Cutaneous Hyperpigmentation Secondary to High-Dose Tigecycline: A Case Report

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***Abstract*:** High-dose tigecycline therapy is gaining wide acceptance in treating infections caused by multidrug-resistant bacteria. There are no reports of cutaneous hyperpigmentation with the use of high-dose tigecycline. Here we report a case of a woman who developed reversible cutaneous hyperpigmentation within 48 h of receiving high-dose tigecycline.

Keywords: adverse effect, high dose, hyperpigmentation, tigecycline

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Introduction

Tigecycline is a broad-spectrum antibiotic derived from minocycline and specifically developed to overcome mechanisms of bacterial resistance.[1] *In vitro*, tigecycline exerts antibacterial activity against multidrug-resistant Gram-positive and Gram-negative bacteria, including methicillin-resistant staphylococci, vancomycin-resistant enterococci, and extended-spectrum β-lactamase-producing Enterobacteriaceae. Clinically, tigecycline demonstrated efficacy similar to that of comparator antibiotics in treating various bacterial infections.[2] The US Food and Drug Administration (FDA) and the European Medicines Agency have approved tigecycline for the treatment of complicated intra-abdominal infections and skin and soft-tissue infections at a dose of 50 mg every 12 h following a loading dose of 100 mg.[2]

In 2010, the US FDA issued a box warning for tigecycline use after a pooled analysis of 13 trials for approved and unapproved indications demonstrated a relative mortality increase of 33%.[3] The highest incidence of mortality was observed in patients treated for ventilator-associated pneumonia (VAP).[3] Inadequate concentrations of tigecycline in pulmonary alveolar cells were postulated as an explanation for the increased mortality in patients with VAP treated with the standard dose of tigecycline.[4] Therefore, tigecycline was reintroduced to clinical practice at higher doses to boost its tissue concentration. A recent meta-analysis has supported this approach by demonstrating lower mortality with the high-dose regimen compared with the conventional dose.[5] Tigecycline extensively distributes into soft tissues, with a viable skin tissue concentration 3.9 times its serum level.[6] Despite this pharmacokinetic feature of tigecycline, cutaneous side-effects were uncommon, and typically appeared in the form of a rash and pruritus at rates of less than 4%, as reported by phase III trials.[3]

Here, we report a case of a woman who developed cutaneous hyperpigmentation within 48 h of receiving high-dose tigecycline (100 mg every 12 h).

Case report

A 59-year-old woman underwent an elective pancreaticoduodenectomy for a duodenal neuroendocrine tumor. A computed tomography scan, performed on day 10 postoperatively, revealed intra-abdominal collections suggestive of a pancreaticojejunal leak. Owing to her positive history of penicillin allergy, described as shortness of breath and generalized skin rash, the patient was started on tigecycline 100 mg as a loading dose followed by 50 mg every 12 h in combination with aztreonam and anidulafungin. On day 36 postoperatively, while on the same antimicrobials, the

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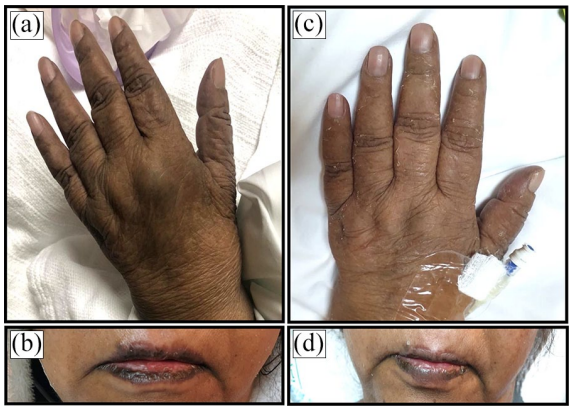

Figure 1. (a) and (b) Patient 48 h after receiving high-dose tigecycline, (c) and (d) Patient 10 days after reverting to the conventional dose of tigecycline.

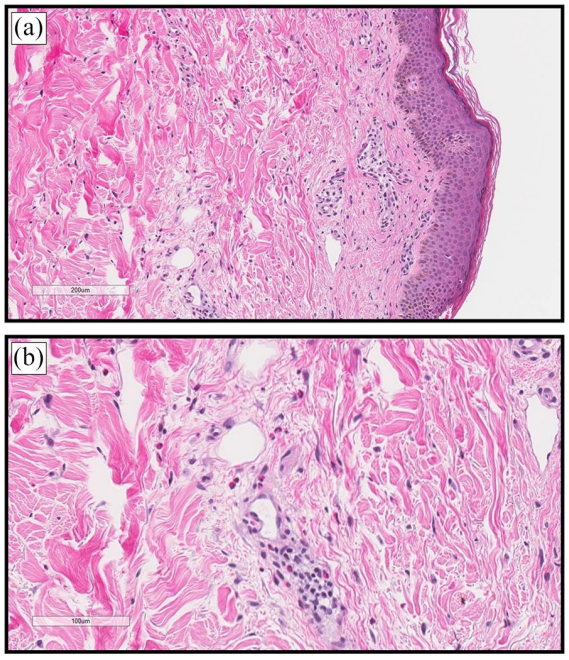

Figure 2. Skin section obtained from a skin punch biopsy from the right thigh of the patient 20 days after tigecycline dose reduction. (Hematoxylin and eosin, (a) original magnification ×100, (b) original magnification ×200.)

