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Case Report

Infusion-Related Reaction Following Daptomycin Two-Minute Rapid Intravenous Administration

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Abstract

Background: Erythroderma, or red man's syndrome, is a common infusion-related reaction following vancomycin administration. Erythroderma following daptomycin rapid infusion has not been documented.

Objective: To report a case of erythroderma following daptomycin 2-minute intravenous (IV) injection.

Case Report: A review of published literature suggests that this is the first published case of a flushing (nonallergic) reaction resulting from a 2-minute IV injection of daptomycin that is not present with standard IV infusion. A 69-year-old woman following right knee reconstructive surgery presented with right knee joint swelling, purulent discharge, and fever. Subsequently, she was diagnosed with a presumed postsurgical infection and was initiated on vancomycin therapy. Following removal of the infected hardware, the patient was discharged and continued outpatient vancomycin therapy. The patient's renal function began to decline and therapy was discontinued. Daptomycin 6 mg/kg every 48 hours was initiated via 2-minute IV push. On the initial dose, approximately 2 hours post IV infusion, the patient began to notice redness and a warm sensation on her face, neck, and upper part of the chest. Diphenhydramine 25 mg provided limited immediate relief, but all symptoms subsided within 3 to 4 hours. The patient received her next dose 48 hours later over a 40-minute IV infusion with no adverse effects. Subsequent infusions continued at the same dose over 30 minutes for 4 weeks with no further adverse effects.

Conclusion: A 2-minute intravenous injection of daptomycin in this patient yielded a reaction that was not present on rechallenge with standard, extended infusion.

Key Words—daptomycin, erythroderma, rapid infusion, red man's syndrome, *Staphylococcus aureus*

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Daptomycin is a bactericidal lipopeptide antibiotic commonly used for drug-resistant gram-positive pathogens.[1] Daptomycin was originally approved by the US Food and Drug Administration (FDA) in September 2003 as a once-daily 30-minute intravenous (IV) infusion. In November 2010, the FDA approved a 2-minute rapid IV injection based on data from 2 consecutive pharmacokinetic and safety evaluation studies.[2,3] Daptomycin pharmacokinetic parameters were comparable with the 2-minute IV administration group when compared to the 30-minute IV infusion at a dose of 6

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mg/kg.[4] Although rapid infusions offer convenience and potential cost-savings opportunities, there is potential increased risk of infusion-related adverse events. Infusion-related events may include local reactions, such as phlebitis, pain, tenderness, or local erythema, and systemic reactions manifesting as either dermatologic and cardiovascular complications or anaphylaxis. These reactions have been documented with several antimicrobial infusions including ciprofloxacin, amphotericin B, vancomycin, and others agents that stimulate histamine release.[5] Vancomycin has been classically associated with infusion-related erythroderma or red man's syndrome. Signs and symptoms of a reaction will often initiate within 1 hour from the start of the infusion.[5,6] For this reason, the preferred infusion rate for vancomycin is no more than 10 mg/min.[7] In reports to date, local infusion site–related reactions following 2-minute rapid infusion of daptomycin were mild and of short duration, with no systemic flushing reported in the peer-reviewed literature. We report a case of an infusion-related reaction with significant flushing secondary to daptomycin following 2-minute IV push that was absent on rechallenge with an extended infusion.

