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UNEXPECTED FALSELY HIGH VANCOMYCIN CONCENTRATIONS IN A PATIENT WITH ENDOCARDITIS DURING ROUTINE THERAPEUTIC DRUG MONITORING

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ABSTRACT

Introduction: Vancomycin is a glycopeptide antibiotic indicated for the treatment of infections caused by methicillin-resistant *Staphylococcus aureus*. Appropriate vancomycin therapeutic drug monitoring is an essential exercise to improve the achievement of the target therapeutic levels.

Case description: An 87-year-old female was admitted with diagnosis of endocarditis. She was started on antibiotic therapy with intravenous vancomycin. The first vancomycin level registered in our hospital was 36.4 µg/ml. Because this value exceeded the critical threshold (15–20 µg/ml) the prescription was interrupted. New vancomycin concentration tests were indicated for the next days with 65.8 µg/ml, 73 µg/ml, 55.1 µg/ml, 77.9 µg/ml and 100 µg/ml results. Two samples were reanalysed in Hospital Universitario La Paz and were undetectable. Our Clinical Analysis Department found an analytical interference; however, the responsible molecule could not be identified, so the clinical team changed antibiotic treatment to daptomycin, and the infectious condition of the patient improved.

Conclusions: It is recommended that clinicians have a high index of suspicion to investigate cases where drug concentrations do not correlate with clinical expectations. Healthcare professionals need to understand that occasional interference still occurs due to the binding of proteins.

KEYWORDS

Vancomycin, interference, immunoassay, therapeutic drug monitoring

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LEARNING POINTS

- Unknown compounds or mechanisms may interfere with vancomycin assays.
- Assay interference should be suspected in patients with persistently high vancomycin levels who continue to deteriorate clinically.

INTRODUCTION/BACKGROUND

Vancomycin is a broad-spectrum glycopeptide antibiotic, which is derived from the organism *Streptococcus orientalis*[1]. It is administered intravenously and is primarily prescribed for Gram-positive infections such as sepsis, endocarditis, skin and soft tissue infection, bone and joint infections, central nervous system infections, lower respiratory tract infections and central nervous system infections caused by methicillin-resistant *Staphylococcus aureus*.

Correct dosing and therapeutic drug monitoring (TDM) practices are essential when aiming for optimal therapeutic vancomycin levels to guide treatment[2]. TDM of vancomycin through concentrations is recommended to minimise the risks of therapeutic failure and/or toxicity (nephrotoxicity, ototoxicity).

Immunoassay has been the first choice for vancomycin concentration monitoring due to its simplicity and practicality[3]. Like other laboratory tests, sporadic errors can occur as a result of interference from substances in human serum, and lead to false results.

CASE DESCRIPTION

An 87-year-old woman was transferred to Hospital Clínico San Carlos's Cardiology Department with infective endocarditis without immune-related comorbidities. She was colonised with *Staphylococcus epidermidis* (positive in 3/3 blood cultures). The patient received intravenous vancomycin doses of 750 mg every 12 h and rifampicin 600 mg every 24 h guided by antibiogram and adjusted to her weight (50 kg), in addition to her usual medication.

After 14 days of vancomycin treatment (the fifth day after admission in our hospital), trough levels were requested. At that time, her serum creatinine was 0.7 mg/dl and the first vancomycin determination we obtained was 36.4 µg/ml. Due to the high concentration exceeding the threshold (15–20 µg/ml) the prescription was interrupted. A new vancomycin determination was indicated for the next day. The second vancomycin concentration result was 65.8 µg/ml. We reviewed the blood sample collected and talked with the clinical team, doctors and nurses, to confirm the discontinuation of the vancomycin treatment and that no extra dose was wrongly administered to the patient. Additionally, a new serum sample was collected that day to confirm the previous vancomycin concentration, resulting once again in a higher concentration (73 µg/ml).

