

Case Report

High-dose tigecycline-induced cutaneous hyperpigmentation

Souvik Majumder¹, Agnimitra Bhattacharya²

¹Department of Pharmacology, Medical College, Kolkata, ²Department of Internal Medicine, Nehru Memorial Techno Global Hospital, Barrackpore, West Bengal, India

*Corresponding author:

Souvik Majumder,
Department of Pharmacology,
Medical College, Kolkata, West
Bengal, India.

souvik.majumder@ymail.com

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ABSTRACT

Urinary tract infection (UTI) is a common infectious ailment with significant mortality, morbidity and overall financial burden. This case report describes an elderly diabetic lady with chronic kidney disease and other multiple comorbidities who during the hospital stay, develops a nosocomial UTI with multidrug-resistant (MDR) *Enterococcus faecium* (vancomycin-resistant *Enterococcus*), intermediately sensitive to daptomycin and tigecycline. Accordingly, tigecycline 100 mg intravenous (iv) twice daily and daptomycin 350 mg iv every alternate day was initiated. 3 days after initiation, a diffuse darkening of skin and generalised blackish pigmentation was noted. The patient showed clinical improvement with respect to the UTI; hence, the ongoing treatment was continued till the improvement of procalcitonin levels, irrespective of the observed adverse drug reaction (ADR), which was deemed to be non-serious. Post stoppage of tigecycline, the patient showed betterment of skin tone by 1 month without any medical intervention. Concerning temporal relationship and causality assessment, diffuse skin hyperpigmentation is thus a probable ADR of tigecycline. Existing literature does not document much about skin hyperpigmentation as ADR of tigecycline. With the increasing incidence of infections by MDR organisms and the greater use of the rReserved category of antibiotics, high-dose tigecycline is thought to become increasingly popular in the days to come due to its wide antimicrobial spectrum. However, cutaneous hyperpigmentation is a probable complication of such a therapy, especially in the presence of other contributing factors. Knowledge of this ADR and its further case reporting may pave the way to better patient outcome communications, lesser psychological burdens and minimising litigations.

Keywords: Adverse drug reaction, Cutaneous hyperpigmentation, *Enterococcus*, Tigecycline, Urinary tract infection

INTRODUCTION

Urinary tract infections (UTIs) are amongst the most common infectious diseases affecting people across age and gender. The rate of infection, mortality and morbidity of UTI is increasing with the greater use of antibiotics for various infections in hospital settings. The financial burden of UTI-associated hospitalisations and prolongation of hospital stays is substantial. Nosocomial UTIs are a common complication in healthcare systems worldwide. A UTI is defined as nosocomial when it is acquired in any healthcare institution or more generally when it is related to patient management. Particularly, high-risk groups include patients with indwelling urinary catheters, recurrent hospitalisation and those undergoing urological procedures amongst others. The most frequently isolated micro-organisms in patients with nosocomial UTIs are *Escherichia coli*, *Candida* spp., *Klebsiella* spp. and *Enterococcus* spp. Nosocomial pathogens causing UTIs tend to have a higher antibiotic resistance than community-acquired UTIs.^[1]

Enterococci are Gram-positive, facultatively anaerobic commensal organisms of the gastrointestinal tract. Multidrug-resistant (MDR) Enterococci spp. has become a leading

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cause of healthcare-associated infections, ranging from endocarditis to UTIs. Resistance to beta-lactams is almost universal amongst strains of *Enterococcus faecium* and there is frequent concomitant resistance to aminoglycosides and vancomycin. Vancomycin, daptomycin, linezolid, fosfomycin and tigecycline remain viable treatment strategies, depending on the sensitivity pattern.^[2]

Tigecycline – a glycylcycline is a tetracycline congener that inhibits bacterial protein synthesis by binding to the 30S bacterial ribosome and preventing access of aminoacyl tRNA (Ribonucleic acid) to the acceptor (A) site on the mRNA-ribosome complex. Tigecycline displays excellent activity against Enterococci, *Enterobacteriaceae*, *Acinetobacter* and *Bacteroides fragilis*. Tigecycline distributes rapidly and extensively into tissues, with an estimated wide apparent volume of distribution of 7–10 L/kg and a viable skin tissue concentration 3.9 times its serum level. Despite this pharmacokinetic feature of tigecycline, cutaneous adverse effects were uncommon and typically appeared in the form of rash and pruritus at rates of <4%. The main adverse effects of tigecycline include gastrointestinal (GI) disturbances such as nausea and vomiting, hepatotoxicity and irreversible brownish discolouration of teeth and may very rarely cause pseudotumor cerebri, stunted growth and various skin reactions.^[3]

Here, we report a clinical case of a woman who developed diffuse generalised cutaneous hyperpigmentation within 3 days of receiving high-dose tigecycline.