patient developed severe hypotension mandating surgical exploration for source control. Cultures obtained intraoperatively revealed *Stenotrophomonas maltophilia* resistant to ceftazidime, levofloxacin, and sulfamethoxazole/trimethoprim, but sensitive to colistin. Fungal cultures were positive for *Candida parapsilosis*. Antimicrobials were accordingly changed to colistin plus tigecycline, in addition to fluconazole as an antifungal. Two days after changing the antimicrobials, the patient developed an acute kidney injury with a nadir estimated glomerular filtration rate (e-GFR) of 34 ml/min/1.72 m^2. The colistin and fluconazole doses were adjusted according to the e-GFR, whereas the tigecycline dose was increased to 100 mg every 12 h. Kidney function improved slowly after 5 days of vigorous hydration with intravenous crystalloid solution and the e-GFR increased to 44 ml/min/1.72 m^2. After 48 h of increasing tigecycline dose, the patient developed generalized diffuse cutaneous hyperpigmentation, most notably on the lips, hands, thighs, neck, and anterior trunk (Figure 1(a) and (b)). Physical examination revealed extensive darkening of the skin, with no scales, hair loss, or blisters. The patient reported pruritus over the affected areas of her body. On counseling the patient, she denied using any recent topical formulations and stated that she had never experienced such a skin reaction previously. A tigecycline-induced cutaneous adverse effect was suspected, therefore, the high-dose therapy was reverted to the conventional dose. The skin color and pruritus gradually improved over the subsequent 10 days following tigecycline dose reduction. There were noted areas of desquamation involving both hands, but absent in the remaining affected areas. Medications received concomitantly with the high-dose tigecycline included acetaminophen, omeprazole, octreotide, metoclopramide, amlodipine, enoxaparin, colistin, and fluconazole. None of these medications were stopped in the 7 days following the onset of skin discoloration. A skin punch biopsy was obtained from the right thigh of the patient 20 days after tigecycline dose reduction. It revealed a spongiotic epidermis and a dermal perivascular mononuclear infiltrate and scattered eosinophils. Increased basal keratinocyte pigmentation was observed. No histological features suggestive of ischemia were observed (Figure 2). These findings are histologically consistent with drug-related skin changes. The patient continued the conventional dose of tigecycline for 24 days, with gradual convalescence in skin discoloration (Figure 1(c) and (d)).

Discussion

In this report, we describe the occurrence of a reversible cutaneous hyperpigmentation following the use of high-dose tigecycline therapy.

Cutaneous adverse reactions have been reported with minocycline, the parent compound of tigecycline.[7,8] Minocycline-induced skin hyperpigmentation occurs in a dose-dependent fashion, at an incidence exceeding 14%.[8] Although the mechanism of developing skin hyperpigmentation with minocycline has not been completely delineated, it is postulated to occur secondary to the accumulation of black-colored degradation products of minocycline in body tissues.[9] It is unknown if tigecycline metabolism produces similar metabolites to explain the skin discoloration observed in our patient.

Vandecasteele *et al.* described skin hyperpigmentation of the upper trunk and arms in a woman with osteomyelitis treated for 102 days with a conventional dose of tigecycline.[10] A skin biopsy revealed melanin-containing macrophages. Although the authors reported the cessation of tigecycline therapy after the appearance of skin hyperpigmentation, no information was given regarding the prognosis of this side effect. To our knowledge, that was the only report of cutaneous hyperpigmentation attributed solely to tigecycline therapy.[10]

In comparison, our patient developed cutaneous hyperpigmentation as early as 48 h of high-dose tigecycline therapy. This rapid skin discoloration could be attributed to increased tigecycline levels in the skin secondary to the use of a high dose during an episode of acute kidney injury. Although there is no recommendation for dose adjustment of tigecycline in patients with renal impairment, 15% of the tigecycline dose is known to be excreted unchanged in the urine.[3,11] The gradual abatement of skin hyperpigmentation following the reduction in tigecycline dose and the improvement in renal function further support our presumption of a tigecycline-related cutaneous reaction. Other concomitant medications such as omeprazole and colistin have been reported to induce skin discolorations.[12,13] However, their continuation during the evident improvement in skin color lessens their likelihood of involvement in the observed hyperpigmentation. An unreported drug–drug interaction developing at high levels of tigecycline could be another explanation of the cutaneous discoloration in our patient. It is unknown whether skin hyperpigmentation is linked to more serious complications of tigecycline therapy; however, their unsightly nature may be a source of patient discomfort.

With the expanding use of high-dose tigecycline therapy, clinicians need to be vigilant regarding this cutaneous adverse effect that may affect patients' acceptance of the therapy. An objective causality assessment, using the Naranjo Adverse Reaction Probability Scale, indicated a 'probable' relationship between the development of skin hyperpigmentation and the high-dose tigecycline therapy.[14]

Conflict of interest statement

The authors declare that there is no conflict of interest.

Ethics statement

Written informed consent was obtained from the patient, with documentation in the patient's chart, to publish this case with the accompanying images.

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