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Nephrotoxicity in suspected reports of adverse events to vancomycin: cross-sectional study of data reported on VigiMed System in 2022

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ABSTRACT

OBJECTIVE

To describe vancomycin-related or suspected nephrotoxicity-related notifications at Brazil's pharmacovigilance system (VigiMed).

METHODS

Cross-sectional study of adverse events notifications to vancomycin associated with nephrotoxicity reported on VigiMed System in 2022. The variables were vancomycin, terminology that characterised nephrotoxicity, sex, notification by professional, and region of Brazil. Data were expressed in absolute and relative frequencies.

RESULTS

From the total of 777 notifications regarding vancomycin, 44 were related to nephrotoxicity only. From this total, 22 have showed concomitant use with other drugs, mostly other antibiotics. There was no discrepancy between male (52.38%) and female (47.62%). There were no notifications in the northern regions of Brazil during this period and the south-eastern region has showed the highest number of notifications. Most of the notifiers were pharmacists (80.95%) and other health professionals (14.29%).

CONCLUSION

Professionals have insufficient information about adverse events and access to reporting systems, contributing to under-report these events. Actions that promote knowledge about adverse events and pharmacovigilance services strengthen the notification system. It is possible to adopt appropriate control measures and improve protocols based on information obtained at the system.

DESCRIPTORS

Pharmacovigilance, Notifications, Adverse drug events, Nephrotoxicity, vancomycin.

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INTRODUCTION

The regulation, control and surveillance of medicines for human use were achieved by implementing a Brazilian national pharmacovigilance programme, the National Medicines Policy approved in 1998, and the National Health Surveillance Agency (ANVISA) in 1999[1].

Pharmacovigilance aims to promote the safe use of medicines by the population. It is defined as the science which identify, evaluate, understand, and prevent adverse events or any other problems related to medicines[1].

World Health Organisation (WHO) defines an adverse drug event (ADE) as "any undesirable medical occurrence that can happen during treatment with a drug, without necessarily establishing a causal relationship with this treatment". ADE are considered to be a serious public health problem since they are responsible for the increase of morbidity and mortality among patients. They also cause unnecessary costs for health systems, and therefore, causing a negative impact in the clinical, humanistic and economic spheres[2].

An electronic system was developed by ANVISA in 2006, NOTIVISA, dedicated to collect reports of ADE and technical complaints[1]. However, the electronic system VigiMed has replaced NOTIVISA in 2018, facilitating the notification of events by health professionals, citizens, drug registration holders, and study sponsors[1,3].

The information at the pharmacovigilance system refers to suspected adverse events. Although events have been observed following the administration of a particular drug, it is not possible to be certain that they are related to or have been caused by this drug. The possibility must be considered that the adverse events occurred due to other factors, such as the underlying disease itself, the association between two or more medicines, among others[4]. Reports are analysed according to their severity, the risk associated with the adverse event, predictability, i.e. whether the event was expected or not, and the causal relationship between the event and the medicine used. Depending on the case, the notification may lead to the opening of an investigation and, as a result, a series of measures may be taken[5].

In this context, drug therapy is widely used as a treatment for patients hospitalised for various health conditions. Despite its considerable benefits, it can also lead to risk of adverse events[6].

Vancomycin is indicated for the treatment of pneumonia, osteomyelitis, septicaemia, skin and soft tissue infections, and endocarditis caused by gram-positive bacteria susceptible to this drug7. However it is the main cause of acute kidney injury (AKI) due to its widespread use in the hospital environment, accounting for 5 to 15% of patients, depending on different specific risk factors: daily dose > 4g, treatment time > 14 days, and high serum concentration, although there are cases of AKI at appropriate therapeutic levels (15 to 20mg/L). The mechanism of injury is unclear, but some experimental studies suggest the induction of tubular ischaemia due to oxidative stress, leading to an early increase in creatinine when compared to other nephrotoxic drugs[7] .

The association with other potentially nephrotoxic drugs is a well-established risk factor, in addition to advanced age, longer hospitalisation, sepsis, diabetes mellitus, systemic arterial hypertension, and chronic use of non-steroidal anti-inflammatory drugs[8].

Because of these factors, nephrotoxicity due to the use of vancomycin can be considered an adverse event. Thus, pharmacovigilance is an important tool for detecting, evaluating and preventing ADE such as nephrotoxicity. To this end, ADE must be reported to VigiMed[9,10].

Therefore, this study aimed to describe the notifications related to vancomycin or suspected vancomycin-related nephrotoxicity in 2022 on Brazil's national pharmacovigilance system (VigiMed).

METHODS

This is a cross-sectional study of adverse events reports to vancomycin related to nephrotoxicity made on the VigiMed system by following the inclusion criteria: a) reports made between 1 January 2022 and 31 December 2022; b) drug and active ingredient vancomycin; c) research terms characterising nephrotoxicity such as: nephrotoxicity, renal dysfunction, increased serum creatinine, increased creatinine, high creatinine, renal failure, acute renal failure, tubular dysfunction, acute kidney injury, elevated serum creatinine and kidney failure.

The exclusion criteria were related to those that indicated chronic kidney damage, and those in which vancomycin was not identified.

Data were collected by using the information available at the pharmacovigilance notifications section under "Notification Panel" on ANVISA website[10].

The variables analysed were the use of drugs concomitant with vancomycin, age, gender, region of notification and the person´s profile who reported the ADE.

The analysis was carried out after processing the data by using Microsoft Office Excel® for Windows programme. Data were presented in tables and graphs and described in absolute and relative frequency measures.

