PERSPECTIVE

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Pediatric Nephrotoxicity: How Aware Are We?

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ABSTRACT

Vancomycin and aminoglycosides are potentially nephrotoxic broad-spectrum antibiotics, which can be used both in the treatment of severe infections and in surgical prophylaxis, in pediatric patients. Prolonged antibiotic therapy and high trough concentrations are associated with toxicity. Additionally, several individual factors contribute to nephrotoxicity increasing the risk of acute kidney injury (AKI) and consequent chronic kidney disease in the future. We developed a retrospective and observational study in the Pediatrics Department of a tertiary hospital in Portugal, to analyze clinical practice regarding monitoring and surveillance of vancomycin and aminoglycosides. The results showed low rates of monitoring, which reinforces the importance of raising awareness about this issue, recognizing its importance, and adopting preventive measures that may mitigate the risk of toxicity and improve children's renal prognosis in adult life.

Keywords: Acute Kidney Injury/complications; Aminoglycosides/adverse effects; Child; Kidney/drug effects; Kidney Diseases/chemically induced; Renal Insufficiency, Chronic/chemically induced; Vancomycin/adverse effects

INTRODUCTION

Acute kidney injury (AKI) is a common but underdiagnosed complication and a previous study estimated that it can affect almost 33% of critically and non-critically hospitalized children.[1] The etiology in developed countries has shifted from primary glomerular disorders to hospital-acquired AKI, with one of the most common causes being nephrotoxins.[1]

The most common drugs that cause drug-induced kidney disease include antibiotics, such as vancomycin and aminoglycosides, immunosuppressive antiviral, non-steroidal anti-inflammatory, anti-ulcer, and chemotherapeutic agents.[2] The increasing exposure to more nephrotoxic drugs showed to contribute to a greater risk of AKI, with consequent higher patient morbidity, hospital costs, and risk of chronic kidney disease (CKD).[3,4]

It is crucial to increase awareness about this issue and adopt strategies to prevent drug-induced nephrotoxicity, focused on prevention and early detection of the use of drugs with a high risk of toxicity.

USE OF VANCOMYCIN AND AMINOGLYCOSIDES IN A PORTUGUESE PEDIATRIC DEPARTMENT

We developed a retrospective, observational and longitudinal study from January to December 2021 in the Pediatrics Department of a tertiary hospital in Portugal (Santa Maria Hospital, in Lisbon). The main aim was to describe and recognize the real clinical practice regarding monitoring and surveillance of vancomycin and aminoglycosides in this Pediatric Department. All children and adolescents (0-18 years) hospitalized in the Pediatrics Department [Pediatric Surgery, Neonatology, and Medical Pediatrics, which also comprises the Pediatric Intensive Care Unit (PICU)], treated with intravenous vancomycin, gentamicin, and/or amikacin were included. The total number of prescriptions, duration of antibiotic therapy, and trough levels measurements performed were evaluated. We also quantified the number of supra-therapeutic levels.

We verified 397 prescriptions [289 of gentamicin (72.8%), 84 of vancomycin (21.2%), and 24 of amikacin (6.0%)] in 319 patients. Fig. 1 shows the number of prescriptions for vancomycin, gentamicin, and amikacin in the several Services and Units of the Pediatrics Department.

Most patients observed were male (n=184; 57.7%) with a mean age of 7.3±5.9 years. Seven patients (2.2%) had more than one hospitalization requiring gentamicin, amikacin, and/or vancomycin.

Of the total prescriptions, only 92 (23.2%) were monitored: 51 for vancomycin, 31 for gentamicin, and 10 for amikacin.

