Novel treatment (new drug/intervention; established drug/procedure in new situation)

Teicoplanin-induced leucopenia with immediate resolution after administration of G-CSF

Peysh Patel,¹ Jonathan Sandoe,² Wazir Baig³¹Leeds General Infirmary, Leeds, UK;²Microbiology Department, Leeds General Infirmary, Leeds, UK;³Cardiology Department, Leeds General Infirmary, Leeds, UK

Correspondence to Dr Peysh Patel, peysh@doctors.org.uk

Summary

Teicoplanin is used in a wide range of clinical settings, owing to its wide antiGram positive bacterial activity. Although it is generally well tolerated, adverse reactions such as fever and rash are well recognised. Haematological sequelae have been rarely reported. This case report describes the development of teicoplanin-induced leucopenia in a patient with infective endocarditis. A short course of lenograstim, a recombinant granulocyte colony-stimulating factor (G-CSF) reverted biochemical abnormalities. To the authors' best knowledge, this is the first documented example of implementation of G-CSF in such a clinical setting.

BACKGROUND

This case highlights a distinct and rare example of teicoplanin-induced leucopenia. With its prolonged halflife, total clearance of teicoplanin may take over a month, even in those with unimpaired renal function. In such instances, administration of granulocyte colony-stimulating factor (G-CSF) may be relevant in facilitating a resolution of biochemical parameters. This case highlights this, and advocates the need for close monitoring of haematological complications in all patients who are administered teicoplanin.

CASE PRESENTATION

A 77-year-old man presented with a 2 week history of rigors and fever. Before admission, he had self-medicated with a 10 day course of ciprofloxacin for presumed urinary tract infection, but his symptoms had persisted. He had no specific localising symptoms and had not undergone any recent dental procedures. His medical history was relevant for a porcine bioprosthetic aortic valve replacement in 2008. He had no known drug allergies.

INVESTIGATIONS

On admission, he was feverish at 37.7°C and had a sinus tachycardia at 104 beats per min. Auscultation revealed an ejection systolic murmur loudest at the left sternal edge, with no evidence of aortic regurgitation. There were no cutaneous stigmata of infective endocarditis and the remainder of the examination was unremarkable. Initial blood investigations showed a normal full blood count (haemoglobin 14.6 g/l, white cell count $9.51 \times 10^9/l$, platelets $319 \times 10^9/l$) and renal function (urea 7.1 mmol/l, creatinine 107 $\mu\text{mol/l}$). C reactive protein was elevated at 117 mg/l. Three sets of blood cultures taken 2 days apart were positive for *Streptococcus anguinis*, which was susceptible to penicillin.

TREATMENT

He was commenced on intravenous gentamicin (1 mg/kg twice daily) and benzylpenicillin (2.4 g 4 hourly). A trans-

oesophageal echocardiogram performed 7 days postadmission revealed a well-seated aortic valve replacement with no definitive features of infective endocarditis. The patient improved clinically and this was correlated with an improvement in his inflammatory markers (C reactive protein 12.8 mg/l after 12 days of antibiotics). Gentamicin was discontinued as per protocol after 14 days of therapy.

OUTCOME AND FOLLOW-UP

However, in the proceeding week, he began to document recurrence of symptoms with intermittent fever and sweating. Although failure of therapy with penicillin was considered, a delayed hypersensitivity to the agent was considered most likely. His regime was altered to intravenous teicoplanin (800 mg once daily), 26 days postadmission. There was an initial improvement in his condition but after a few days, he developed a generalised, non-blanching purpuric rash over his abdomen and upper thighs accompanied by general malaise and recurrence of fever. Repeat blood cultures were negative. A CT of chest, abdomen and pelvis showed no obvious focus of infection and a repeat trans-oesophageal echocardiogram was unremarkable.