RESULTS AND DISCUSSION

A total of 777 notifications regarding vancomycin were reported by NOTIVISA between January 2022 and December 2022. After the inclusion and exclusion criteria application, 735 notifications were excluded. A total of 42 notifications related to vancomycin nephrotoxicity matched the inclusion criteria.

We have found notifications distributed according to sex, age, by region/state of Brazil, by type of notifier, and notifications that were associated with other antibiotics.

Table 1 shows the notifications by sex, demonstrating that there were no discrepancy between them.

Table 1. Notifications by sex.

Sex	Total	% of total
Female	22	52,38%
Male	20	47,62%
Total	42	100,00%

Twenty (20) notifications were reported by males and twenty-two (22) by females, with the mean age, 49.55 years and 38.72 years, respectively.

Table 2 shows that the largest number of notifications was from people aged between 45 and 64, partially corroborated by the studies carried out by Menegat[11], who indicates that as well as nephrotoxic substances being a risk factor for nephropathy, advanced age (≥ 65 years) and chronic comorbidities (systemic arterial hypertension, diabetes mellitus, previous CKD, hyperlipidaemia, cardiac syndromes and neoplasia) indicate other factors for the development of nephropathy. Another study[12] carried out in the countryside of Santa Catarina showed an average of between 60 and 70 years in patients admitted to an intensive care unit, and the frequency of nephropathies was directly proportional to the age of the patients.

Table 2. Notification by age group.

Age group	Total	% of total
Less than 1 year old	2	4,76%
01 - 11 years	2	4,76%
12 - 17 years	1	2,38%
18 - 44 years	11	26,19%
45 - 64 years	16	38,10%
Over 65	10	23,81%
Total	42	100,00%

Table 3 shows that the northern region of Brazil has had no reports of nephropathies as adverse events, while the south and centre-west regions have one each only; and the north-east and southeast regions have more reports, with the latter accusing the highest number, represented by São Paulo. Five (5) notifications did not provide information on their state of origin. In a report published by the Federal Pharmacy Council in 2015[13], it was noted that the northern region has showed the lowest number of pharmacists registered in the council when compared to other regions of the country. It might be an explanation for the lack of adverse events reports to vancomycin related to nephrotoxicity in this region.

Table 3. Notification by region/state.

State	Total	% of total
São Paulo	16	38,10%
Not informed	5	11,90%
Federal District	4	9,52%
Goiás	4	9,52%
Espírito Santo	3	7,14%
Rio de Janeiro	3	7,14%
Ceará	2	4,76%
Paraná	2	4,76%
Rio Grande do Norte	2	4,76%
Bahia	1	2,38%
Total	42	100%

The data showed in Table 4 indicate pharmacists as the main notifiers in Brazil's pharmacovigilance system. Indeed these data is confirmed by a study which aimed to identify the profile of professionals who notifies in the pharmacovigilance system between 2009 and 2018. Pharmacists were responsible for 75.6% of the notifications, followed by nursing professionals (14.8%), medical professionals (7.9%) and dentists (0.34%)[14].

Another study indicates that the main causes of under-reporting are the lack of knowledge about ADE, and their impact, importance of reporting them and how to do so. Furthermore, the lack of time to fill in the necessary documentation, perception and understanding of the incidents and fear of punishment[15]. Modesto *et al*. (2016)[16] have concluded that initiatives for disseminate knowledge about ADEs and the pharmacovigilance service to all hospital professionals provide better reporting practices.

Table 4. Notification by type of notifier

Notifier	Total	% of total
Pharmacist	34	80,95%
Other health professionals	6	14,29%
No information	2	4,76%
Total	42	100,00%

Educational strategies have shown effective results in terms of increasing the number of notifications, improving professionals' knowledge levels and adopting good pharmacovigilance practices[17].

When the notifications that have matched the criteria were re-analysed, 22 reported concomitant use with other medicines only, most of which were with other antibiotics.

Table 5. Notifications associated with the use of other antibiotics.

Antibiotics	Total
Amikacin	2
Cefepime	1
Ceftriaxone	2
Daptomycin	1
Meropenem	4
Piperacillin	2
Piperacillin + tazobactam	5
Polymyxin b	1
Sulfamethoxazole/trimethoprim	2
Polymyxin B sulphate	1
Grand total	21

Table 5 shows that there were twenty-one (21) reports of vancomycin with other antibiotics, data corroborated by Sales[8], showing that the epidemiology of AKI related to drug toxicity reaches 25% of cases. Approximately 20% of cases require renal replacement therapy, which is related to increased mortality, with rates of over 60% in developing countries. In clinical practice, it is common to see septic, hypotensive patients with signs of dehydration and using possibly toxic drugs, which are common causes of kidney damage.

The simultaneous use of one or more antibiotics is recommended in specific defined situations. However, knowledge of interactions between antibiotics needs to be considered because they may have an effect on both the bacteria and the patient[18].

This study has tried to draw up a profile of suspected reports of adverse reactions to vancomycin, but some of its own limitations jeopardize the results. The selection bias might be due to the search strategies, and inclusion and exclusion criteria of the selected articles.

CONCLUSION

These under-reporting data might indicate that there is a gap in health professionals education since they are essential for preventing ADE and improve the quality of care as a result.

Therefore these findings may alert pharmacovigilance managers to the importance of improving or developing ADE reporting systems that can be easy handling by health professionals.

Finally information systems are important tools for surveillance practices. VigiMed has emerged as a strategic management element which accounts for highlight information to health professionals, increase control measures and improve protocols.

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