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Case Report

CASE REPORT

When not to trust therapeutic drug monitoring

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Abstract

Therapeutic drug monitoring (TDM) is the measurement of serum or plasma drug concentration to allow the individualization of dosing. We describe the case of a patient who was prescribed inappropriately large doses of vancomycin due to inaccurate TDM. Specifically, our laboratory reported progressively lower vancomycin concentrations despite dose increases. Eventually, when duplicate samples were sent to a different laboratory vancomycin concentrations were found to be in the toxic range. We hypothesize this was due to the patient generating immunoglobulin antibodies against her infection that interfered with the original TDM immunoassay. Immunogenic TDM interference has been known to rarely occur in patients with immune related comorbidities; however, if we are correct, this is a unique case as this patient did not have such a background. This case illustrates the importance of using clinical judgement when interpreting TDM as, in this case, substantial harm to the patient was likely only narrowly avoided.

INTRODUCTION

Therapeutic drug monitoring (TDM) has been used since the 1960s to individualize drug therapy. TDM is frequently used for monitoring antibiotics, immunosuppressants and many other medications. However, like all clinical tests, TDM is not infallible. If in sufficiently abnormal quantities, normal serum components can interfere with TDM assays and lead to an improper dose being administered; potentially causing substantial patient harm.

Until now, the published literature has only described immunogenic TDM interference in those with immune related comorbidities. Here, we report the rare case of a peritonitis patient without such a background being treated with large and potentially harmful doses of vancomycin from hypothesized TDM interference due to sustained immunoglobulin M (IgM) generation by the patient against their infection. The anomaly was detected only when the sample was processed at a different laboratory, using a different immunoassay technique not prone to such interference. This case illustrates the importance of having an index of clinical suspicion when interpreting TDM.

CASE REPORT

Mrs B was a 71 year old lady established on peritoneal dialysis (PD) due to a history of glomerulo-sclerosis secondary to diabetes mellitus. Her medical background included hypertension and cerebrovascular disease but was without immune related comorbidities. Her most recent PD adequacy and equilibration tests were satisfactory, inferring adequate diffusion of compounds through the peritoneal membrane .

She presented to the PD clinic with a purulent discharge from her PD catheter exit site that subsequently grew

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Table 1: Serum vancomycin concentrations measured using the PETINIA immunoassay at our centre, and the repeat serum vancomycin concentrations performed at an alternative laboratory using the EMIT immunoassay (CRP: C-reactive protein; PETINIA: particle-enhanced turbidimetric inhibition immunoassay; EMIT: enzyme-multiplied immunoassay technique)

Day of treatment	WCC (*Ref. Range: 4–11 10^9/L*)	Neutrophils (*Ref. Range: 2–7.5 10^9/L*)	CRP (mg/dL)	Serum vancomycin concentration (mg/L)			Action taken
				Sample timing	PETINIA (*Ref. Range: 20–30 mg/L*)	EMIT (*Ref. Range: 5–10 mg/L*)	
1	15.4	13.6	–	–	–	–	Vancomycin 30 mg/kg given. Next dose in 72 h
4	9.0	6.1	74	Pre-Dose Trough Level	11.2	–	Vancomycin 30 mg/kg given. Next dose in 72 h
7	9.2	6.4	60	Pre-Dose Trough Level	17.8	–	Vancomycin 30 mg/kg given. Next dose in 48 h
9	9.4	6.2	–	Pre-Dose Trough Level	3.9	–	Vancomycin 30 mg/kg given. Next dose in 24 h
10	10.8	8.2	18	Pre-Dose Trough Level	<1.1	24.2	Vancomycin 30 mg/kg given. Next dose in 24 h. Duplicate sample sent to alternative laboratory for EMIT testing.
11	7.6	5.3	25	Pre-Dose Trough Level	<1.1	30.2	Vancomycin held indefinitely following high EMIT day 10 result. Duplicate, confirmatory pre-dose and post-dose levels resent for EMIT. Flucloxacillin commenced
				Duplicate Pre-Dose Trough Level	<1.1	31.2	
				45 Minutes Post-Dose Level	<1.1	36.3	
20	6.4	3.9	–	N/A	N/A	N/A	Completes course of antibiotics with clinical resolution of symptoms.

Staphyloccocus aureus on culture; otherwise, she was asymptomatic and not septic. She was diagnosed with PD-associated peritonitis and commenced on a regimen of intraperitoneal (IP) vancomycin (30 mg/kg) and oral rifampicin as *per* our centre's protocol.

