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Hypofibrinogenemia caused by tigecycline use in a patient with acute cholecystitis: a case report and review of the literature

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ABSTRACT

Objectives: Tigecycline is the first member of glicylcycline class of antibiotics, which has a broad spectrum of action. In previous reports, coagulopathy and hypofibrinogenemia caused by tigecycline use was described. We aimed to present a case of hypofibrinogenemia in association with tigecycline use. A 79-years-old male was admitted to medical intensive care unit for acute cholecystitis and acute renal failure. He had no history of coagulation disorder. He was receiving meropenem for septic shock on the admission. On the 7th day of meropenem, his infection didn't improve and fever continued. Because of that tigecycline was added to treatment. Patient's infection parameters improved, his fever dropped under treatment, but his prothrombin time, international normalized ratio and activated partial thromboplastin time levels increased and fibrinogen level decreased (0.96 g/L). Tigecycline was discontinued that day. On the fifth day after cessation of tigecycline, his fibrinogen levels and other coagulation parameters returned to normal ranges. The mechanisms of coagulopathy and hypofibrinogenemia should be elucidated in futher studies. We strictly suggest, regular monitoring of coagulation parameters in patients receiving tigecycline treatment.

Keywords: Tigecycline, hypofibrinogenemia, adverse effect, coagulopathy, antibiotics

Tigecycline is the first member of glicylcycline class of antibiotics, which is structurally similar to tetracyclines. It has broad spectrum activity, particularly against multi-drug resistant bacteria (e.g Methicillin resistant *Staphylococcus aureus*, vancomycin resistant enterococcus, *Acinetobacter baumannii*) [1, 2]. It is indicated in patients who are 18 years or older for complicated intraabdominal infections, complicated skin and skin structure infections and community acquired pneumonia [3]. Tigecycline was well tolerated in registry trials, with the exception of increased rates of nausea and vomiting. But after post-marketing data signaling increased mortality rates in tigecycline treated patients have brought its use in patients with complicated infections into question, prompting other clinicians to consider other potential adverse effects which was not found in initial studies [4]. Some previous case reports showed that tigecycline seems to cause coagulation disorders, which manifested with bleeding or abnormalities in coagulation paremeters [1-5]. In this report we presented a case of hipofibrinogenemia in a patient treated with tigecycline.

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CASE PRESENTATION

A 79-year-old male who had a history of diabetes, hypertension, congestive heart failure and chronic obstructive pulmonary disease was admitted to medical intensive care unit with diagnosis of acute cholecystitis and acute renal failure from another healthcare facility. He had no history of coagulation disorder, and family history did not shown any bleeding condition. He had no underlying disorder or family history of hereditary coagulation disorder. He had been initiated on meropenem therapy for acute cholesistitis. He was on first day of meropenem and in septic shock on the admission day, and was taking noradrenaline. Blood and urine cultures were provided. Selected laboratory findings (and institutional normal ranges) were as follows: Serum creatinine level, 5.9 mg/dL (normal range 0.7-1.3 mg/dL); blood urea nitrogen 217 mg/dL (normal range 19-49 mg/dL); alanine aminotransferase (ALT), 340 U/L (normal range < 50 U/L); aspartate aminotransferase (AST), 309 U/L (normal range < 50 U/L); white blood cell count, 29.020 cells/mm^3 (normal range 3600-10500 cells/mm3); hemoglobin concentration, 15 g/dL (normal range 12.5-17.2 g/dL); platelet count 108×10^9 /L (normal range 160-400×10^9 /L); INR, 1.37 (normal range 0.8-1.2). Liver enzymes of patient, C-reactive protein (CRP) 0.155 g/L (0-0.005 g/L) and fibrinogen level 8.7 g/L (1.7-4.2 g/L) were high, INR was slightly elevated on the admission day. Peripheral blood smear on the admission showed leukocytosis with neutrophilia and platelet count was consistent with counter. On the 7th day of meropenem, patient's acute phase reactant levels increased, his fever continued and tigecycline was added to the treatment (tigecycline dose: 100mg q24 h loading dose, 50mg q12 h maintenance dose) The coagulation parameters were within the normal range before tigecycline treatment. On the 14th day of tigecycline, patient's infection improved with a dropped temperature (36.2^{o}C), white blood cell count (9.200 cells/mm3), platelet count 130×10^9 /L, and CRP (0.0259 g/L). Erythrocyte morphology was normal in the peripheral smear and platelet count was consistent with 150×10^9 /L.

