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Case Report

Severe tremor due to vancomycin therapy: a case report and literature review

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SUMMARY

Vancomycin is a popular antimicrobial used to treat a variety of Gram-positive infections. Its side effect profile has been well defined due to its high global utilization as a result of the emergence of antimicrobial-resistant organisms in recent decades. Despite its widespread use, however, various idiosyncratic reactions may occur without adequate or universal reporting. We present a case of severe tremor due to vancomycin that has not been previously reported in the literature. Our patient might have been prone to this adverse effect given an underlying essential tremor. Causality is presumed based on the temporal association, while the pathophysiological link remains elusive.

1. Introduction

Vancomycin is a commonly prescribed antimicrobial used in a variety of infections, in particular beta-lactam-resistant Gram-positive infections. Given its popularity and high utilization, its side effect profile has been well elucidated. However, rare idiosyncratic reactions continue to be observed. In this report, we present a case of severe tremor due to vancomycin therapy.

2. Case report

The case was a 69-year-old female patient treated for prosthetic valve infective endocarditis. The patient's past medical history included rheumatoid arthritis, hypothyroidism, essential tremor (as per a neurology consultation), restless legs syndrome, bicuspid aortic valve, and ascending aorta and aortic arch aneurysm. In February 2011 she underwent an aortic valve and hemiarch replacement. The post-operative course was complicated by hemorrhage and atrial fibrillation, but the patient recovered well and was discharged home in early March on spironolactone, perindopril, metoprolol, furosemide, aspirin, lansoprazole, levothyroxine, ropinirole, methotrexate, etanercept, prednisone, and albuterol. Later that month, she was admitted to her local hospital for pneumonia. She was treated with piperacillin–tazobactam and subsequently oral moxifloxacin post-discharge.

Approximately 1 month later, the patient presented with fever and tachycardia. Computed tomography scanning of the chest revealed an extensive right-sided pulmonary embolism for which the patient was treated with enoxaparin. A transesophageal echocardiogram subsequently revealed a 1.4 × 0.9 cm mass with a mobile component superior to the aortic valve leaflet and a 1.1 cm circumferential thickening of the aortic graft, consistent with infective endocarditis and peri-graft abscess. Numerous blood cultures performed were negative, presumably as a result of prior/ongoing antibiotic use.

The patient was treated empirically with vancomycin (1 g intravenous every 8 h), gentamicin (60 mg intravenous every 8 h), and rifampin (300 mg oral twice a day). Initially she tolerated these drugs well and her fever subsided. However, 1 week into therapy gentamicin was discontinued due to acute renal dysfunction, and ceftriaxone was added. The patient remained afebrile and asymptomatic. Vancomycin trough levels were therapeutic (15–20 μg/ml).

Two weeks into therapy, the patient developed an acute, severe, whole-body tremor during infusion of vancomycin, increasing in severity with ongoing drug administration. The tremor was high amplitude and frequency, affecting all four limbs at rest. The patient's level of consciousness was unaffected and motor control was preserved, however the tremor persisted during voluntary movement of the extremities. The infusion was stopped and the tremor subsided within 30 min. The severity of the tremor

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rendered the patient unable to perform even basic activities until it abated. The patient described the tremor as significantly different in character and considerably more severe than any symptoms of tremor previously experienced.

Therapy with vancomycin was continued due to the uncommon nature of the event, however the tremor recurred with the next two infusions. Premedication with diphenhydramine and symptomatic treatment with lorazepam were attempted, but no benefit was observed. On all three occasions, the tremor subsided after discontinuation of vancomycin. Given significant patient discomfort and the seemingly apparent association, vancomycin was discontinued and substituted with daptomycin. The tremor did not recur.