According to trust policy, TDM was utilized to ensure appropriate vancomycin dosing. Table 1 illustrates our laboratory's vancomycin level measurements using PETINIA (particle-enhanced turbidimetric inhibition immunoassay): one of the assay types used in TDM. Paradoxically, despite repeated dose frequency increases and clinical improvement, serum vancomycin levels were reported progressively lower, eventually becoming undetectable. Even a post-dose serum level on day 11 was undetectable despite the half-life of vancomycin being 48–72 h in patients with end stage renal failure. Post-dose IP vancomycin levels were however within expected limits. After ensuring all doses had been administered correctly we sent a duplicate sample to another laboratory for verification using a different immunoassay (EMIT: enzyme-multiplied immunoassay technique); meanwhile, we held vancomycin and commenced oral flucloxacillin instead.

Serum vancomycin concentrations later returned from the alternative laboratory at the toxic concentration of 36.3 mg/L (target range: 5–10 mg/L). The vancomycin was held indefinitely and she was continued on oral rifampicin and flucloxacillin for a further 9 days. Fortunately, in addition to a full clinical resolution of her PD-peritonitis, she demonstrated no ototoxicity, neutropenia or other signs of vancomycin toxicity.

DISCUSSION

Here, we report the case of a PD-peritonitis patient whose TDM became so inaccurate that vancomycin had to be stopped; substantial patient harm likely only narrowly avoided. Despite duplicate samples, the initial laboratory using PETINIA immunoassay reported undetectable vancomycin concentrations whilst the alternative laboratory using EMIT immunoassay reported exceedingly high vancomycin concentrations. Ordinarily, EMIT has good correlation with PETINIA when interference is not present and both laboratories were up to date with external control programs [1]. Without a gold standard test available to the laboratory (e.g. mass spectrometry), we are left to conclude that either both or one of the utilized assays were inaccurate. However, clinical sense points to EMIT being less affected as the high concentrations reported fitted with the clinical scenario of multiple dose frequency increases. This indicates an interferent was likely preferentially interacting with PETINIA over EMIT, though difficult to establish for certain.

A large number of exogenous and endogenous compounds are known to interfere with the accuracy of TDM assays. Well characterized interferents include hyperlipidemia, hyperbilirubinemia and metabolites of the parent drugs themselves in certain assays [2–4]. Common laboratory practice is to concurrently check if common interferents for a given assay are in sufficient quantities to significantly affect results. However, in this case, nothing was flagged by the laboratory.

Due to the serial errors and no other concomitant reports of inaccurate vancomycin TDM for others by the initial laboratory, this points to a TDM interferent likely endogenous to the patient. We know the interferent was not present in the PD fluid as IP vancomycin levels were sensical. Therefore, the interferent was likely to be a serum component, one that was accumulating over a period of 4–10 days as inferred by the progressively lower vancomycin readings despite frequent increases to the dose prescribed.

Hence, in discussion with local biochemistry and immunology departments, we hypothesize that a mounting antibody response to infection caused an increasingly large Ig interference to PETINIA over several days. An autoimmune and myeloma screen had not been performed at the time. However, an autoimmune screen (ANA, ANCA, anti GBM antibody, complement C3, C4), plasma protein electrophoresis and immunoglobulin profile performed 2 years prior were normal, apart from an elevated IgM of 2.8 g/L (0.5–2.0). The patient had received a single dose of prophylactic IV Vancomycin prior to PD catheter insertion, but no subsequent level check was required then. Others have hypothesized immunogenic interference to PETINIA assays but, if correct, ours would be the first recorded patient without pre-existing immune related comorbidities. [5–7].

PETINIA is thought to be particularly prone to interference by immunoglobulins as it calculates drug concentrations by monitoring the turbidity of the reagent mixture when exposed to the analyte. IgM has high potential for cross-reacting and binding together various antigens into large complexes and it is thought this process brings about agglutination and inaccuracy in certain cases [8, 9]. Conversely, EMIT calculates drug concentration via enzymatic reaction when reagent and analyte are mixed and hence is less prone to inaccuracy from agglutination.

Crucially, regardless of the cause of assay interference, what is certainly true is that if solely drug concentrations were used, with no thought to clinical context, it could have resulted in substantial morbidity to this patient.

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CONFLICT OF INTEREST

None declared.

FUNDING

None.

ETHICAL APPROVAL

As per trust policy, ethical approval is not required for case reports if appropriate patient or next of kin consent is obtained as in this case.

CONSENT

Next of kin consent was obtained as the patient had sadly passed away from unrelated causes at the time of writing.

GUARANTOR

Dr Mathew Westergreen-Thorne, MBBS, BSc.

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