A full blood count at this time revealed a new leucopenia (white cell count $3.41 \times 10^9/l$, neutrophils $1.58 \times 10^9/l$), 19 days after commencement of teicoplanin. The C reactive protein was static at around 20 mg/l and teicoplanin levels returned at 14.6 mg/l. Blood film showed evidence of occasional immature granulocytes with anisocytosis and monocytosis. In the absence of an alternative explanation, the leucopenia was deemed to be secondary to teicoplanin and it was discontinued 39 days postadmission. An alternative regimen of intravenous daptomycin (480 mg once daily) and oral rifampicin (300 mg twice daily) was introduced.

Despite this intervention, biochemical monitoring revealed persistence of the leucopenia. On day 61 of admission (22 days after discontinuation of teicoplanin), blood tests revealed a white cell count of $2.11 \times 10^9/l$ and a

neutrophil count of $0.07 \times 10^9/l$, the lowest recorded during admission. Teicoplanin levels were found to be 4.8 mg/l. After immediate consultation with immunology, a course of lenograstim at 264 ug/day (a recombinant G-CSF) was implemented. This resulted in a dramatic response in white cell count, returning to normal levels within 2 days of administration. The patient symptomatically improved with no further concerns and was discharged 72 days after initial presentation.

DISCUSSION

Teicoplanin is a bactericidal glycopeptide derived from *Actinoplanes teichomyceticus*.¹ It has activity against both aerobic and anaerobic Gram-positive bacteria. It is generally well tolerated, with transient side-effects which rarely require cessation of therapy. The most commonly reported adverse events include hypersensitivity reactions (manifesting as urticaria, fever and rigors) and gastrointestinal side-effects such as vomiting and diarrhoea. Uncommon haematological sequelae include eosinophilia, thrombocytopenia and, more rarely, leucopenia.

The first documented observation of teicoplanin-induced leucopenia was reported in 1989.² They outlined the case of a 73-year-old man developing a profound leucopenia (white cell count $2.00 \times 10^9/l$) after 20 days of teicoplanin therapy for *Enterococcus faecalis* endocarditis. Levels reverted to normal after discontinuation of antibiotic. A similar phenomenon of mild leucopenia was observed in seven of a cohort of 26 patients with endocarditis caused by Gram-positive infection.³ Interestingly, the leucopenia in these cases did not warrant discontinuation of therapy or administration of G-CSF.

A literature review suggests that the association of leucopenia with vancomycin, a compound that shares structural resemblance and antibacterial spectrum with teicoplanin, is more established. A systematic analysis suggests that this phenomenon is likely to be duration rather than dose-related.⁴ A study in 2007 highlighted the case of a 57-year-old female with osteomyelitis who developed vancomycin-induced leucopenia.⁵ The regime was switched

to teicoplanin. After initial resolution of agranulocytosis, a new episode of leucopenia occurred which was deemed to be secondary to teicoplanin administration. With the existence of structural correlations between the two compounds, cross-reactivity may occur. However, conflicting information also exists. A report in 2000 describes the case of a 35-year-old man with vancomycin-induced leucopenia (white cell count $2.8 \times 10^9/l$), which resolved immediately after direct substitution with teicoplanin.⁶ An explanation for this fundamental disparity may be that the mechanism of action of teicoplanin is not entirely understood. An immune-mediated process has been postulated,⁷ but there is still much to decipher.

An understanding of the pharmacokinetic profile of teicoplanin is relevant in any clinical context where an adverse drug reaction is suspected. It can be described as an open, three-compartment model when given intravenously at 6 mg/kg.⁸ In healthy volunteers, its plasma level profile indicates a biphasic distribution with a rapid phase (half-life of 0.3 h) followed by a more prolonged distribution phase (half-life of 3.2 h). There is no evidence for extensive hepatic metabolism of the drug,⁹ and excretion is therefore via the kidneys. Notably, elimination is slow with a terminal half-life of around 150 h. Even in those with normal baseline renal function, therefore, total clearance may take up to 32 days, with a vastly prolonged duration in those with renal impairment. This was exemplified well in this case report, where teicoplanin levels were found to be 4.8 mg/l (approximately 25% of peak measured value) 22 days after antibiotic discontinuation.

