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The First Case of Vancomycin Induced Neurotoxicity and Literature Review

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ABSTRACT

A 53-year-old female patient was admitted to the hospital due to "occasional lower back pain, burning pain in urination, and bilateral kidney stones for 4 months". After admission, she was diagnosed with urinary tract infection based on urine routine examination and received anti infection treatment with ceftazidime 2g Q12H. The patient's burning pain in urination and urine routine examination improved compared to before. Reexamination of urine culture showed that multidrug resistant Enterococcus faecium (vancomycin sensitive), so vancomycin 1g Q12H was added. The patient complained of double eyelid swelling, scalp itching, both legs weakness and pain after each infusion of vancomycin. After stopping the drug, the patient slightly improved. After another infusion, the above discomfort occurred again. Therefore, the clinician asked the Pharmaceutical Department for consultation. The clinical pharmacist considered that the above discomfort was vancomycin-related adverse reactions. Considering that the symptoms of urinary tract infection and urine routine were significantly improved, clinical pharmacists recommended to discontinue vancomycin. After discontinuation of vancomycin, the patient's double eyelid swelling, scalp itching, legs fatigue and pain gradually subsided. On the 14th day after admission, the patient was discharged after there were no significant abnormalities in urine routine.

Vancomycin is a narrow-spectrum antibiotic of glycopeptides. It exerts a rapid bactericidal effect by inhibiting the synthesis of glycopeptides in bacterial cell walls. It can also change the permeability of bacterial cell walls and selectively inhibit RNA biosynthesis. Its oral absorption is poor, mainly for intravenous administration. Its main adverse reactions were hypotension, phlebitis, nephrotoxicity, ototoxicity, hypersensitivity, red man syndrome, neutropenia, chills, fever and interstitial nephritis [1]. Other cases reported adverse reactions such as liver damage, bone marrow suppression, shortness of breath, limb tremor, Kounis syndrome, etc [2-7].

This study reported a case of double eyelid swelling, scalp itching, legs weakness and pain and prolonged hospitalization after the use of vancomycin due to urinary system infection, in order to reduce and prevent such adverse reactions. No adverse reactions similar to this case have been reported yet.

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Medical History Summary

A 53-year-old female patient was admitted to the hospital due to "occasional lower back pain, burning pain in urination, and bilateral kidney stones for 4 months". Four months before admission, the patient was found to have bilateral kidney stones in other hospitals. During the course of the disease, there was occasional pain in the lower back, urinary tract burning pain during urination, no fever, chills, no frequent urination, urgency and other discomfort. Past physical health, denied hypertension, diabetes, coronary heart disease' and other chronic disease history, denied hepatitis, tuberculosis and other infectious disease history, denied drug and food allergy history, denied surgical trauma history, denied family genetic disease history and infectious disease history.

Admission examination: body temperature 36.3°C, heart rate 73 times/min, breathing 20 times/min, BP115/75mmHg, height 160cm, weight 61kg. The vital signs were stable, the respiratory sounds in both lungs were clear, no obvious dry and wet rales were heard. The heart rate was 73 beats/min, the heart rhythm was uniform, no obvious murmurs were heard in each valve. The abdomen was soft, there was no obvious tenderness, rebound pain or muscle tension in the abdomen. There was no percussion pain in the kidney area and no edema in the lower limbs. Abdominal ultrasound showed double kidney stones. Urine routine: urine protein1+(30) mg/dl; urinary albumin 15.00mg/dl; leukocyte 1156.40/μl; nitrite+; occult blood 2+(0.15) mg/d. The initial diagnosis was double kidney stones and urinary tract infection.

After admission, ceftazidime 2g Q12H was given empirical anti-infective treatment. Escherichia coli ESBL (-) was cultured in urine on the 3rd day of admission. On the 6th day of admission, quantitative urine routine analysis showed that white blood cells were 46.90/μl. Urine white blood cells decreased compared with the previous. Considering the effectiveness of the current anti

infection treatment plan, Ceftazidime was continued. On the 9th day of admission, the patient still complained of mild urinary pain, and the urine culture showed multi-drug resistant Enterococcus faecium, vancomycin sensitive (S), and then added 1g Q12H of vancomycin for injection, the solvent was 100 ml NS. On the 11th day of admission, the patient complained of swelling of both eyelids, itching of the scalp, weakness and pain of both legs after each infusion of vancomycin. After stopping the drug, the patient improved slightly, and the above discomfort occurred again after the second infusion. The patient refused to continue to use vancomycin treatment, and the clinician asked the pharmacy department for consultation. Clinical pharmacists considered it was vancomycin-related adverse reactions, and analyzed that when ceftazidime was used alone, the patient 's urinary tract burning pain and urine routine were improved, and Enterococcus faecium was more likely to be non-pathogenic bacteria. Therefore, it was recommended to discontinue vancomycin and continue ceftazidime treatment alone. After discontinuation of vancomycin, the above discomfort gradually subsided. On the 14th day of admission, the patient 's urinary tract burning pain was completely disappeared, and there were no obvious abnormalities in the urine routine examination. Therefore, Ceftazidime was discontinued, and the patient was scheduled to undergo transurethral flexible ureteroscopic holmium laser lithotripsy and left ureteral stent implantation. The patient refused the surgery and was discharged.

