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A Case Report of Critically Ill Patient with Tigecycline Induced Hypofibrinogenemia

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Abstract

Tigecycline has a broad antibacterial spectrum and is widely used for severely infected patient. Hypofibrinogenemia is a rare adverse reaction of tigecycline and scarcely reported. We present a case of 58-year-old woman who developed hypofibrinogenemia after tigecycline treatment, without other coagulation parameters changing. Moreover, hypofibrinogenemia reappeared when tigecycline was readministered, and fibrinogen concentration restored to normal level after withdrawing tigecycline. We found that hypofibrinogenemia was probably induced by tigecycline through assessing the causality by Naranjo adverse drug reaction probability scale. Therefore, our case raises concern about an adverse reaction of tigecycline-induced hypofibrinogenemia, especially for critically ill patients with high risk of coagulopathy. In conclusion, we suggest that fibrinogen should be monitored for patients with coagulopathy risk during tigecycline treatment, especially for critically ill patients.

Keywords: Adverse drug reaction • Critically Ill • Coagulopathy • Hypofibrinogenemia

Introduction

Tigecycline is the first member of glycylcycline agents with broad antibacterial spectrum, which is susceptible for methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant Enterococci, extended-spectrum beta-lactamase-producing Enterobacteriaceae and multi drug-resistant *Acinetobacter baumannii* [1]. Its indications include complicated intra-abdominal infections, complicated skin and skin structure infections and community-acquired bacterial pneumonia. Tigecycline was approved for listing in China and has been widely used for treatment of drug-resistant bacterial infections. Tigecycline is well tolerated, most common adverse reaction is symptoms of gastrointestinal tract, including nausea and vomiting [2]. With the clinical application of tigecycline, there has been found other severe adverse reactions. Hypofibrinogenemia is a rare side effect of tigecycline and scarcely reported. Here we present a critically ill patient of whom fibrinogen concentrate decreased significantly after treated with tigecycline [3].

Case Study

A 58-year-old female patient was referred to our Intensive Care Unit (ICU) due to abdominal pain with fever for more than half month and coma for half month with main diagnosis of acute cholecystitis with gallstones, respiratory failure, pulmonary infection and coma of unknown origin [4]. On admission, the patient received related laboratory tests, assisted mechanical ventilation, and intermittent hemodialysis. The reason of coma was still unknown after magnetic resonance image of brain and lumbar puncture. Immunology consultation suggested symptomatic treatment with glucocorticoids considering immune factors could not be excluded, nevertheless, glucocorticoids was then discontinued because of inefficacy.

Subsequently, the patient received intravenous immunoglobulin treatment to regulate immunity, intermittent infusion of red blood cells to correct anemia, and intermittent infusion of human albumin to correct hypoalbuminemia after consulting neurologist and immunologist. Transaminase and bilirubin restore to baseline level through liver protection therapy [5].

Gallbladder drainage was carried out to control the infection immediately after admission, and draining tube removed. During hospitalization, the patient was administered with cefoperazone/sulbactam, linezolid, tigecycline, imipenem/cilastatin, voriconazole successively for anti-infective treatment. Sputum culture from bronchoscopy revealed pan-resistant *Acinetobacter baumannii*, therefore according to antibiotic sensitivity test was initiated on at a loading dose of 100 mg followed by 50 mg every combined with etimicin sodium chloride injection with 0.3 g once daily [6]. On the start day of tigecycline treatment, platelet count was 99.0 × 10^9/L, coagulation parameters include Prothrombin Time (PT), Activated

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Partial Thromboplastin Time (APTT), International Normalized Ratio (INR) were within normal range, and fibrinogen was 2.78 g/L. It was noteworthy that only fibrinogen decreased markedly during tigecycline treatment, platelet count and other coagulation parameters had no significant change. Fibrinogen basically restored to normal 7 days after tigecycline discontinuation. The patient stayed in the ICU for hospitalization due to necessity of continuous assisted mechanical ventilation [7].

Tigecycline was readministered for pulmonary infection, with maintenance dose of 100 mg every 12 hours. A strict monitoring of coagulation parameters was executed after administration, and fibrinogen decreased again significantly [8]. Therefore, the patient received intravenous infusion treatment of lyophilized fibrinogen powder for 3 days. Although patient's temperature was high, inflammation parameters were normal. Tigecycline treatment, considering the fever may associate with connective tissue disease, tigecycline was withdrawn. After tigecycline withdrawal, fibrinogen gradually reversed to normal on February 25 (2.25 g/L). During tigecycline administration, the patient had no obvious bleeding tendency [9].