CASE REPORT

A 67-year-old Indian lady with hypertension, hypothyroidism controlled with levothyroxine (75 mcg once daily), oliguric chronic kidney disease – V (estimated Glomerular Filtration Rate [eGFR]- 14 mL/min/1.73 m²) on maintenance haemodialysis (HD), chronic coronary syndrome with history of recurrent recent hospitalisation with heart failure with reduced ejection fraction (HFrEF) (left ventricular ejection fraction [LVEF]- 35%) and status post-primary coronary intervention to left anterior descending artery was admitted with complains of gradually worsening shortness of breath, even at rest for a few days without any associated fever or chest pain.

Initial examination revealed sinus tachycardia with a heart rate of 126/min, blood pressure of 186/112 mmHg, oxygen saturation (SpO₂) of 78% in room air, bilateral pitting pedal oedema and profuse inspiratory crackles on chest auscultation and jugular venous engorgement. A point-of-care ultrasound revealed profuse B lines in bilateral lung fields with bilateral pleural effusion and compromised cardiac contractility with dilated inferior vena cava with no respiratory variation. Chest X-ray showed diffuse pulmonary

oedema with obliteration of bilateral costophrenic angles. The patient was provisionally diagnosed as HFrEF and put on non-invasive positive pressure ventilation with supplemental oxygen to maintain SpO₂ >90%; intravenous (iv) furosemide infusion was started at 4 mg/h after a bolus of 40 mg and glyceryl trinitrate was initiated intravenously at 10 mcg/min. Urgent HD with an ultrafiltrate of 3 L was started and empirical antibiotics in the form of piperacillin-tazobactam and doxycycline were initiated after collecting relevant cultures. Initial blood investigations revealed polymorphic leucocytosis with a marginally elevated C-reactive protein with normal procalcitonin, azotaemia and normal electrolytes. The patient showed clinical improvement with treatment and was gradually weaned of supplemental oxygen.

However, on the 5th day of hospitalisation, she turned febrile with a T_{max} of 102.3°F. All invasive lines were changed; however, she remained persistently febrile - high grade, remission with paracetamol and no diurnal variation and haemodynamically stable. Blood and urine samples were sent for culture and sensitivity, and routine blood examinations were done which revealed worsened infective parameters (total leucocyte count – 19,400/cu mm with neutrophilic predominance, procalcitonin levels of 4 ng/mL). Antibiotics were empirically escalated to meropenem (M) and teicoplanin (T) and dose adjusted according to eGFR; however, the patient remained febrile. Urine cultures received on the 8th day of hospitalisation revealed growth of *E. faecium* (>10⁵ cfu/mL), sensitive to only daptomycin and intermediately sensitive to tigecycline.

Tigecycline (Ti) 100 mg intravenously twice daily (high-dose tigecycline given the intermediate drug sensitivity) and daptomycin (D) 350 mg intravenously every alternate day (after HD) were started. The patient showed clinical and haematological improvement and she was afebrile from the 11th day onwards [Table 1]. However, she developed a generalised diffuse skin hyperpigmentation from around the same time, mainly over the face, lips, neck and anterior trunk. This was not associated with pruritus, hair loss, scales, any aggravating or relieving factors, raised lesions or any pain/discharge [Figure 1]. There was no history of application of any topical formulation and there were no such events in her past.

Tigecycline and daptomycin were the only two new drugs that were introduced, hence providing a temporal association with the adverse effect. However, since the patient showed clinical improvement and due to the unanimously decided non-serious nature of the adverse effect, a continuation of the above two drugs was decided in the best interest of the patient. Her other concomitant medications are enumerated in Table 2. On the 15th day of hospitalisation, tigecycline was discontinued after a normal procalcitonin level was obtained. The patient was discharged in a haemodynamically stable state on the 18th day of hospitalisation with advice to continue daptomycin intravenously for a total of 14 doses.

Table 1: Table showing in-hospital total blood count, procalcitonin levels and corresponding antibiotic.