3. Discussion

Vancomycin is a glycopeptide antibiotic with broad activity against Gram-positive bacteria. It inhibits cell wall synthesis by binding to the D-alanyl-D-alanine portion of the cell wall – blocking further polymerization. First discovered in 1953, it is commonly utilized for the treatment of catheter-related infections, bacteremia, endocarditis, hospital-acquired pneumonia, soft tissue infections, osteomyelitis, meningitis, and other central nervous system infections due to Gram-positive microorganisms. Early impure forms of vancomycin (colloquially referred to as 'Mississippi mud') were found to be both nephrotoxic and ototoxic, limiting their clinical use. However, the combination of increased tolerability due to further drug purification and the emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) have resulted in greatly increased contemporary vancomycin use.[1]

Common reactions due to vancomycin include 'red man syndrome' (an erythematous rash on the face and upper body with or without associated hypotension; a result of histamine release due to rapid drug administration), eosinophilia, reversible neutropenia, and phlebitis. Less common reactions include DRESS syndrome (drug rash with eosinophilia and systemic symptoms), drug fever, Stevens–Johnson syndrome, thrombocytopenia, and vasculitis. Vancomycin-associated nephrotoxicity appears to be dose-related, with increased incidence occurring with high trough levels,[2] or when combined with other nephrotoxic agents (e.g., aminoglycosides).[3]

Drug-induced tremor is common. Caffeine and beta-adrenergic agonists are well recognized as both causing and exacerbating tremors. Less commonly implicated drugs include selective serotonin reuptake inhibitors and tricyclic antidepressants. Drug-induced tremor is usually symmetric. Diagnosis requires the exclusion of other medical causes of tremor, a temporal relation to the start of therapy, a dose-dependent response, and a lack of tremor progression. The Naranjo scale can also be used to aid in the diagnosis of drug-induced reactions by assessing the probability of cause and effect.[4]

A comprehensive search of the following key electronic biomedical databases from inception to September 1, 2011 was performed: Medline, Embase, Database of Abstracts of Reviews of Effects, Health Technology Assessment, PubMed, Web of Science, and Google Scholar. Tremor has not been previously reported as an adverse reaction to vancomycin administration in these databases. One case of tremor was reported in an open efficacy and safety study of teicoplanin – a related glycopeptide.[5] Although the tremor was described as mild, therapy was discontinued.

A subsequent search of the Health Canada adverse events database (Canada Vigilance Summary of Reported Adverse Reactions) searched September 1, 2011, yielded six cases of tremor potentially related to vancomycin therapy. The Summary is a spontaneous voluntary reporting system aimed at detecting signals of potential health product safety issues during the post-market period. Of the six cases identified, the median patient age was 73 years, 67% were female, 33% were documented as serious reactions, and all but one case suspected vancomycin as the sole drug responsible for the adverse event. Associated symptoms included chills, pyrexia, rash, flushing, vomiting, dizziness, and abdominal pain. Doses ranged from 0.5 to 2 g every 6–24 h, and the duration of therapy ranged from 1 to 14 days. Data on prevalence of renal dysfunction/failure and trough levels were not available.

A similar search of the Federal Drug Administration (FDA) Adverse Drug Events Database (AERS/Medwatch) from 1997 to 2011 yielded a total of 34 reports of tremor in which vancomycin was the primary suspect drug. Thirty-one (91%) cases were in adults, of which 26 (76%) were male. The highest incidence (26%) was observed in those aged 80–89 years. Seventeen (50%) patients required hospitalization, and five (15%) cases were considered to be life-threatening. The most common associated symptoms included chills, pyrexia, dyspnea, and rigors.

Though no clear evidence or pharmacological explanation can be put forward to explain this adverse event, the temporal and dose-dependent relationship, as well as reproducibility, support vancomycin causality in this case. Using the Naranjo scale, this case scores 7 out of a potential 13 points, which is considered to be a probable association. It is surprising, given our findings, that reports of this reaction have not been previously published, nor is this reaction listed in any common drug information databases (such as Lexi-Comp or Micromedex).

In summary, we report a case of severe tremor due to vancomycin that has not been previously described in the literature. Our patient might have been prone to this given her underlying diagnosis of essential tremor. Causality is presumed based on the temporal association, given the acute onset of symptoms with vancomycin infusion and abrupt cessation with drug discontinuation. The pathophysiological link remains elusive. With awareness of our case and ongoing reporting perhaps the epidemiology of this reaction can be further described and its pathophysiology further elucidated.

Conflict of interest: No conflicts of interest to declare.

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