Results

The labeling of tigecycline indicates that adverse reactions in the hemic and lymphatic system were reported infrequently (≥ 0.2% and ≤ 2%), including prolonged ATPP, prolonged PT, eosinophilia, increased INR, thrombocytopenia, which doesn't mention hypofibrinogenemia. analyzed all tigecycline related adverse events submitted to the U.S. Food and Drug Administration (FDA) from mentioned none about hypofibrinogenemia among 248 adverse events suggested as tigecycline associated [10].

This patient was received tigecycline treatment twice, subsequently both time fibrinogen decreased markedly and reserved to normal after withdrawing tigecycline, which performed remarkable correlation between the occurrence of adverse event and administration [11]. Naranjo Adverse Drug Reaction (ADR) probability scale, based on evidence-based medicine and the logic of clinical medication, is usually used as an ADR analysis tool in clinical practice, which is simple to apply and widely used [12]. Therefore, we used Naranjo scale to assess whether there is a causal relationship between hypofibrinogenemia and tigecycline. Since this patient stayed in the ICU for quite a long time, it is complicated and difficult to objectively analyze ADR, especially to assess the reason of hypofibrinogenemia and the related drugs. Fibrinogen decreased twice during hospitalization, however there is no time correlation between fibrinogen variations and primary disease (pulmonary infection and connective tissue disease), and between fibrinogen variable trend and disease progression [13]. According to the total score acquired by Naranjo scale hypofibrinogenemia was probably induced by tigecycline. Tigecycline is mostly used for combination therapy of drug-resistant bacterial, and for this patient, the first treatment of tigecycline was combined with etimicin, but monotherapy in the second time. There are no adverse reactions in the hemic system in the labeling of etimicin, and we also found no reports about etimicin-induced hypofibrinogenemia, no related reports about other drugs administered by the patient either [14]. Moreover, re-challenge test is generally considered as a direct and effective evidence of confirming the causality of ADR, and in our case, fibrinogen decreased again since tigecycline was readministered for sever pulmonary infection 2 months after the first tigecycline treatment, which showed obvious causality.

It is not common among case reports about drug-derived hypofibrinogenemia, tigecycline-associated hypofibrinogenemia was scarcely reported. A common feature of all related reports was that tigecycline-associated hypofibrinogenemia was accompanied by obvious coagulation disorders, prolonged PT and prolonged APTT. However, in our case, only fibrinogen decreased without markedly prolonged PT or APTT, meanwhile there was no correlation between platelet count change and administration time. The maintenance dose in labeling of tigecycline is 50 mg every 12 hours, nevertheless 100 mg every 12 hours is general dosage regimen for severe infections. Some retrospective analyses showed that high dose tigecycline might lead to more extent of fibrinogen decrease, and more cases of bleeding. It is worth noting that no specific therapy is needed for drug-derived fibrinogen decrease, which could gradually restore after withdrawing tigecycline, but tigecycline should be immediately discontinued to prevent severe adverse events once suspicious coagulopathy occurred. Fibrinogen, produced in hepatocytes, is one of the acute phase proteins. Fibrinogen plays a major role in coagulation, and it is a component of the common pathway of endogenous and exogenous coagulation. Normal level of fibrinogen is 2.0 g/L~4.0 g/L, and a reduction in fibrinogen level can be led to extensive coagulation disorder and bleeding tendency, which is commonly seen in hepatic dysfunction, active bleeding, acidosis, hypothermia. In our case, transaminase and bilirubin increased briefly on early admission, but maintained within normal range during administration [15]. The exact mechanism of tigecycline induced hypofibrinogenemia and coagulation disorder is still unknown, and some scholars speculated that it may be related to alteration of intestinal flora or synthesis of vitamin K, or it could affect waterfall of coagulation cascade directly. Research of fibrinogen gene regulation suggested that glucocorticoids and interleukin (IL)-6 could promote fibrinogen mRNA expression by activating STAT3, on the contrary, IL-1β inhibited IL-6-induced fibrinogen expression. Further study is needed to verify whether tigecycline or its metabolite affects fibrinogen gene expression through influencing endogenous glucocorticoids, IL-6 or IL-1β level or its target receptors.

Discussion

A recent *in vitro* study aimed to illuminate the mechanism of tigecycline-associated fibrinogen decrease through qualitative and quantitative research by using peripheral blood of healthy volunteers suggested that tigecycline didn't react with fibrinogen directly to influence coagulation parameters, but might increase the consumption of fibrinogen by promoting fibrin networks polymerization, leading to fibrinogen decrease. However, considering the limitation of the samples, whether this study could explain the reason of tigecycline-induced fibrinogen decrease in critically ill patients remains to be further explored. With the ever-increasing problem of bacterial resistance, application of tigecycline will be more widespread. Therefore, we suggest that coagulation parameters should be strictly monitored and avoid long-term and high-dose administration for patients with coagulopathy risk during tigecycline treatment.

