A case of vancomycin–induced drug hypersensitivity syndrome

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Abstract

Drug hypersensitivity syndrome (DHS) has rarely been reported in association with vancomycin treatment. Here, we describe an 11-year-old girl who developed fever and a maculopapular rash on day 18 of intravenous vancomycin for treatment of infective endocarditis. The patient presented with fever, a maculopapular skin rash, hepatitis, and acute renal failure caused by vancomycin-induced DHS. The symptoms resolved in less than 24 h after withdrawal of vancomycin and treatment with corticosteroids. We present this case of DHS associated with vancomycin. (Korean J Pediatr 2008;51:1228-1231)

Key Words: Drug hypersensitivity syndrome, Vancomycin

Introduction

The drug hypersensitivity syndrome (DHS) is a severe, idiosyncratic multi–system reaction caused by drugs. It is defined by the clinical triad of fever, rash and internal organ involvement. Vancomycin has rarely been reported as a cause of the DHS. There are only a few cases of suspected DHS due to vancomycin previously reported in the medical literature. In 1990, Hannah et al. reported a patient who had renal transplantation for end–stage renal disease. This patient was treated for fever and presumed sepsis with intravenous tobramycin and vancomycin, with the subsequent development of persistent fever, eosinophilia and a maculopapular rash that progressed to linear bullae. Sustained measurable serum concentrations of vancomycin, the temporal response to the drug exposure and the response to steroid therapy suggested that vancomycin was the causative agent.

Here, we describe a case of vancomycin–induced DHS in a patient receiving vancomycin for infective endocarditis.

Case report

An 11-year-old girl was transferred to our hospital because of fever, chest pain and palpitations for three days. There was no known history of drug allergy. The history revealed a patent ductus arteriosus (PDA) and mitral valve prolapse (MVP) with mitral regurgitation (MR) detected at our hospital during the neonatal period; cardiac surgery was recommended. However, the parents refused the surgery. The patient was then lost to follow up. On admission, the vital signs showed a body temperature of 39.6°C and pulse rate of 140/min. The patient looked weak and pale. On physical examination, a grade 4/6 systolic murmur was auscultated at the left upper sternal border. The initial laboratory findings were a white blood cell count of 16.1×10^3/mm^3 (74.5% neutrophils, 17.2% lymphocytes), hemoglobin level of 8.0 g/dL and a platelet count of 211×10^3/mm^3. The ESR value was 58 mm/hr. The level of C–reactive protein was elevated to 18.0 mg/dL. The electrocardiogram (ECG) showed a sinus tachycardia and left ventricular hypertrophy. Chest radiography showed cardiomegaly and increased pulmonary vascularity. The echocardiography showed infective endocarditis with large vegetation in the main pulmonary artery (MPA), PDA (diameter of 11 mm size) and MVP with MR (Fig. 1).

After blood was taken for culture, the patient was empirically started on nafcillin and netilmicin intravenously. All blood cultures after admission were negative; the fever abated within four days. On the fifth day after admission, a
direct closure of the PDA and removal of the vegetation in the MPA were performed. Three days after surgery, a fever developed again and nafcillin was changed to intravenous vancomycin. Five days after vancomycin treatment was started, the fever subsided. And then netilmicin was discontinued on eleventh day after vancomycin treatment. However, 18 days after vancomycin treatment was started, the patient developed a fever and a maculopapular rash on the trunk and extremities (Fig. 2). The maculopapular rash became generalized and progressed to purpuric lesions. The vital signs showed a body temperature of 39.3°C and a pulse rate of 132/min. The blood counts were a white blood cell count of $3.7 \times 10^9$/mm$^3$ (66.3% neutrophils, 19.9% lymphocytes), hemoglobin level of 10.1 g/dL and platelet count of $304 \times 10^9$/mm$^3$. The ESR was 86 mm/hr. The serum biochemistry revealed high levels of aspartate aminotransferase (422 U/L), alanine aminotransferase (494 U/L), CRP (8.0 mg/dL), blood urea nitrogen (BUN) (54.4 mg/dL), and creatinine (3.4 mg/dL). The level of IgE was 20.1 IU/mL. The repeated blood cultures were negative. A skin biopsy of the lesion was not performed. Serum levels of vancomycin could not be obtained. Chest radiography and ECG showed no remarkable differences compared to the previous exam.

Under suspicion of the DHS, the vancomycin was discontinued after 19 days of treatment and no additional antibiotic was administrated. Methylprednisolone was started with a dose of 2 mg/kg/day (0.5 mg/kg/dose) every 6 hours. Gradually, the skin rash improved and the patient became afebrile in less than 24 hours. As the fever subsided, the steroid treatment was tapered after approximately four days. The abnormal laboratory findings normalized within seven days of methylprednisolone therapy (Fig. 3). The patient was discharged without any signs or symptoms of DHS. The patient remains symptom-free with normal renal and hepatic

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**Fig. 1.** On the parasternal short-axis view, two-dimensional echocardiography (A) and color Doppler (B) showed a patent ductus arteriosus (cross) and floating vegetation (arrow) in the main pulmonary artery.

