CASE REPORT

Case Report

Artificial Elevation of Prothrombin Time by Telavancin

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Received: 11 May 2012 / Accepted: 10 September 2012 / Published online: 6 November 2012
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Abstract

Background Methicillin-resistant *Staphylococcus aureus* infections are a well-documented risk of surgery and are becoming increasingly difficult to treat owing to continued acquired resistance. A new antibiotic for treatment of *Staphylococcus aureus* is telavancin.

Case Description A patient at our institution was prescribed telavancin for multiple spinal abscesses before spinal surgery. Routine preoperative testing revealed an international normalized ratio (INR) of 2.05 with no clear cause. Careful review of the patient's medication history and prescriber information revealed that telavancin may interfere with prothrombin time (PT/INR) testing. In vitro

testing by our laboratory confirmed an association between telavancin dose and an increase in PT/INR. An alternative reagent for PT/INR testing unaffected by telavancin dose revealed a PT/INR of 0.97.

Literature Review Telavancin interacts with artificial phospholipid surfaces used to monitor coagulation while having no actual effect on coagulation.

Purposes and Clinical Relevance All physicians, especially orthopaedic surgeons, should be aware of the effects of telavancin and ensure proper measures are taken to acquire the true INR by switching the reagent used to test PT/INR or ensuring the PT/INR is drawn before telavancin dosing.

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Introduction

Surgical site infection with methicillin-resistant *Staphylococcus aureus* (MRSA) is a well-described surgical complication. Prescreening patients, having elective orthopaedic surgery, with nasal swabs suggested 22.6% patients were *S aureus* carriers and 4.4% were identified as MRSA carriers [8]. MRSA carriers have a sevenfold higher rate of surgical site infection than noncarriers [8]. MRSA infection leads to substantial increases in morbidity, mortality, and medical cost [11].

The treatment of MRSA is reliant on various antibiotics, most notably vancomycin. However, the emergence of vancomycin-resistant *S aureus* (VRSA) required the development and use of new antibiotics. One such antibiotic is telavancin. The Infectious Disease Society of America recommends telavancin for hospitalized patients with complicated skin and soft tissue infections with gram-positive organisms, including MRSA and VRSA [4, 9]. The safety information provided for telavancin

acknowledges telavancin will interact with artificial phospholipid surfaces used to monitor coagulation [1, 2]. However, the safety information does not specify which products may have this interaction.

This case report describes one orthopaedic patient who, after being prescribed telavancin for MRSA infection, showed a false increase in her prothrombin/international normalized ratio (PT/INR). We also highlight how the different reagents used to test PT/INR are affected by telavancin.

Case Report

A 63-year-old woman with a long-standing history of scoliosis underwent T4 to sacrum posterior spinal fusion in August 2009. Postoperatively, she had several MRSA hardware infections develop leading to chronic osteomyelitis of the spine (Table 1). Multiple abscesses formed requiring a series of débridements and chronic antibiotic suppression with daptomycin or vancomycin during the subsequent 1.5 years until she had adequate spinal fusion. During this hospitalization, she was admitted with an abscess while receiving therapeutic vancomycin and the orthopaedic surgery and infectious disease teams suspected VRSA despite the culture results. She was prescribed 10 mg/kg (510 mg) of telavancin (Vibativ[®]; Astellas Pharma US Inc, Northbrook, IL, USA) once a day before her final débridement and hardware exchange 25 days later. Her creatinine was 0.63 mg/dL and creatinine clearance was calculated to be 73.6 mL/minute; therefore, her dose and rate of administration were not adjusted for renal insufficiency.

Routine preoperative blood work obtained 13 days after beginning telavancin showed a PT/INR of 2.51 and an activated partial thromboplastin time (aPTT) of 29.6 seconds (drawn 125 minutes after last dose of telavancin). Before telavancin therapy, the patient's PT/INR was 1.02

and aPTT was 27.7 seconds. Vitamin K was administered and a repeat PT/INR showed it had corrected to 0.99 (drawn 1735 minutes after last dose of telavancin). Surgery then was scheduled. Repeat preoperative blood work 16 days after initiation of telavancin showed the PT/INR had increased to 2.41 (drawn 138 minutes after last dose of telavancin). Additional vitamin K administration had no measurable effect, and surgery was postponed. During the next 4 days, her PT/INR varied between 1.65 and 2.35 with no clear cause (Fig. 1). The rest of her coagulation studies came back normal, as did her coagulation factor assays.