The mean duration of vancomycin intake was 9.9±6.7 days (median: 8 days [minimum: 1; maximum: 32 days]) and was mostly prescribed in Neonatology (n=28; 33.3%), followed by Medical Pediatrics (n=20; 23.8%) and PICU (n=19; 22.6%) with monitoring rates of 57.1%, 50%,

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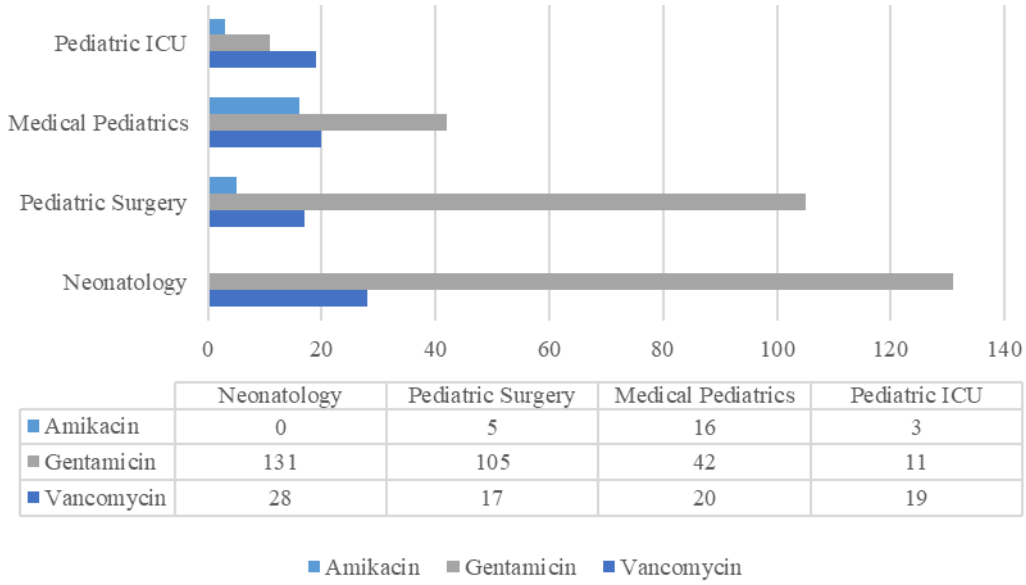

	Neonatology	Pediatric Surgery	Medical Pediatrics	Pediatric ICU
Amikacin	0	5	16	3
Gentamicin	131	105	42	11
Vancomycin	28	17	20	19

Figure 1

Number of prescriptions for vancomycin, gentamicin and amikacin in the different Services and Units of the Pediatrics Department; ICU – Intensive Care Unit

and 94.7%, respectively. The monitoring rate was lower in Pediatric Surgery (41.2%). The total monitoring rate of vancomycin was 60.7% and there were seven toxic levels (13.7%).

Gentamicin was prescribed with a mean duration of 6.2±3.6 days (median: 6 days [minimum: 1; maximum: 27 days]), mostly in Neonatology (n=131; 45.3%) and Pediatric Surgery (n=105; 36.3%), with low monitoring rates in both services: 6.1% and 2.9%, respectively. The total monitoring rate was 10.7% and PICU was the sector with the highest monitoring rate (81.8%). No toxic levels of gentamycin were found.

Amikacin, prescribed with a mean duration of 7.0±3.9 days (median: 7 days [minimum: 1; maximum: 15 days]), was mostly prescribed in medical pediatric wards (n=16; 66.7%) with a monitoring rate of 37.5%. PICU had a monitoring rate of 100% (3 prescriptions; 3 monitorings). In general, the total monitoring rate of amikacin in the Department was 41.7% and there were two toxic levels (20%).

Overall, only 18.6% of prescriptions (n=74) had an antibiotic duration equal to or less than 3 days and could dismiss monitoring.

Even though it was not the aim of our study, the lack of evaluation of kidney function before and after antibiotic therapy limited the determination of the rate of AKI associated with nephrotoxicity, in our population.