Item	Day 1	Day 4	Day 5	Day 7	Day 9	Day 12	Day 15	Day 18
TLC (cells/cu mm)	12300	11400	19400	20300	17600	14000	6900	7200
Procalcitonin (ng/mL)	0.05	--	4.00	--	2.6	0.2	--	0.05
Antibiotics	Pip-taz+doxy	Pip-taz+doxy	M+T	M+T	Ti+D	Ti+D (ADR started)	Ti+D	D

Pip-taz: Piperacillin-tazobactam, Doxy: Doxycycline, M: Meropenem, T: Teicoplanin, Ti: Tigecycline, D: Daptomycin, ADR: Adverse drug reaction, TLC: Total leucocyte count

Table 2: Summary of medications along with their indication

Sr No	Name	Dose	Route	Frequency	Started on	Stopped on	Indication
1	Daptomycin	350 mg	iv	q48hr	Day 8	Day 33	UTI-VRE
2	Tigecycline	100 mg	iv	q12hr	Day 8	Day 15	UTI-VRE
3	Aspirin	75 mg	oral	q24hr	2016	cont'd	CCS
4	Atorvastatin	20 mg	oral	q24hr	2016	cont'd	CCS
5	Pantoprazole	40 mg	iv	q24hr	Day 1	Day 16	Ulcer prophylaxis
6	Pantoprazole	41 mg	oral	q24hr	Day 17	cont'd	Ulcer prophylaxis
7	Ondansetron	8 mg	iv	q8hr	Day 1	Day 18	Nausea
8	Bisoprolol	5 mg	oral	q24hr	2016	cont'd	CCS
9	Clonidine	100 mcg	oral	q8hr	2020	cont'd	hypertension
10	Prazosin (Extended Release)	5 mg	oral	q24hr	2021	cont'd	hypertension
11	Furosemide	40 mg	oral	q12hr	2021	cont'd	CKD
12	Metolazone	5mg	oral	q24hr	Jan-23	cont'd	CKD
13	Lactulose	15 ml	oral	q24hr	2020	cont'd	stool softener
14	Unfractionated Heparin	5000 IU	s.c	q12hr	Day 1	Day 17	thrombo-prophylaxis
15	Erythropoietin	10000 IU	s.c	q72hr	Jan-23	cont'd	Anemia
16	Formoterol	20 mcg	nebs	q12hr	Day 1	Day 17	Dyspnea
17	Budesonide	0.5 mg	nebs	q12hr	Day 2	Day 18	Dyspnea
18	Furosemide	4 mg/hr	iv	infusion	Day 1	Day 2	Pulmonary edema
19	Glyceryl trinitrate	10 mcg/min	iv	infusion	Day 1	Day 2	Hypertensive emergency
20	Piperacillin-tazobactam	2.25 gm	iv	q8hr	Day 1	Day 4	suspected pneumonia
21	Doxycycline	100 mg	iv	q12hr	Day 1	Day 4	suspected pneumonia
22	Meropenem	500 mg	iv	q8hr	Day 5	Day 7	non-resolving sepsis
23	Teicoplanin	400 mg	iv	q12hr	Day 5	Day 6	non-resolving sepsis
24	Teicoplanin	200 mg	iv	q24hr	Day 7	Day 7	non-resolving sepsis
25	Oral iron	500 mg	oral	q24hr	2021	cont'd	Anemia

Table 3: Causality assessment by WHO-UMC criteria.

WHO-UMC causality criteria: Probable				
Temporal relationship	Explained by other drugs/disease condition	Dechallenge	Rechallenge	Causal relationship
Yes	No	Yes*	No	Related

*Though conventional dechallenge was not done, the skin tone showed betterment after stopping the drug as per schedule, WHO-UMC: World Health Organisation - Uppsala Monitoring Centre

On her scheduled revisit a month later, a gradual, generalised lightening of skin hyperpigmentation was observed [Figure 2]. The patient was doing well during this period

and her repeat urine cultures were sterile. Figure 3 depicts an even greater reduction in hyperpigmentation after 6 months though the baseline was not reached. Owing to the temporal



Figure 1: Cutaneous hyperpigmentation observed over face, lips and neck 3 days after initiation of high-dose tigecycline.

association of symptoms and their waning off after stoppage, tigecycline is concluded to be the probable cause of this adverse drug reaction (ADR) [Tables 3 and 4].

DISCUSSION

In this case report, we describe the occurrence of cutaneous hyperpigmentation due to high-dose tigecycline. Minocycline, the parent compound of tigecycline is known to cause cutaneous adverse reactions in a dose-dependent manner at rates of 14%. This is postulated to be due to cutaneous deposition of black-coloured degradation products. Although it is unknown if tigecycline produces a similar effect by the same mechanism, literature documents very few such cutaneous hyperpigmentation as an ADR of tigecycline.^[4,5]

Vandecasteele *et al.* described skin hyperpigmentation of the upper trunk in a woman with osteomyelitis treated for 102 days with a conventional dose of tigecycline.^[4] A skin biopsy revealed melanin-containing macrophages; prognosis after stopping tigecycline was not reported.