Nevertheless, prolonged prothrombin time (PT), INR, and activated partial thromboplastin time (aPTT) were observed; furthermore, fibrinogen levels were obviously decreased (Table 1). Liver failure findings were not observed, and the abdominal ultrasound was normal. As the patient's clinical signs of infection recovery, peripheral smear or other laboratory tests did not support disseminated intravascular coagulation, at that point we did not consider low fibrinogen, aPTT and PT elongation associated with disseminated intravascular coagulation. On that day tigecycline treatment was discontinued, meropenem was continued. After cessation of tigecycline, on the fifth day fibrinogen level became within the normal ranges and other

Table1. Laboratory parameters of patient according to time course of antimicrobial therapy

	Fibrinogen (g/L)	aPTT (s)	PT (s)	INR	AST (U/L)	ALT (U/L)	Total bilirubin (mg/dL)	CRP (g/L)
ICU admission	8.7	32.6	16.7	1.4	184	143	2.2	0.155
Tigecycline started	4.16	23.3	14.6	1.2	55	9	1.8	0.0564
5th day of tigecycline	2.04	30.7	16.3	1.4	19	7	1.9	0.0815
14th day of tigecycline	0.96	38.9	18.5	1.6	28	16	1.9	0.0259
5th day after tigecycline cessation	2.91	24.2	14.7	1.2	37	28	1.7	0.0731
10th day after tigecycline cessation	3.18	24.6	12.9	1.1	52	79	0.9	0.060

aPTT = activated partial thromboplastin time, PT = prothrombin time, INR = international normalized ratio, AST = aspartate aminotransferase, ALT = alanin aminotransferase, CRP = C-reactive protein, ICU = intensive care unit

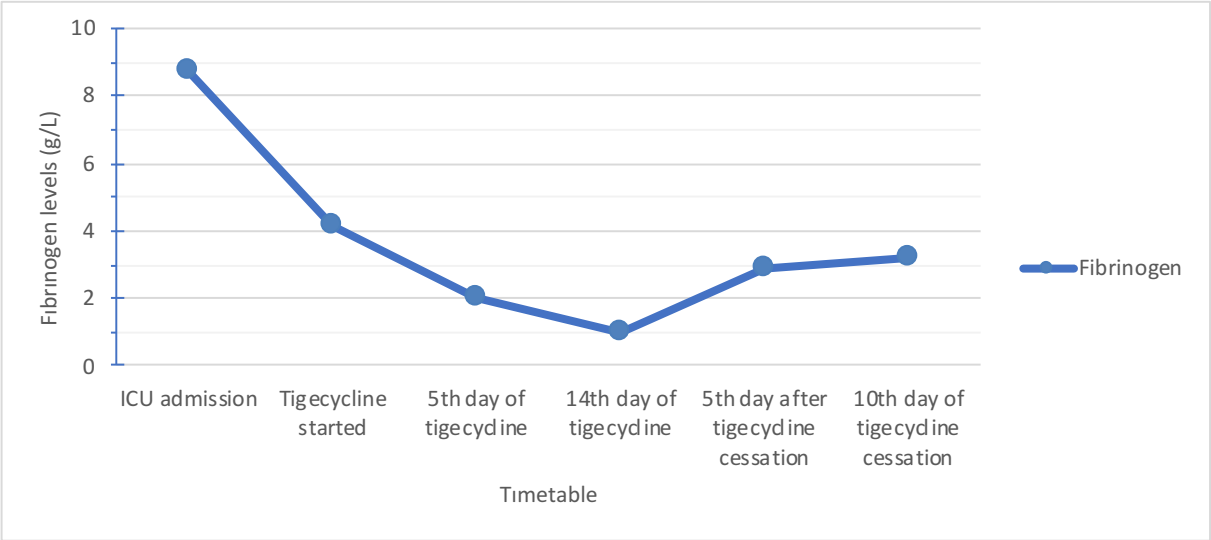

Fig. 1. Fibrinogen levels of patient according to time course of antimicrobial therapy

coagulation parameters became normal (Fig. 1). On the 67th day of ICU admission, patient was transferred to ward and after than discharged from ward.

