Case report

Tigecycline-associated hypofibrinogenemia: A case report and review of the literature

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ABSTRACT

Tigecycline, a glycylcycline-derived antibacterial that has been approved for the treatment of various infections, is widely used for multi-drug resistant bacteria. Coagulopathy is an uncommon side effect during tigecycline treatment and is easily overlooked when it occurs. We reported the effect of tigecycline (50 mg every twelve hours) treatment in an 87-year-old man, with Gram negative bacillary pneumonia and respiratory failure. After 7 days of tigecycline treatment, a significant drop of hemoglobin and patchy ecchymosis over both thighs were suddenly observed despite stable clinical condition. There was no abnormality in his platelet count and coagulation profile except for low fibrinogen level. Ecchymosis and anemia subsided gradually after blood component therapy. Although his clinical condition improved, hypofibrinogenemia persisted and recovered after 5 days of tigecycline discontinuation, suggesting probable tigecycline associated hypofibrinogenemia.

Introduction

Tigecycline is the first member of the glycylcycline class of antibiotics, modified to have broad-spectrum activity against most Gram-positive and Gram-negative, aerobic and anaerobic bacteria. It has been approved for the treatment of complicated skin and soft tissue infections, intra-abdominal infections, and community-acquired pneumonia [1]. It is mainly metabolized through the liver (80%), therefore the doses are recommended to be reduced for patients with Child's class C liver cirrhosis. The remaining 20% of the drug is eliminated through the kidney, and tigecycline clearance is reduced in patients with severe renal impairment. However, dose adjustment has not been recommended for patient with renal insufficiency [2].

The most common adverse effects of tigecycline involve symptoms of the gastrointestinal (GI) tract, including nausea, vomiting, and diarrhea [1]. Coagulopathy is a very rare adverse effect in the clinical settings and post-marketing surveillance. Therefore, clinicians often overlook it connection with adverse drug reaction. Here we report a patient who received tigecycline for ventilator-associated pneumonia caused by a multidrug-resistant *Acinetobacter baumannii* (MDRAB) and suffered from hypofibrinogenemia and a subsequent bleeding event. In addition, we also reviewed the literature to summarize the demographics of these patients, the clinical course, and management of this adverse drug reaction.

Case report

An 87-year-old male had a past medical history of ischemic stroke, atrial fibrillation, hypertension, chronic kidney disease, and relative adrenal insufficiency. The patient was bedridden and ventilator-dependent, and had been regularly taking amiodarone, amlodipine, clopidogrel, cortisone, and digoxin over one year. The patient presented to our facility with blood sputum and dyspnea that had been noted for two days. Initial lab data showed leukocytosis (27830/μL), high C-reactive protein level (7.84 mg/dL), and renal insufficiency (serum creatinine 1.9 mg/dL). Ventilator-associated pneumonia (VAP) was diagnosed based on the clinical presentation and chest-X-ray findings. Cefoperazone/sulbactam was administered for VAP empirically on the first day of admission. Sputum culture on the first day revealed *Proteus mirabilis*, *Klebsiella pneumonia*, and MDRAB. His clinical condition improved and the ventilator setting was reduced to a level similar to that before the incidence after 5 days of antimicrobial treatment.

New-onset fever occurred, however, and the ventilator setting had to be increased on the 9th day of admission, so the patient was switched to a new antibacterial regimen of tigecycline (100 mg initial infusion followed by an 50 mg infusion every 12 h), together with ceftazidime and inhaled colistin, for better MDRAB coverage after consulting an infectious disease (ID) specialist. Fever subsided two days after the antibacterial regimen change. There was no significant bleeding event after this admission until the 7th day of tigecycline use. Hemoglobin level suddenly decreased from 8.5 to 5.7 mg/dL, and hypofibrinogenemia

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(160 mg/dL) was noted on that day (Supplementary Figure). There was no clinically significant bleeding or hemolysis event at that time. Packed red blood cell (4U) was given for anemia, and clopidogrel was discontinued immediately. Two days later, patchy ecchymosis over both thighs was found during routine nursing care, and the level of fibrinogen further decreased (141 mg/dL) without other abnormal coagulopathy or thrombocytopenia. There was no traumatic injury or intravenous cannulation of the thigh before this event. Although cryoprecipitate (10U) was given on the 10th and 11th day of tigecycline use due to low fibrinogen level and ecchymosis, hypofibrinogenemia still persisted. Although tigecycline associated hypofibrinogenemia was highly suspected, the patient was kept on tigecycline to complete the two-week course for MDRAB pneumonia as suggested by the ID specialist. Subsequent tests on the last three days of tigecycline use showed that the fibrinogen level remained low under tigecycline treatment. Tigecycline was discontinued after 2 weeks treatment course, and the fibrinogen level recovered to within the normal range of 200–400 mg/dL after 5 days of tigecycline discontinuation.