Alsemari *et al.* reported a case of cutaneous hyperpigmentation with high-dose tigecycline 48 h after the onset of therapy. The patient had developed acute kidney injury during the treatment process which was treated aggressively with IV fluids and management of the underlying condition resulting in betterment of eGFR levels. The authors reported a betterment of skin tone about 10 days after dose reduction. Skin biopsy revealed a spongiotic epidermis, a dermal perivascular mononuclear infiltrate with scattered eosinophils and increased basal keratinocyte pigmentation consistent with drug-related skin changes.^[5]

Knueppel and Rahimian had reported cutaneous hyperpigmentation over the face, ears and upper trunk in two Hispanic men being treated with tigecycline and



Figure 2: Improvement of skin colour 1 month after stopping tigecycline.



Figure 3: Further betterment of skin colour 6 months after stopping tigecycline (though baseline has not been reached).

polymyxin B for bloodstream infection caused by MDR *Klebsiella pneumoniae*. The reactions occurred after a total

Table 4: Causality assessment by Naranjo's algorithm.

Naranjo's algorithm for causality assessment				
Questions	Yes	No	Unknown	Score
Previous conclusive reports on this reaction?	1	0	0	1
AE appeared after the suspected drug was administered?	2	-1	0	2
AE improved when the drug was discontinued or specific antagonist administered?	1	0	0	1
Did the AE reappear with rechallenge?	2	-1	0	0
Are there any alternative causes for the AE?	-1	2	0	0
Did the AE appear when placebo was given?	-1	1	0	0
Was the drug detected in blood at toxic levels?	1	0	0	0
Was severity of the AE dose-dependent?	1	0	0	1
Did the patient have a similar experience to the same or similar drug in any previous exposure?	1	0	0	0
Was the AE confirmed by any objective evidence?	1	0	0	0
Total				5
Interpretation of Naranjo Score				
>8	Highly probable			
5 to 8	Probable			
1 to 4	Possible			
<=0	Doubtful			

of 29 and 22 days of tigecycline therapy, respectively. The hyperpigmentation subsided gradually; however, skin tone was not completely reversed even after 5 months of stopping the drug.^[6]

Contrary to that reported by Vandecasteele *et al.*,^[4] our patient developed cutaneous hyperpigmentation within 3 days of onset of high-dose tigecycline. 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. This may explain the earlier onset of ADR in our patient of CKD-V. This may also explain the similarity with that reported by Alsemari *et al.*,^[5] where acute renal dysfunction had a temporal relationship with the cutaneous hyperpigmentation caused by high-dose tigecycline. Alsemari *et al.*, and Knuettel and Rahimian *et al* also reported a betterment of skin tone after dose reduction/stoppage and/or betterment of renal function.^[4-6]

In our case, due to the clinical improvement and the perceived non-serious nature of ADR by both patient and physician alike, a unanimous decision to continue high-dose tigecycline was confirmed. The gradual betterment of skin colouration following the stoppage of tigecycline supports our initial assumption that tigecycline, being the 9- (N, N-dimethylglycylamido) derivative of minocycline is probably the causative drug. Cutaneous deposition of breakdown products in the wake of prolonged dosing or under-excretion in renal dysfunction may be the pathophysiologic mechanism. However, non-attainment of baseline skin tone even after 6 months of stoppage may

be an indication that even after a complete washout of tigecycline and its degradational products, the cutaneous hyperpigmentation may not be completely reversible. Other concomitant medications like pantoprazole have been known to rarely cause cutaneous hyperpigmentation; however, their continuation during the evident improvement in skin colour lessens the likelihood of it being the offending drug. No significant drug interaction is noteworthy amongst the concomitant medications; however, any unreported drug-drug interaction occurring at high tigecycline concentrations cannot be entirely ruled out.

Limitations

Owing to the recurrent hospitalisation and chronic suffering of the patient, consent for a skin biopsy could not be obtained. Tigecycline therapeutic monitoring could not be done due to infrastructural limitations.

Adverse Drug Reaction (ADR) Reporting Identification Number (ID)

Worldwide Unique ID IN-IPC-300788232.

CONCLUSION

An objective causality assessment, using both the WHO-UMC scale and Naranjo's algorithm revealed a 'probable' relationship between the development of cutaneous

hyperpigmentation and high-dose tigecycline therapy. The newer extensive use of high-dose tigecycline therapy in view of growing antimicrobial resistance warrants its reporting for future references, better patient communications, minimising psychological trauma and reducing litigations.

Ethical approval: Institutional Review Board approval is not required.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent. However, the consent for skin biopsy could not be obtained.

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