PATIENT CASE

A 69-year-old woman (110 kg [242.5 lbs]) presented with fever, pain, and localized swelling 6 weeks following surgery to repair a torn patellar ligament in the right knee. The patient had a significant history of knee osteoarthritis requiring a right total knee replacement 14 months prior to presentation and type II diabetes mellitus. She had documented allergies to topical neomycin/bacitracin/polymyxin, nonsteroidal anti-inflammatory agents, iodinated radiocontrast die, and latex. Wound site cultures were obtained and resulted in mixed skin flora that was thought as likely commensal organisms. She was treated with IV vancomycin for 8 weeks with retained hardware, with no substantial clinical improvement. Subsequently, she underwent removal of all hardware and an antibiotic cement spacer was placed as part of a 2-stage knee surgery. Operative tissue Gram stain, bacterial, fungal, and acid-fast bacilli cultures were negative. Infectious diseases was consulted; considering the high likelihood of *Staphylococcus aureus* infection, vancomycin 750 mg IV daily was initiated to target 12 weeks of therapy. The patient was discharged to complete home parenteral therapy. Following 8 weeks of outpatient parenteral therapy, the patient's renal function began to deteriorate to a creatinine clearance of 25 mL/minute (baseline, 70 mL/min). As a result, vancomycin was discontinued and the patient was started on daptomycin 650 mg (6 mg/kg) IV 2-minute push every 48 hours for an additional 4 weeks. She received the first dose of daptomycin 2-minute IV push in the outpatient clinic. No adverse effects were noted 1 hour post infusion and the patient was released. Within 1 hour of leaving the clinic, the patient began to notice redness and a warm sensation on her face, neck, and upper part of the chest. She denied itching, lip swelling, cough, palpitations, shortness of breath beyond baseline, sweating, choking, or a skin rash. She denied use of other medications or ingestion of food during this time. The patient was advised to visit the emergency room but refused, and she self-treated with a single dose of over-the-counter oral diphenhydramine 25 mg. She did not experience immediate relief, although symptoms resolved over the next 3 to 4 hours. The following day, the patient returned to the clinic and received daptomycin 650 mg over a 40-minute infusion in a 50 mL dilution. A 40-minute infusion was unintentional and was adjusted to a standard 30-minute infusion for the remainder of the course. The patient continued on daptomycin 650 mg IV daily via 30-minute infusion every 48 hours to complete 4 weeks of therapy with no further adverse effects noted.

CASE DISCUSSION

Our case describes infusion-related erythema that occurred after the rapid 2-minute infusion of daptomycin in a daptomycin-naïve patient. Given the temporal relationship to the rapid infusion and the lack of recurrence upon rechallenge with the extended infusion time, this reaction is considered probable according to the Naranjo adverse reaction causality algorithm.[8] A current review of the literature did not reveal any published cases of daptomycin infusion–related erythroderma or red man's syndrome.

In a single-dose crossover study, the 2-minute daptomycin infusion was well tolerated, with 1 of 16 subjects (6%) experiencing mild tenderness at the infusion site compared to 3 of 15 subjects (20%) receiving the 30-minute infusion.[4] In a second multidose study, subjects received single doses at 6 mg/kg (n = 12) or 4 mg/kg (n = 8) for 7 consecutive days. Seven subjects (35%) experienced mild local-site injection reactions during the study period, all of which resolved within 1 hour.[4] The documented reactions do not suggest an erythroderma or significant systemic reaction.

More commonly known as red man's syndrome, erythroderma is estimated to affect approximately 1 in 100,000 people.[9] Erythroderma is caused by the direct degranulation of basophils and mast cells causing a release of histamine.[5] Erythroderma that is caused by hypersensitivity to medications, such as vancomycin, is most commonly associated with rapid IV infusion and typically manifests within 1 hour post infusion.[5,6] The delayed onset of symptoms in this case is important to note; it occurred approximately 2 hours post infusion. This patient did not experience immediate relief secondary to antihistamine therapy (diphenhydramine 25 mg), which possibly suggests an alternative mechanism. Similar to the symptoms of erythroderma seen secondary to vancomycin rapid infusion, the patient in the case developed areas of redness on the traditional areas of face, neck, and upper torso accompanied by a hot sensation. Although the significance is unknown, the reaction did occur on the first exposure to daptomycin for the patient.

CONCLUSION

This case highlights the potential for a daptomycin-associated erythroderma-like reaction secondary to the rapid 2-minute infusion. Symptoms resolved within 4 hours of onset without sequelae or further recurrence upon rechallenge with the 30-minute infusion. Clinicians should be aware of the potential for this infusion-related reaction, although, based on published literature, this appears to be an infrequent or relatively inconsequential occurrence. This case report should not preclude use of the 2-minute infusion due to its convenience and cost-saving potential.

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