With no other known cause, the anticoagulation team was consulted and we hypothesized one of the patient's medications might have been interfering with the PT/INR testing. A careful search of all her medication side effects uncovered that telavancin was known to bind to the artificial phospholipid surfaces added to common anticoagulation tests [1]. The laboratory at our institution had recently switched from using RecombiPlasTin 2G[®] (Instrumentation Laboratory, Bedford, MA, USA) to Innovin[®] (Siemens Healthcare Diagnostics, Marburg, Germany) as the reagent for PT/INR testing. Innovin[®] is a recombinant tissue factor that contains artificial phospholipids and is insensitive to therapeutic levels of heparin, which can prolong PT/INR values [14]. Once this interaction was discovered and verified, the PT/INR was measured using the RecombiPlasTin 2G[®] reagent. The result revealed a PT/INR of 0.97 (drawn 247 minutes after telavancin was last dosed), within the normal range. Surgery was subsequently scheduled and performed without bleeding complications.

Discussion

MRSA infections are serious surgical complications leading to substantial morbidity and mortality. Telavancin is a

Table 1. MRSA susceptibilities

Antibiotic tested	Concentration (μg/μL)	Outcome
Cefazolin	> 16	Resistant
Clindamycin	> 2	Resistant
Erythromycin	> 4	Resistant
Gentamicin	≤ 1	Sensitive
Minocycline	≤ 1	Sensitive
Penicillin G	> 1	Resistant
Rifampin	≤ 0.5	Sensitive
Tetracycline	≤ 0.5	Sensitive
Trimethoprim/sulfamethoxazole	≤ 0.5/9.5	Sensitive
Vancomycin	≤ 0.5	Sensitive

MRSA = methicillin-resistant *Staphylococcus aureus*.

Fig. 1 A plot shows the linear correlation of minutes from telavancin administration to PT/INR draw with the INR measured using the Innovin[®] reagent.

new antimicrobial approved by the FDA in September 2009 and recommended by the Infectious Disease Society of America for hospitalized patients with complicated skin and soft tissue infections with gram-positive organisms, including MRSA and VRSA [3, 4, 7, 9]. Telavancin is a lipoglycopeptide produced through a chemical modification of vancomycin. When administered at 10 mg/kg once daily, it is able to inhibit bacterial cell wall synthesis by binding lipid II and disrupting peptidoglycan synthesis and bacterial membrane function [6, 10]. After a single dose of telavancin, the serum concentration declines monoexponentially with a half-life of approximately 7 to 8 hours and a steady-state plasma concentration is reached after three to four doses [13]. Plasma levels of telavancin peak between 88 and 186 µg/mL and trough between 6 and 16 µg/mL when given at doses of 7.5 mg/kg and 15 mg/kg, respectively. Telavancin primarily is cleared via urinary excretion [14].

As with all drugs, telavancin is not without side effects, including gastrointestinal side effects such as nausea and vomiting, and cardiac side effects such as QT prolongation [1]. Additionally, the interaction of telavancin with the artificial phospholipid reagent, Innovin® (Dade Behring, Marburg, Germany), used in PT/INR determination delayed surgical intervention and increased our patient's hospital stay. Safety information for telavancin acknowledges the interaction of telavancin with artificial phospholipid surfaces used to monitor coagulation while having no actual effect on coagulation. In addition to PT/INR, telavancin is known to affect aPTT, activated clotting time, and coagulation-based factor Xa tests [1, 2]. All other coagulation tests reportedly are unaffected [1].

The manufacturer recommends drawing blood samples as close as possible before a patient's next daily dose (ie, trough) to minimize any effects of telavancin on PT/INR testing [1, 2]. This effect was observed unknowingly in our patient and at the time was attributed to parenteral administration of vitamin K, when in reality the blood sample had simply been drawn before the daily administration of telavancin while all other draws were performed shortly after the daily administration of telavancin (ie, peak). Retrospectively, we were able to show a linear correlation ($r^2 = 0.846$) between the time from telavancin administration to the PT/INR draw (Fig. 1). Therefore, drawing blood samples as close as possible before a patient's next daily dose of telavancin will minimize the effect, regardless of reagent, on PT/INR testing [1, 2, 12–14].

In vitro testing by our laboratory confirmed telavancin interacted with the Innovin® reagent. At a plasma concentration of 30 µg/mL, the measured PT/INR already was greater than 1.50 when using the Innovin® reagent. The use of the RecombiPlasTin 2G® reagent (diaPharma,

Fig. 2 The relationship of increasing telavancin levels on measured INR with two different INR reagents, Innovin® and RecombiPlasTin 2G®. When the Innovin® reagent is used, the INR falsely increases dramatically. Measurement with RecombiPlasTin 2G® is not affected.

