justify this dissimilarity is related to the difference in the profile of drug consumption between countries, as well as the socioeconomic profile of users of these drugs.

In addition, another point that justifies this difference between the results of studies from different countries may be the magnitude of AE reports received by their pharmacovigilance systems.

In Brazil, the pharmacovigilance system is still little known and used by the population, and its input is anchored in the performance of hospital services and in the pharmaceutical professional. As justifications for the low pharmacovigilance report, the following are listed: the low knowledge of professionals regarding this theme, the inefficient return of the service to the individual who made the notification, as well as the fear, on the part of health service professionals, of retaliation by the managers[25]. Oladipo and Renz[26] propose, in order to improve the performance of this service, dissemination actions in health services and awareness of professionals to carry out pharmacovigilance actions.

CONCLUSIONS

The most frequent therapeutic groups in reports of suspected nephrotoxicity as drug-related AEs were antibacterials for systemic use, antineoplastic agents, antimycotics for systemic use, and contrasts, groups already observed in clinical studies as nephrotoxic agents. The most reported drugs were vancomycin and amphotericin B, drugs often associated with this AE. In addition to these, there was a significant presence of diuretics, agents of the renin-angiotensin system and immunosuppressants, drugs described in the scientific literature with potential nephrotoxicity.

However, establishing a causal relationship between the drugs present in the reports and the AEs is neither the proposal nor the purpose of the study. This is due to the number of notifications and the AEs described in their scope that are not sufficient for the cause-and-effect relationship. This process presupposes that the AEs are evaluated and validated by the pharmacovigilance system.

The notification of AEs to medicines through VigiMed is of paramount importance so that pharmacovigilance actions are

stimulated in Brazil, through the identification of safety signals. By receiving it, it is possible to detect and evaluate the most frequent adverse effects during the use of drugs and, consequently, the reports can be used for prevention, as in the suspension of sale and distribution of drugs, or for the creation of guidelines for their use.

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Author's Contributions

Santos JFR - Conception, planning (study design), acquisition, analysis, data interpretation, and writing of the work. Xavier RMF – Conception, planning (study design), and writing of the work. All authors approved the final version of the work.

Conflict of Interests

The authors inform that there is no potential conflict of interest with peers and institutions, politicians, or financial in this study.