**Fig. 2.** A maculopapular rash erupted on the hand (A) and foot (B) of the patient 18 days after vancomycin treatment.
function for eight months after discharge.

**Discussion**

Vancomycin, a glycopeptide antibiotic, has been used with increased frequency in the past 10 years for serious infections due to methicillin-resistant strains of *Staphylococcus aureus*, coagulase-negative Staphylococci and various resistant gram-positive organisms (such as resistant strains of *Streptococcus pneumoniae*). In patients with intolerance or allergy to beta-lactam antibiotics, vancomycin is used for treatment of serious gram-positive infections and bacterial endocarditis. Although known to be safe with therapeutic serum concentrations, vancomycin has been shown to have numerous adverse skin reactions ranging from the most common red man syndrome to urticaria, anaphylaxis, linear IgA bullous disease, acute generalized exanthematous pustulosis, exfoliative dermatitis, exanthems, lupus erythematosus, vasculitis, erythema multiforme, Stevens–Johnson syndrome, and toxic epidermal necrolysis.

The characteristic features of DHS with vancomycin range from mild to severe and include fever, skin lesion, arthralgia, lymphadenopathy, urticaria, hepatic, renal, pulmonary involvement, and hematological abnormalities. DHS commonly manifests with dermatological symptoms caused by the metabolic and immunologic activity in the skin. The most common dermatologic manifestation of a drug reaction is morbilliform rashes. Typically, an erythematous, maculopapular rash appears within one to three weeks after drug exposure, it originates on the trunk and eventually spreads to the limbs.

Severe adverse drug reactions such as the DHS caused by vancomycin are rare with only a few cases reported in the medical literature, despite its more frequent association with cutaneous hypersensitivity reactions. The lesions of DHS related to vancomycin treatment occur 1 to 3 weeks after starting the drug. Recurrences are more severe with a vancomycin rechallenge. The diagnosis is made based on the signs and symptoms associated with the DHS, which rapidly resolve after withdrawal of the drug. The diagnosis of DHS is usually based on clinical judgment, because definitive, confirmatory drug-specific testing is often difficult. The most important and effective therapeutic measure in managing the DHS is the discontinuation of the offending medication.

The clinical consequences of medication cessation or substitution should be closely monitored. In the majority of patients, symptoms will resolve within two weeks if the diagnosis of drug hypersensitivity is correct. Additional therapy for the DHS is largely supportive and symptomatic. Systemic corticosteroids may speed to recovery in the severe cases of DHS involving exfoliative dermatitis, pneumonitis and/or hepatitis. Topical corticosteroids and antihistamines may improve the dermatologic symptoms. In our patient, vancomycin was suspected initially as the cause of the fever and erythematous rash. Other possibilities included the other medications including digoxin, atenolol, spironolactone, enalapril, and furosemide. However, none of the other drugs were considered likely causes of the skin rash. Improvement of the maculopapular skin rash and the fever after discontinuation of vancomycin, suggested that vancomycin caused the DHS. Skin testing for vancomycin was not performed. No well-defined standards are available for vancomycin skin testing. A vancomycin challenge to evaluate reproducible symptoms was not performed due to the severity of the present reaction. The other medications taken by the patient have not been associated with the development of the DHS, to our knowledge.

The duration of therapy, greater than 7 days, and an age less than 40 years have been reported as risk factors for the development of the DHS by both univariate and multivariate analysis. In our patient, the onset of fever and the maculopapular rash occurred 18 days after starting vancomycin therapy. Fever, maculopapular skin lesions, hepatitis, and glomerulonephritis were striking features in our patient with vancomycin-induced DHS. Our patient’s cutaneous lesions
resolved by day 3 of methylprednisolone administration and the abnormal liver and renal function tests resolved by day 8 of methylprednisolone administration.

In conclusion, vancomycin should be considered among the causative agents of the DHS.

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반코마이신 투여 후 발생한 약물 과민성 중후군은 매우 드문 경우 보고되고 있다. 저자들은 11세 여자가 와이어에서 감염성 심내막염에 대한 치료로 반코마이신을 투여한 후 18일째부터 발열, 반구진성 발진이 관찰되어, 반코마이신 투여 중단 및 코르티코스테로이드를 투여한 지 24시간 이내에 임상 증상의 호전을 보인 약물 과민성 중후군 1예를 경험하였다. 본 증례의 원인에서 안발열, 반구진성 발진, 간염, 급성 신부전 등이 약물 과민성 중후군의 증상으로 관찰되었다.

References