West Chester, OH, USA) at any given plasma concentration of telavancin resulted in the correct PT/INR measurement (Fig. 2). Gosselin et al. [5] recently described a dose-dependent effect of telavancin on Innovin® and RecombiPlasTin 2G® reagents. However, the effect of telavancin on the Innovin® reagent is at least an order of magnitude greater than that on the RecombiPlasTin 2G® reagent [5]. This observation supports our finding that the effect of telavancin on the Innovin® reagent has a clinically relevant change in the PT/INR measurement. Additionally, we did not observe an elevation of aPTT in our patient.

As MRSA and other bacteria continue to become more resistant, telavancin use will continue to increase and orthopaedic surgeons will be faced with the same presurgical issues encountered by our patient. It is essential all physicians become aware of the effect of telavancin on the reagents used to test PT/INR and aPTT. It is recommended the appropriate hospital-based measures are taken to ensure PT/INR testing in patients receiving telavancin avoid artificial phospholipid reagents and ensure blood sampling before telavancin administration.

References

1. Astellas Pharma US Inc. *Telavancin Package Insert*. Deerfield, IL: Astellas Pharma US, Inc; 2009.
2. Barriere SL, Goldberg MR, Janc JW, Higgins DL, Macy PA, Adcock DM. Effects of telavancin on coagulation test results. *Int J Clin Pract*. 2011;65:784–789.
3. Corey GR, Stryjewski ME, Weyenberg W, Yasothan U, Kirkpatrick P. Telavancin. *Nat Rev Drug Discov*. 2009;8:929–930.
4. Damodaran SE, Madham S. Telavancin: a novel lipoglycopeptide antibiotic. *J Pharmacol Pharmacother*. 2011;2:135–137.
5. Gosselin R, Dager W, Roberts A, Freeman L, Gandy L, Gregg J, Dwyre D. Effect of telavancin (Vibativ) on routine coagulation test results. *Am J Clin Pathol*. 2011;136:848–854.

6. Higgins DL, Chang R, Debabov DV, Leung J, Wu T, Krause KM, Sandvik E, Hubbard JM, Kaniga K, Schmidt DE Jr, Gao Q, Cass RT, Karr DE, Benton BM, Humphrey PP. Telavancin, a multi-functional lipoglycopeptide, disrupts both cell wall synthesis and cell membrane integrity in methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2005;49:1127–1134.
7. Hughes B. 2009 FDA drug approvals. *Nat Rev Drug Discov*. 2010;9:89–92.
8. Kim DH, Spencer M, Davidson SM, Li L, Shaw JD, Gulczynski D, Hunter DJ, Martha JF, Miley GB, Parazin SJ, Dejoie P, Richmond JC. Institutional prescreening for detection and eradication of methicillin-resistant *Staphylococcus aureus* in patients undergoing elective orthopaedic surgery. *J Bone Joint Surg Am*. 2010;92:1820–1826.
9. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, Kaplan SL, Karchmer AW, Levine DP, Murray BE, Rybak MJ, Talan DA, Chambers HF. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis*. 2011;52:e18–e55.
10. Lunde CS, Hartouni SR, Janc JW, Mammen M, Humphrey PP, Benton BM. Telavancin disrupts the functional integrity of the bacterial membrane through targeted interaction with the cell wall precursor lipid II. *Antimicrob Agents Chemother*. 2009;53:3375–3383.
11. Nixon M, Jackson B, Varghese P, Jenkins D, Taylor G. Methicillin-resistant *Staphylococcus aureus* on orthopaedic wards: incidence, spread, mortality, cost and control. *J Bone Joint Surg Br*. 2006;88:812–817.
12. Shaw JP, Cheong J, Goldberg MR, Kitt MM. Mass balance and pharmacokinetics of [¹⁴C]telavancin following intravenous administration to healthy male volunteers. *Antimicrob Agents Chemother*. 2010;54:3365–3371.
13. Shaw JP, Seroogy J, Kaniga K, Higgins DL, Kitt M, Barriere S. Pharmacokinetics, serum inhibitory and bactericidal activity, and safety of telavancin in healthy subjects. *Antimicrob Agents Chemother*. 2005;49:195–201.
14. Wong SL, Barriere SL, Kitt MM, Goldberg MR. Multiple-dose pharmacokinetics of intravenous telavancin in healthy male and female subjects. *J Antimicrob Chemother*. 2008;62:780–783.