Conclusion

In conclusion, our case showed that hypofibrinogenemia was probably induced by tigecycline and provides an evidence of an adverse reaction of tigecycline-induced hypofibrinogenemia. Therefore, we suggest that coagulation parameters, especially fibrinogen should be strictly monitored for critically ill patients with coagulopathy risk during tigecycline treatment.

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None

Conflict of Interest

The authors have no conflict of interest to declare

References

1. Zhanel, George G, Karlowsky James A, Rubinstein Ethan, and Hoban Daryl J. "Tigecycline: A Novel Glycylcycline Antibiotic." *Expert Rev Anti Infect Ther* 4 (2006): 9-25.
2. K, Kadoyama, Sakaeda T, Tamon A, and Okuno Y. "Adverse Event Profile of Tigecycline: Data Mining of the Public Version of the U.S. Food and Drug Administration Adverse Event Reporting System." *Biol Pharm Bull* 35 (2012): 967-970.
3. Naranjo, Cláudio A, Busto Usoa, Sellers Edward, Sandor P, and Ruiz I, et al. "A Method for Estimating the Probability of Adverse Drug Reactions." *Clin Pharmacol Ther* 30 (1981): 239-245.
4. Pieringer, Herwig, Schmeka Bernhard, Biesenbach Georg, and Pohanka Erich. "Severe Coagulation Disorder with Hypofibrinogenemia Associated with the Use of Tigecycline." *Ann Hematol* 89 (2010): 1063-1064.
5. Rossitto, Giacomo, Piano Salvatore, Rosi Silvia, Simioni Paolo, and Angeli Paolo. " Life Threatening Coagulopathy and Hypofibrinogenaemia Induced by tigecycline in a patient with advanced liver cirrhosis." *Eur J Gastroenterol Hepatol* 26 (2014): 681-684.
6. Sabanis, Nikolaos, Paschou Eleni, Gavriilaki Eleni, Kalaitzoglou Asterios, and Vasileiou Sotirios. "Hypofibrinogenemia induced by tigecycline: A potentially life-threatening coagulation disorder." *Infect Dis* 47 (2015): 743-746.
7. Wu, Xiaoqin, Zhao Ping, Dong Liang, and Zhang Xiuhong. "A case report of patient with severe acute cholangitis with tigecycline treatment causing coagulopathy and hypofibrinogenemia." *Med* 96 (2017):e9124.
8. D Yilmaz, Yıldırım Halil, and Sen Mehmet Emre. "A Lesser Known Side Effect of Tigecycline: Hypofibrinogenemia." *Turk J Haematol* 35 (2018): 83-84.
9. Wu, Pei-Chun, and Wu Chien-Chih. "Tigecycline-Associated Hypofibrinogenemia: A Case Report and Review of the Literature." *IDCase* 11 (2018): 56-57.
10. Balfousias, Theodore, Angelis Stavros, Maris Spyridon, and Papanikolaou Athanasios. "Spontaneous Knee Hemarthrosis Due to Hypofibrinogenemia Following Tigecycline Treatment for Periprosthetic Joint Infection." *Cure* 11 (2019): e5883.
11. Routsi, Christina, Kokkoris Stelios, Douka Evangelia, Ekonomidou Foteini, and Giamarellou Helen. "High-dose Tigecycline-Associated Alterations in Coagulation Parameters in Critically Ill Patients with Severe Infections." *Int J Antimicrob Agent* 45(2015): 90-93.
12. Zhang, Qian, Zhou Suming, and Zhou Jing. "Tigecycline Treatment Causes a Decrease in Fibrinogen Levels." *Antimicrob Agent Chemother* 59 (2015):1650-1655.
13. Cui, Nannan, Cai Hongliu, Li Zhitao, Lu Yuting, and Lu Anwei. "Tigecycline-Induced Coagulopathy: A Literature review." *Int J Clin Pharm* 41(2019):1408-1413.
14. Fish, Richard J, and Neerman-Arbez Marguerite. "Fibrinogen Gene Regulation." *Thromb Haemost* 108(2012): 419-426.
15. Brandtner, Anna, Bachler Mirjam, Fries Dietmar, Hermann Martin, and Ruehlicke Jacqueline, et al., "Tigecycline Interferes with Fibrinogen Polymerization Independent of Peripheral Interactions with the Coagulation System." *Antibio* 9 (2020): e84.

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