Discussion

One of the common adverse reactions of vancomycin is vancomycin infusion reaction (VIR), which is related to the infusion rate and is not a real allergic reaction [8]. VIR may occur when vancomycin is given for the first time. VIR is characterized by flushing, erythema and itching. The upper body, neck and face are more susceptible to damage than the lower body. Pain and muscle spasms in the back and chest, difficulty breathing, and unexplained hypotension can also occur [9-12]. There may be two mechanisms for skin adverse reactions such as pruritus, facial, neck and upper trunk erythema caused by vancomycin. One is histamine release after rapid infusion, and the other is non-immune mast cell degranulation [13]. The former is directly induced by drugs and their metabolites to release histamine from mast cells, such as 'red man syndrome', which is related to the rapid infusion of vancomycin. The latter is mediated by IgE to release histamine, causing eosinophilia. It has also been described that these adverse drug reactions are usually caused by local or systemic drug-mediated histamine release [8]. It can be prevented by reducing the infusion speed of vancomycin, reducing the dosage and using antihistamines before administration [13].

Vancomycin infusion reaction is usually related to the infusion rate. Renz CL gave 10 healthy patients a 10-minute rapid infusion of 1g vancomycin [14]. As a result, VIR occurred in all patients, severe skin reactions occurred in 7 patients, and blood pressure decreased by at least 20 % in 5 patients, and infusion must be stopped. Healy DP compared the incidence and severity of VIR in 10 adult male volunteers after infusion of 1g vancomycin for 1 hour or 2 hours [15]. Eight cases of VIR occurred in the 1-hour infusion group (two severe, three moderates, three mild), while only 3 cases of VIR occurred in the 2-hour infusion group (all mild). The instructions clearly stipulate that vancomycin is dissolved in 10 ml of water for injection every 0.5 g, diluted with at least 100 ml of diluent, and intravenously dripped for more than 1 hour. The infusion rate should be maintained at 10-15 mg/min. The drug concentration should not exceed 5mg/ml for adults, and should not exceed 10 mg/ml for liquid restriction [16]. In this case, the patient used 1g of vancomycin, the solvent was 100 ml of 0.9% sodium chloride injection, the concentration was 10mg/ml and the infusion speed was 30-50 gtt/m, the infusion speed was fast. Therefore, the patient 's bilateral eyelid swelling and scalp itching after medication were considered to be vancomycin infusion reactions.

Vancomycin-induced weakness and pain in both lower limbs have not been reported. Chen Li and other scholars reported that a patient developed numbness and pain in both feet after infusion of norvancomycin, and the symptoms improved after drug withdrawal [17]. It was considered that norvancomycin caused adverse reactions of peripheral neuropathy. Korver Gretchen reported a case of neuropathic muscle atrophy with bilateral shoulder pain and weakened upper limb function after 2 days of treatment with vancomycin, tobramycin and piperacillin tazobactam in a patient with cystic fibrosis [18]. Although it is impossible to determine which drug caused it, vancomycin is likely to be the only culprit. Finally, vancomycin-induced neurotoxicity is considered, and the correlation is 'very likely'. Ahmed Almohammadi reported a 57-year-old man who developed rare symptoms of nervous system poisoning during oral vancomycin treatment for clostridium difficile pseudomembranous colitis, including headache, altered state of consciousness, confusion of consciousness and somnolence with sexual dysfunction [19]. The patient did not take other drugs that cause neurotoxicity or may interact with vancomycin at the same time, so it was considered to be caused by oral vancomycin, and the correlation was 'possible'. The vancomycin used in this case was similar to norvancomycin, and the adverse reactions recorded in the two drug instructions were basically the same. There are limited reports on vancomycin-induced neurotoxicity, and there are almost no accurate reports of neurotoxicity. Combined with the above literature, it is considered that the fatigue and pain of both lower limbs in this case are neurotoxicity caused by vancomycin. Due to the unclear mechanism of neurotoxicity induced by the drug, it is not known how to prevent it.

In this case, after the use of vancomycin, there were swelling of the eyelids in both eyes, itching of the scalp, fatigue and pain of both legs. After stopping the drug, it improved slightly. After the re-infusion, the above discomfort reappeared, and the hospitalization time was prolonged because of the above discomfort. In summary, there was a reasonable time sequence between the occurrence of the above adverse reactions and medication in the patient. After discontinuation of the medication, the adverse reactions were recovered. No above adverse reactions were recorded in the instruction manual. Moreover, the adverse reactions cannot be explained by the combination of medication, patient's condition, or other treatment effects, and leading to an extension of the patient's hospitalization time. Therefore, this adverse reaction is a new serious adverse reaction, and the correlation of this adverse reaction evaluated using the Naranjo scale is confirmed.

Conclusion

This study first reported vancomycin-induced fatigue and pain in both legs, considering vancomycin-induced neurotoxicity. The eyelid swelling and scalp itching were considered as vancomycin rapid infusion reaction. The case reports of vancomycin-induced neurotoxicity are limited, and the mechanism is still unclear, so how to prevent it is still unknown. The rapid infusion reaction of vancomycin may be related to direct hypersensitivity reaction caused by vancomycin or its metabolites, or histamine release mediated by IgE. This drug reaction is a rare but relatively benign adverse drug reaction, and the symptoms quickly subsided after stopping intravenous infusion.

In summary, controlling the concentration and infusion rate of the drug can effectively reduce the occurrence of adverse drug reactions. The participation of clinical pharmacists in clinical diagnosis and treatment, identification and management of drug-related adverse reactions, is of great significance for improving the effectiveness, safety, and cost-effectiveness of patient drug treatment.

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Author Contributions
Wenjing Li tracked the case, conceived and completed the entire paper writing, and made a major contribution to writing the report. Suxin Wan undertook the analysis and accuracy of the report, and made amendment to the report. Yi Xiang, Gu Huang, and Li Shen participated in the writing of the report. Guangcan Li and Wei Fang participated in the amendment of the report.

Conflicts of Interest
All authors declare no conflicts of interest.

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