Discussion

Tigecycline is a broad-spectrum antimicrobial mainly prescribed for multidrug-resistant bacterial infections. Nausea and vomiting were the most common adverse events with tigecycline. However, coagulopathy is rarely reported and hypofibrinogenemia was even not mentioned in the package insert [1]. Besides the case in this report, we have performed literature search for similar case reports on PubMed from 2000 to 2017 using keywords including "tigecycline" and "coagulopathy" or "hypofibrinogenemia." Four cases were identified and summarized in the Supplementary Table [3–6]. In these case reports; all of the subjects had acute or chronic kidney disease; and one case also had liver cirrhosis. The onset time of coagulopathy was within 1 week for 3 cases. For the other two cases; the onset time was 10 days and 1 month; respectively. For the case with longest onset time; it may be related to be unaware of this side effect and without follow up this side effect regularly. All cases recovered within 7 days after the discontinuation of tigecycline. Three of the 5 subjects (including this case) had severe bleeding events.

In addition to these reports, there were two small scale studies that showed similar results. Routsi et al. explored the effect of high dose tigecycline (100 mg every twelve hours) on coagulation in critical patients and found that fibrinogen decreased and international normalized ratio (INR) prolonged significantly after 3 days of tigecycline use [7]. This adverse effect recovered after tigecycline was discontinued for 3 days [7]. Zhang et al. studied the adverse effect of coagulation between tigecycline and cefoperazone/sulbactam. Compared to cefoperazone/sulbactam, which is well-known to cause INR prolongation associated with vitamin K deficiency, tigecycline reduced fibrinogen and prolonged INR more significantly [8]. Besides, the effect was more obvious in patients received the high dose of tigecycline than those receiving usual dose [8]. This adverse effect was also reversible after the discontinuation of tigecycline.

The mechanism of tigecycline-associated coagulopathy is still unclear. For INR prolongation, alteration of GI flora which led to decreasing synthesis of vitamin K is a commonly cited mechanism. However, based on the previous study compared to cefoperazone/sulbactam, which could not only alter GI flora but also affect vitamin K synthesis directly by its N-methylthiotetrazole side chain, tigecycline still had more significant effect on INR than cefoperazone/sulbactam [8]. Therefore, further study is still needed to explore the underlying mechanism of tigecycline-associated INR prolongation.

For hypofibrinogenemia, the mechanism is also unknown. Fibrinogen is produced by hepatocytes, and it could be converted to insoluble fibrin to form blood clots when the patient suffered from trauma or sepsis [9]. It is also considered to be an acute phase protein and its production is regulated by cytokines. For example, interleukin (IL)-6 enhanced the biosynthesis of fibrinogen, but IL-1, IL-4, IL-10, IL-13, and tumor necrosis factor-alpha (TNF-α) suppressed its production [10,11]. Tigecycline has been shown to reduce the levels of IL-6 and TNF-α, and the different extents of inhibition on these two cytokines

may interfere with the production of fibrinogen [11]. There are no data available about the effect of tigecycline on IL-4, IL-10, IL-13. Therefore, further study is needed to explore whether tigecycline modulate fibrinogen level via affecting the levels of different cytokines.

The risk factors for developing tigecycline-associated coagulopathy are not known. Based on our review, all of the cases of tigecycline associated coagulopathy had renal impairment. It is estimated that 20% of tigecycline is eliminated through the kidneys, and around 30% of drug accumulated in patients with severe renal impairment [2]. Based on previous studies, patients who received higher doses of tigecycline had more significant reduction of fibrinogen and prolonged INR than those receiving normal doses [8]. Therefore, renal insufficiency may be a risk factor for tigecycline-associated coagulopathy, and more closely monitoring coagulation profile in renal failure patients may be necessary. Further study is needed to delineate the interrelationship between tigecycline and kidney function.

In summary, tigecycline-associated coagulopathy may occur within 7 days after tigecycline use and resolved within 7 days after tigecycline discontinuation. Regularly monitoring fibrinogen and INR during tigecycline use is suggested, especially when patients suffered from bleeding events. Tigecycline should be changed to another antimicrobial if coagulopathy or bleeding event occurs.

Conflict of interest

All authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Chien-Chih Wu: revising it critically for important intellectual content, final approval of the version to be submitted.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.idcr.2018.01.003.

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