To rule out other possible explanations for the levels found, the patient's concomitant treatments as well as kidney function were reviewed. No treatment was found that could increase vancomycin serum concentrations and the patient's renal function was normal. Therefore, we could not find a pharmacokinetic explanation for the progressive increase in vancomycin concentration. Keeping in mind what was previously mentioned, we reviewed the analytical process with the Clinical Analysis Department. No analytical issues with calibration, quality controls or other issues related with the analysis equipment (Indiko Plus®, Thermo Fisher Scientific) were identified. Vancomycin was measured during TDM on this automated immunoassay analyser. The study of a possible interference was carried out by two different procedures in the Clinical Analysis Department: serial dilutions and precipitation with polyethylene glycol. In parallel, two samples were reanalysed with the Abbott Architect ci4100 autoanalyzer in La Paz University Hospital. Three days after the first extraction, the vancomycin concentration was 55.1 µg/ml and the next day it was 77.9 µg/ml. The maximum level of vancomycin reported was on the fifth day with a value of 100 µg/ml, the highest value that the equipment is able to quantify. The same value was obtained on the next day *(Table 1)*.

These last two samples were reanalysed at the Clinical Pharmacology Department, La Paz University Hospital, using a chemiluminescent microparticle immunoassay (CMIA) technique with the Abbott Architect ci4100 autoanalyser yielding undetectable results in both samples. This confirmed to us that the patient did not really have the high concentrations of vancomycin we previously found, after stopping treatment six days before.

In view of the falsely elevated serum vancomycin concentration, the probability of a possible interference with the immunochemical assay was raised. To study this possible interference the Clinical Analysis Department carried out serial dilutions and precipitation with polyethylene glycol (PEG), according to the recommendations of the National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines.

Serial dilutions showed a lack of parallelism in the behaviour of the drug between the patient's sample and the two positive controls used in the assay. This means that the metabolite measured in the patient did not have the same behaviour as vancomycin measured in the controls. The precipitation with PEG indicates that it would be a macromolecule interfering with the determination, giving rise to a false positive in the quantification of the drug. The results for serial dilution and PEG precipitation results suggested the assay interference but they could not find the responsible molecule.

Day of TDM	Serum creatinine (mg/dl)	Creatinine clearance (ml/min)	Dose (mg/h)	Serum vancomycin concentration (µg/ml)
1	0.7	78	750/12	Trough level: 36.4 Peak level: 49.6
2	0.76	71	Vancomycin discontinued	Trough level before vancomycin discontinued: 65.8 New sample collected: 73
3	0.67	79	-	55.1
4	1.13	44	-	77.9
5	0.73	74	-	100
6	0.77	70	-	100

Abbreviations: TDM, therapeutic drug monitoring.

Table 1. Serum vancomycin concentrations measured at our centre.

DISCUSSION

Vancomycin has long been considered the gold standard therapy against severe Gram-positive bacterial infections. Appropriate vancomycin TDM is an essential exercise to improve optimal therapeutic levels, minimising toxicity. False vancomycin concentrations may result in an incorrect dosage or inappropriate treatment interruption, leading to a worse clinical outcome.

Even though modern immunoassays use blocking agents to neutralise interfering antibodies, it is important for healthcare professionals to understand that occasional interference still occurs due to binding proteins/macromolecules.

In our hospital, the Clinical Analysis Department quantified vancomycin using Indiko Plus® (Thermo Fisher), a quantitative microsphere system (two-component assay system) based on the competitive inhibition principle.

We found few cases related to false high levels of vancomycin in the TDM. Tsoi et al.[4] described a patient with detectable vancomycin serum concentration before initiation of treatment for a septic joint. They analysed the possibility of assay interference caused by endogenous proteins including paraproteins, immunoglobulin (Ig) G, IgA and IgM, C-reactive protein, rheumatoid factor, heterophile antibodies and total plasma protein. The responsible interference was removed by PEG precipitation; they were unable to attribute the differences to any substance in the assays[4].

In addition, Singer et al.[5] described a case of a 52-year-old woman who, after receiving five doses of vancomycin, showed her serum concentrations continuing to rise for several days in the absence of ongoing vancomycin administration. Later, the case of vancomycin enzyme immunoassay interference was confirmed by high-performance liquid chromatography. This revealed vancomycin concentrations that were less than 50% of those measured by vancomycin enzyme immunoassay. Again, the substance responsible for the interference was not identified[5].

Later, Rice et al.[6] observed elevated vancomycin serum concentrations in two patients. In both cases, laboratory analysis revealed abnormal vancomycin protein-binding profiles with macromolecular complex formation. IgG played a role in the macrocomplex formation in both patients[6].