This attribute may appropriately explain the continued decline in white cell count and persistence of symptoms long after cessation of therapy. If so, one may speculate whether such sequelae could have been predicted. Indeed, if this is the case, earlier administration of G-CSF may have been appropriate in this scenario to facilitate a more prompt resolution in clinical and biochemical parameters. However, it is relevant to note that two new agents, daptomycin and rifampicin, were commenced as alternative therapy after teicoplanin was discontinued. Rifampicin in particular has documented associations with leucopenia,¹⁰ and it is therefore difficult to predict what contribution, if any, this may have had on the observed biochemical correlations.

Figure 1 Graph showing correlation between white cell count (normal value: $4\text{--}11 \times 10^9/l$), teicoplanin levels (normal value in deep seated infections: trough of 20–40 mg/l) and neutrophil count (normal value: $2.5\text{--}7.5 \times 10^9/l$).

Learning points

- ▶ Teicoplanin is an effective antibiotic for second line therapy. Side-effects are usually tolerable and rarely require specific intervention.
- ▶ This case highlights a distinct and rare example of teicoplanin-induced leucopenia.
- ▶ With its prolonged half-life, total clearance of teicoplanin may take over a month, even in those with unimpaired renal function. In such instances, administration of G-CSF may be indicated. To the authors' best knowledge, this is the first example of implementation of this agent in such a setting.
- ▶ We advocate close monitoring for potential haematological complications in all patients who receive teicoplanin, and an awareness of the potential role of G-CSF in reversing it.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. **Van Bambeke F.** Glycopeptides and glycopeptides in clinical development: a comparative review of their antibacterial spectrum, pharmacokinetics and clinical efficacy. *Curr Opin Investig Drugs* 2006;**7**:740–9.
2. **Del Favero A,** Patoia L, Bucaneve G, *et al.* Leukopenia with neutropenia associated with teicoplanin therapy. *DICP* 1989;**23**:45–7.
3. **Presterl E,** Graninger W, Georgopoulos A. The efficacy of teicoplanin in the treatment of endocarditis caused by gram-positive bacteria. *J Antimicrob Chemother* 1993;**31**:755–66.
4. **Black E,** Lau TT, Ensom MH. Vancomycin-induced neutropenia: is it dose- or duration-related? *Ann Pharmacother* 2011;**45**:629–38.
5. **Hsiao SH,** Chang CM, Tsai JC, *et al.* Glycopeptide-induced neutropenia: cross-reactivity between vancomycin and teicoplanin. *Ann Pharmacother* 2007;**41**:891–4.
6. **Sanche SE,** Dust WN, Shevchuk YM. Vancomycin-induced neutropenia resolves after substitution with teicoplanin. *Clin Infect Dis* 2000;**31**:824–5.
7. **Parenti F.** Structure and mechanism of action of teicoplanin. *J Hosp Infect* 1986;**7** (Suppl A):79–83.
8. **Verbist L,** Tjandramaga B, Hendrickx B, *et al.* *In vitro* activity and human pharmacokinetics of teicoplanin. *Antimicrob Agents Chemother* 1984;**26**:881–6.
9. **Neville LO,** Baillod R, Grady D, *et al.* Teicoplanin in patients with chronic renal failure on dialysis: microbiological and pharmacokinetic aspects. *Int J Clin Pharmacol Res* 1987;**7**:485–90.
10. **Nagayama N,** Shishido Y, Masuda K, *et al.* [Leukopenia due to anti-tuberculous chemotherapy including rifampicin and isoniazid]. *Kekkaku* 2004;**79**:341–8.

This pdf has been created automatically from the final edited text and images.

Copyright 2012 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Patel P, Sandoe J, Baig W. Teicoplanin-induced leucopenia with immediate resolution after administration of G-CSF. *BMJ Case Reports* 2012;10.1136/bcr.01.2012.5668, Published XXX

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow

Keep up to date with all published cases by signing up for an alert (all we need is your email address) <http://casereports.bmj.com/cgi/alerts/etoc>