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Adverse effects of vancomycin in children: a review of 22 cases

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Vancomycin has been frequently recommended for the treatment of multi-resistant infections. Twenty-two children undergoing vancomycin treatment were observed. Nine adverse effects were registered in 6 children: eosinophilia in 5 cases, skin rash in 2 cases, and an increase in plasma creatinine in 2 cases. All adverse effects remitted with withdrawal of the drug.

UNITERMS: Vancomycin. Adverse effects. Children. Antibiotics.

Vancomycin is a polypeptide antibiotic isolated in 1956 and introduced into medical practice in 1958 for treating infections caused by penicillin-resistant staphylococci.¹ It has many mechanisms of action, the best known and probably most important being the inhibition of cell wall synthesis in bacteria.² In addition to being extremely effective against Gram-positive bacteria,³⁻⁵ two features of vancomycin are of great interest in medical practice: the low level of bacterial resistance to the antibiotic, and the negligible incidence of cross reactions with other antibiotics.

Initial preparations of vancomycin contained many impurities frequently associated with adverse effects. Today, with drug purification, the number of patients who experience toxic effects is very small. Furthermore, well-controlled drug administration, according to technical

standards, has also contributed to a reduction in the incidence of adverse effects.

After intravenous administration, vancomycin is distributed into various body fluids. Many factors influence the drug's pharmacodynamics, including age. Total body clearance of vancomycin increases with age. Due to the complex pharmacokinetics of the drug, the monitoring of the antibiotic concentration in plasma is recommended to assure successful therapy.⁶⁻⁹

The main adverse effects associated with vancomycin are:¹⁰⁻¹²

- Histamine-like reaction, commonly seen as flushing and a maculo-papular rash of the face, neck, upper thorax, back and arms. The reaction may affect the entire body surface and be accompanied by itching, paresthesia, dizziness, fever, chest pain and edema of the face, lips, and eyelids. More severe symptoms such as tachycardia or bradycardia and, more rarely, systemic arterial hypotension or shock, may be observed;¹³
- Nephrotoxicity has been associated with vancomycin since the beginning of its use. Analysis of these studies are difficult however,

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because many concomitant factors that may impair renal function in vancomycin treatment are also present in these studies;^{14,15}

- Ototoxicity has been difficult to evaluate, as most patients are not submitted to audiometric tests during treatment. Impairment of the auditory nerve, considered the most severe adverse effect, may lead to permanent hearing loss;^{16,17}
- Thrombophlebitis was frequent with initial preparations of vancomycin, occurring in up to 50 percent of cases. The incidence fell to between 6-13 percent after the purification process;¹⁸
- Today, fever and chills are rare adverse effects; they were more commonly observed with initial preparations of the antibiotic;^{10,19}
- Hemotoxicity, mainly represented by neutropenia and eosinophilia, has been described more frequently, and does not seem to be related to dosage or plasma concentration of the drug. Blood count returns to normal values upon withdrawal of the drug;²⁰
- Although increase in serum bilirubin has been associated to the use of vancomycin, there is no clear proof of hepatotoxicity;¹⁰

Arterial hypertension has been described recently, although hypotension is the cardiovascular effect most frequently observed.

The Children's Institute of the Hospital das Clínicas of the University of São Paulo, a major tertiary hospital, treats children with chronic and/or severe diseases in which immunodepression, the use of invasive procedures, and frequent hospital admissions often lead to the development of multi-resistant Gram-positive bacterial infections. Vancomycin plays an important role in the treatment of these infections.

Therefore, we followed 22 children in whom vancomycin was clinically indicated for treating severe infections caused by suspected or confirmed multi-resistant staphylococci. We observed possible adverse effects of the drug through clinical and laboratory follow-up, and attempted to relate these effects to treatment length and plasma concentrations of the drug.

The drug was prepared for intravenous administration at a concentration of 5 mg/ml. The dosage used was 15 mg/kg/dose over a 60-minute period, every 6 hours.

Measurements of plasma concentration of vancomycin were taken at maximal and minimal concentration levels of the phase of equilibrium, that is, after the second day of therapy. Plasma concentration was determined by polarized immunofluorescence on TDx equipment. As plasma concentrations presented great individual variation, levels of 30 to 40 mcg/ml at maximal, and below 10 mcg/ml at minimal were considered adequate.⁹ Optimum plasma levels were observed in only eight children.

Hemogram, urea and creatinine concentration, serum transaminase levels and urinalysis were performed at the beginning of therapy and weekly during treatment in order to monitor adverse effects. Ototoxicity was not evaluated. Concomitant therapy with a cephalosporin or aminoglycoside was necessary in 14 cases.

Nine adverse effects observed in six children are described in the Table. Changes in plasma urea and creatinine levels upon introduction of vancomycin therapy did not occur.

The following adverse effects were observed: two cases of skin rash (9.1 percent), five episodes of eosinophilia (22.7 percent), and two cases of increase in serum creatinine concentration (9.1 percent).

Skin rashes were observed during drug infusion, and after the second week of treatment. Eosinophilia was defined as the number of eosinophils above 500 cells/ml, and was observed after the second week of treatment in five cases. Remission occurred after the end of treatment. Changes in plasma creatinine were observed during the second and third weeks of treatment. Twofold or greater increases were considered significant. Both cases with an increase in plasma creatinine concentration

Table
Adverse effects and serum concentrations of vancomycin

	Serum concentrations Peak (mcg/ml)	Serum concentrations Low (mcg/ml)	Adverse Effects
Case 1	50.4	25.6	eosinophilia
Case 2	37.7	16.7	eosinophilia, skin rash
Case 3	23.1	04.0	skin rash increase in serum creatinine
Case 4	30.9	08.1	eosinophilia
Case 5	54.6	15.0	eosinophilia
Case 6	29.9	05.6	eosinophilia increase in serum creatinine

occurred with simultaneous use of other drugs, in one case amycacin, and in another, ceftriaxone. Creatinine plasma levels returned to normal after the drugs were withdrawn.

Serum concentrations above 40mcg/ml occurred in two of the six children who suffered adverse effects, and in four children the serum concentrations were below 40 mcg/ml.

From the analysis of the data above we can conclude that:

- Plasma concentrations presented great individual variation, confirming that the recommended dosage of vancomycin is suitable for initial therapy, but serum concentrations should be monitored to adjust dosage;
- Significant adverse effects were not observed during infusion, suggesting that administration standards have a protective role;
- Adverse effects were transient and remitted after vancomycin was withdrawn.

RESUMO

Vancomicina é frequentemente recomendada para o tratamento de infecções causadas por *Staphylococcus aureus* multi-resistente. Foram observadas vinte e duas crianças recebendo tratamento com vancomicina. Foram registrados nove efeitos adversos em seis crianças: eosinofilia em cinco casos, exantema em dois casos e aumento da creatinina plasmática em dois casos. Todas as reações adversas regrediram com a retirada da droga.

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