A falsely elevated vancomycin level because of cross-reactivity was described by Smelter et al.[7] with a long-acting lipoglycopeptide – oritavancin. The interference from the oritavancin results in falsely elevated vancomycin concentrations and, subsequently, inappropriately adjusted vancomycin doses[7].

Also, falsely low vancomycin concentrations have been reported. Simons et al. described two patients with abnormal vancomycin concentrations using a turbidimetric immunoassay. Both patients had high levels of immunoglobulins (due to lymphoma), which are known by the manufacturer to interfere with particle-enhanced turbidimetric inhibition immunoassays[8].

Westergreen-Thorne et al.[9] reported the case of a patient who was inappropriately prescribed with large doses of vancomycin due to inaccurate TDM. Eventually, when duplicated samples were sent to a different laboratory, vancomycin concentrations were found to be in the toxic range. In this case, the initial laboratory reported undetectable vancomycin concentrations using PETINIA immunoassay while the alternative laboratory using the enzyme multiplied immunoassay technique reported high vancomycin concentrations[9].

In some cases, the substance causing the interference was discovered. Tang et al. presented a suspected case of free-kappa light chains-mediated falsely low digoxin and vancomycin concentrations with the Abbott particle-enhanced turbidimetric inhibition immunoassay (PETINIA) method[10]. Elzieny et al. published a case of rheumatoid factor-mediated falsely low vancomycin measurement with the same Abbott determination assay[11].

Pokhriyal et al.[12] reported a case of falsely and persistently elevated vancomycin serum levels detected during routine monitoring, despite no further vancomycin administration. High-performance liquid chromatography eventually confirmed the absence of vancomycin in the blood,

suggesting assay interference as the cause. Unfortunately, the results came at a time when the patient had already died[12].

Commercial companies, who also design the analytical techniques, patent their reagents. In the case of immunofluorescence, the binding of the antibody to vancomycin varies from one company to another. This is the reason why different laboratories can obtain such variable outcomes with the same sample. In our case, the Clinical Pharmacology Department of La Paz University Hospital (using the Abbott Architect c4100 autoanalyzer,) did not detect vancomycin levels in the sample that had the highest levels in our laboratory. Further exploration is needed to identify additional substances that may interfere with different commercially available vancomycin assays.

In our case, the clinical team requested TDM after the administration of at least 10 doses of vancomycin in our hospital. An earlier TDM, especially in patients transferred from another centre, would allow for a proper dose adjustment and the timely detection of problems, minimising the interruption of antibiotic therapy.

It is necessary to assign an appropriate warning regarding this patient, since if she was prescribed vancomycin (and had falsely high levels) the sample would need to be processed with another automated analyser to confirm the results.

Considering the patient's renal function and her clinical situation, and after confirming the suspension of treatment with the clinical team, the vancomycin levels obtained were completely unexpected. The delay between the levels found and the decision regarding them may have been due to the fact that between the second and third day of sampling there was a slight decrease as expected. When the levels were once again high, the patient had an increase in serum creatinine from 0.67 mg/dl to 1.13 mg/dl. At this time, we were trying to find a clinical explanation and ascribed it to the impaired kidney function. Therefore, a new sample of vancomycin was drawn the next day, and we obtained the highest value that the equipment is able to quantify, regardless of the recovered kidney function.

This shows the importance of the patient's clinical evaluation, collaboration between medical teams – the Clinical Pharmacology Department and the Clinical Analysis Laboratory side by side – and avoiding a focus only on the isolated concentration values.

CONCLUSIONS

TDM is not only the quantification of the plasma concentration of a drug, but it also includes the interpretation according to the clinical situation of the patient as it is the only way to individualise treatments.

If the results do not correlate with the patient's clinical situation, possible interferences from certain plasma proteins/macromolecules in the patient's serum with commercially available assays should also be considered. Identifying the precise molecule causing the interference is complex and may not always be possible.

Therefore, we want to highlight the importance of collaboration and coordination among the interprofessional teams to enhance patient care when dosing and monitoring vancomycin therapy.

Further studies are necessary for the appropriate identification of the causal interference and more research is recommended to identify additional substances that may interfere with commercially available vancomycin assays.

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