DISCUSSION

Tigecycline is a broad spectrum antibiotic, which is generally used for infections due to multidrug-resistant (MDR) bacteria [2]. It requires intravenous administration with a loading dose of 100 mg followed by a maintenance dose 50 mg every 12 hours. No dose adjustment is needed in patients with renal impairment, but only in patients with severe hepatic disfunction (Child-Pugh class C), the dosage should be reduced to 25 mg every 12 hours [1, 3]. Adverse reactions, in terms of haematologic and lymphatic system, as increased partial tromboplastin time, increased PT, increased INR, eosinophilia, and trombocytopenia, might be observed during usage was stated in the instructions of tigecycline [4]. But hypofibrinogenemia was not referred and a new adverse reaction. Life threatening coagulopathy and hypofibrinogenemia cases, induced by tigecycline use, were reported in the literature, by Wu and Wu [1], Wu *et al*. [3], Routsi *et al*. [6], Sabanis *et al*. [7], Pieringer *et al*. [8], Rossito *et al*. [9], and Yılmaz Duran *et al*. [10] (Table 2).

A few clinical studies reported hypofibrinogenemia and other coagulation abnormalities caused by tigecycline use [5, 6]. Our patient received routine dose, but in the literature some cases, which developed hypofibrinogenemia had received off-label higher doses of tigecycline [3, 6]. The mechanism in which tigecycline induced coagulopathy and caused hypofibrinogenemia, is unknown. Fibrinogen is produced by hepatocytes. It could be converted to insoluble fibrin to form blood clots, when trauma or sepsis occurs [1]. Effects of vitamin K deficiency on gut flora and inflammation due to serious infections are also commonly cited mechanisms resulting in coagulopathy. However, vitamin K replacement is reported not to improve coagulopathy, which is caused by tigecycline use [2]. In our case, serious infection might be thought to cause hypofibrinogenemia, but patient's infection parameters improved when fibrinogen level started to decrease. Furthermore, effect of tigecycline on liver functions could implicate decreased levels of fibrinogen [7]. Therefore, the underlying mechanisms of coagulopathy and hypofibrinogenemia and risk factors for these adverse effects should be elucidated. Also we suggest, regular monitoring of coagulation parameters, including fibrinogen level in patients receiving tigecycline. If patients develop hypofibrinogenemia, discontinuation of drug should be considered.

CONCLUSION

We presented a patient who developed hypofibrinogenemia because of tigecycline use. The underlying mechanisms of coagulopathy and hypofibrinogenemia and risk factors for these adverse

Table 2. **Previous case reports and clinical studies about hypofibrinogenemia because of tigecycline use**

References	Country	Study Type	Sex	Age	Admission Diagnosis	Renal/Liver Disease	TGC dose	Time of hypofibrinogenemia	Prognosis (days after TGC cessation)
Pieringer et al. [8]	Austria	Case report	F	54	Peritonitis	CRD	NM	Day 5	Within 6 days
Rossito et al.[9]	Italy	Case report	F	43	Acute kidney injury	CRD+ Liver cirrhosis	100mg loading dose 25 mg twice daily	Day 5	Within 1 day
Sabanis et al.[7]	Greece	Case report	F	74	Prosthetic joint infection	CRD	100 mg loading dose, 50 mg twice daily	Day 5	Within 4 days
Routsi et al.[6]	Greece	Retrospective study	31 M 14 F	48 ± 20	20 severe sepsis 25 septic shock	NM	100mg loading dose 6 patients 75mg teice Daily 39 patients 100mg twice daily	Day 1	Within 10 days
Yılmaz Duran et al.[10]	Turkey	Case report	F	90	Pneumonia	CRD	NM	Day 10	Within 8 days
Wu X et al. [3]	China	Case report	M	47	Acute cholangitis	No	100mg loading dose, 100mg twice daily	Day 2	Within 5 days
Wu and Wu [1]	China	Case report	M	87	Pneumonia	CRD	100mg loading dose 50 mg twice daily	Day 7	Within 5 days
Zhang et al.[4]	China	Retrospective control	16 M 4 F	62.5 ± 22.1	4 intraabdominal 1 skin and soft tissue 4 bacteremia 11 pneumoniae	4 patients CRD 4 patients CHD		NM	NM

F = female, M = male, CRD = chronic renal disease, CHD = chronic hepatic disease, NM =not mentioned, TGC = Tigecycline

effects should be elucidated. We suggest, regular monitoring of coagulation parameters including fibrinogen level in patients receiving tigecycline. If patients develop hypofibrinogenemia, discontinuation of drug should be considered.

Authors' Contribution

Study Conception: HRG, MA, SK, FC; Study Design: RG, MA, SK, FC; Supervision: RG, MA, SK, FC; Fundings: MA; Materials: MA, SK, FC; Data Collection and/or Processing: MA; Statistical Analysis and/or Data Interpretation: MA, RG; Literature Review: MA; Manuscript Preparation: MA and Critical Review: MA, RG.

Informed consent

Written informed consent was obtained from the patient for publication of this case and any accompanying images.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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