DISCUSSION

Aminoglycosides are potent broad-spectrum antibiotics used in pediatric patients to treat severe infections caused by Gram-negative organisms. Kidney toxicity is essentially tubular and the risk increases with higher trough drug concentrations and a longer duration of therapy.[5,6] Gentamicin is one of the drugs used as first-line therapy in neonates with suspected early-onset sepsis, as observed in our population, but despite its widespread use, there are lacking data quantifying gentamicin-induced nephrotoxicity in neonates.[5,6] Vancomycin is a glycopeptide antibiotic commonly used for the empiric and targeted treatment of Gram-positive infections in critically ill patients.[7-9] Kidney injury is also one of the most reported vancomycin adverse effects, which directly produces kidney tubular damage through oxidative stress, resulting in AKI.[7,9,10] Several risk factors might contribute to it and some authors suggest that vancomycin serum levels greater than 15 mg/L and concomitant use of nephrotoxic drugs may increase the risk of AKI.[10,11]

A retrospective cohort study of inpatients who developed AKI associated to aminoglycoside exposure for ≥3 days or ≥3 nephrotoxic medications simultaneously, showed that 70% of children had signs of kidney damage after 6 months, such as reduced estimated glomerular filtration rate (eGFR), hyperfiltration, proteinuria, or hypertension.[4]

Strategies to prevent drug-induced nephrotoxicity remain focused on increased awareness, prevention, and early detection of the use of drugs with a particularly high risk of toxicity. Dose adjustment to kidney function and the monitoring of drug and serum creatinine (SCr) are key approaches. Drug monitoring helps to control both the efficacy and toxicity of several drugs, including aminoglycosides and vancomycin. Elevated trough levels suggest reduced kidney clearance of the drug, which may reflect pre-existing kidney dysfunction, and is a risk factor for developing nephrotoxicity.[5] Another approach includes

the monitoring of SCr in children exposed to nephrotoxins.[5] In the NINJA study (Nephrotoxic Injury Negated by Just-in-time Action), systematic screening of electronic health records was instituted to identify noncritically hospitalized children receiving intravenous aminoglycosides for ≥3 days or ≥3 simultaneous nephrotoxins.[12] For these patients daily monitoring of SCr was recommended. A 42% reduction in AKI rate (number of AKI days per 100 susceptible patient-days) was reported during the first year, after 3 years of implementation of this screening program, there was a 38% reduction in exposure to nephrotoxic medications and a 64 % decrease in the AKI rate.[13,14] Studies like this highlight the importance of creating pharmacovigilance programs. They can identify patients with a higher risk of developing AKI, such as those exposed to multiple and/or prolonged nephrotoxic medications with high serum drug concentrations, limiting the effects of nephrotoxicity.[2,13,15]

CONCLUSION AND FUTURE PERSPECTIVES

Overall, in our study, we found monitoring rates below 50% in noncritical ill children in the Pediatrics Department, which may underestimate the true toxicity. The rates of all drugs monitoring were higher in PICU, related to the greater concern about drug-associated toxicity in critically ill patients. However, Menon S *et al*[4] already demonstrated that children with noncritical illnesses, who developed AKI associated with a high nephrotoxic medication burden, were also at a higher risk of developing signs of CKD after 6 months. The recognition of toxicity is crucial in this population, given their relatively long-life expectancy compared with adults and the progressive rate of eGFR decline observed in children with CKD.[16] For all these reasons, it is important to raise awareness of the risks associated with nephrotoxicity, in the entire pediatric population, and invest in the adoption of preventive measures. There are some international and national (National Authority of Medicines and Health Products – INFARMED) recommendations[17,18] about dosing and monitoring these drugs, however, at the local level, the protocols are not well established and practices are not completely standardized. Besides, there is a lack of information about how often kidney function should be monitored, during and after therapy, especially when supra-therapeutic levels are detected.

Changing practices start at the local level. The knowledge of the results of this work led to the creation of monitoring protocols for vancomycin and aminoglycosides, in the Pediatrics Department of Santa Maria's Hospital. These protocols define the indications for dose adjustment, drug and kidney function monitoring and surveillance. In the future, it is intended to create pharmacovigilance programs, like the one used in the NINJA study, to minimize the nephrotoxic medication burden. We hope and believe that by improving awareness of this issue, standardizing practices, and increasing the monitoring rates, we will minimize nephrotoxicity and associated AKI, ensuring a better kidney outcome in the future.

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