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Letter to the Editor

Fibrinogenopenia caused by Tigecycline: a case report

Dear Editor,

Tigecycline is the first glycylcycline approved by the U.S. Food and Drug Administration (FDA), in 2005[1]. It has expanded broad spectrum activity against a variety of Gram-positive and Gram-negative bacterial pathogens, many of which are resistant to existing antibiotics[2]. Tigecycline successfully completed phase III trials in which it treated complicated skin and intra-abdominal infections. The drug was licensed for the treatment of skin, soft tissue, and intra-abdominal infections.

Tigecycline has similar side effects as tetracycline, the most common being diarrhea (28.5%), and nausea and vomiting (19.4%). Other side effects include pain at the injection site (8.2%), fever (6.3%), abdominal pain (6.0%), and headache (5.6%), as well as adverse effects on developing teeth and bone[3]. Other related adverse effects include elevated levels of alanine aminotransferase, bilirubin, alkaline phosphatase, and aspartate aminotransferase, the occurrence of hepatic dysfunction and acute pancreatitis[4,5]. Tigecycline treatment was associated with an increased mortality in patients treated for hospital-acquired pneumonia, especially ventilator-associated pneumonia, patients with complicated skin and soft tissue infections, complicated intra-abdominal infections and diabetic foot infection. Coagulation disorders caused by tigecycline have not yet been described.

43-year-old patient with a 19-year history of type 2 diabetes presented with elevated blood pressure (up to 150/100 mmHg), urinary protein, elevated serum creatinine levels, and renal biopsy confirmed diabetic nephropathy. The patient was diagnosed with diabetes in 1995, and started insulin treatment in 2004. The patient was managed with Chinese medicine to preserve renal function, insulin to lower blood sugar levels, and anti-hypertensive therapy. The patient's blood pressure and blood sugar levels were controlled, but he developed chronic diarrhea. The diarrhea symptoms worsened and the patient developed green watery stools on Jan 18th, 2014. The patient was hydrated in the outpatient department of a local hospital, but the symptoms recurred. The patient presented to our hospital with decreased urine output on January 23. Blood tests revealed a WBC of 31.5 × 10^9/L, N 91%, BUN of 24.6 mmol/L, and Cr of 768.5 μmol/L. The patient was treated with hemodialysis antibiotics, anti-diarrhea medications, and nutritional support. No improvement in the diarrhea was seen. The patient had more than 10 watery stools per day, with no mucus, pus or blood. The patient complained of abdominal distension with no chills or fever. KUB showed little abdominal gas and gas-fluid levels in the lower abdomen. Chest CT showed mild atelectasis in both lungs and a small amount of pleural effusion. The patient was admitted to the hospital on January 28, 2014.

Physical examination on admission showed no fever, mild abdominal guarding, tenderness, but no rebound pain. The patient was empirically administrated Imipenem and Cilastatin sodium. Blood tests showed a WBC of 37.47 × 10^9/L, N 96.80%, PLT of 366 × 10^9/L, and C-reactive protein of 273 mg/L. Coagulation function tests showed a PT of 15.10 s, APTT of 53.70 s, and FIB of 8.62 g/L (normal values: 2-4 g/L). Chest CT imaging showed atelectasis in both lower lobes and the upper lobe of the left lung lobe, and a pleural effusion on both sides. Abdominal CT imaging showed an abdominal and pelvic fluid effusion, with encapsulated fluid formation. Abdominal paracentesis revealed a cloudy yellow liquid. Severe abdominal infection with accompanying lung infections was considered a possible diagnosis. As the patients had renal failure and other risk factors, he was administrated with tigecycline 50 mg q12h on Jan. 30th. Repeat ascites and fecal bacterial and fungal cultures showed no pathologic growth. Sputum culture showed multi-drug resistant Acinetobacter baumannii. On February 11th, Imipenem and cilastatin was continued and Sulperazon was added. The patient underwent bedside dialysis every other day and received low molecular weight heparin, 2000iu, qd. The patient had no fever and diarrhea symptoms and gradually improved, but his blood tests worsened. On Feb. 21st blood tests showed a WBC of 8.95 × 10^9/L, N 70.5%, PLT of 136 × 10^9/L, and C-reactive protein of 8.23 mg/L.

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The platelet counts gradually decreased, but remained in the normal range (Figure 1). The prothrombin time was normal (Figure 2). The partial thromboplastin time became prolonged, in the range of 50-60 s (normal: 24.5 ± 10s) (Figure 2). Fibrinogen levels were abnormally low (Figure 3). On February 21st, the PT was 15.2 s, APTT 54.5 s, and FIB 1.46 g/L. The patient passed 760 ml of bloody stool and blood clots on February 23rd. Blood tests showed a Hb of 56 g/L, PLT of 80 × 10^9/L, PT of 18.9 s, APTT 87.9 s, and FIB of 1.03 g/L. The patient was immediately administrated for fluid resuscitation and blood, plasma and fibrinogen transfusion. The patient passed 1200 ml of dark red bloody stool on February 23rd. Blood tests on February 24th showed a Hb of 77g/ L, PLT of 64 × 10^9/L, PT of 17.2 s, APTT of 88.2 s, and FIB of 0.6 g /L. The patient was treated with fluids, blood, plasma, blood factors, fibrinogen and cryoprecipitate. Dialysis was performed without heparin. Gastrointestinal bleeding stopped on February 25th and tigecycline was discontinued on February 26th. The partial thromboplastin time was normal 1 week after discontinuing tigecycline. Platelet counts and fibrinogen levels also normalized during this time.

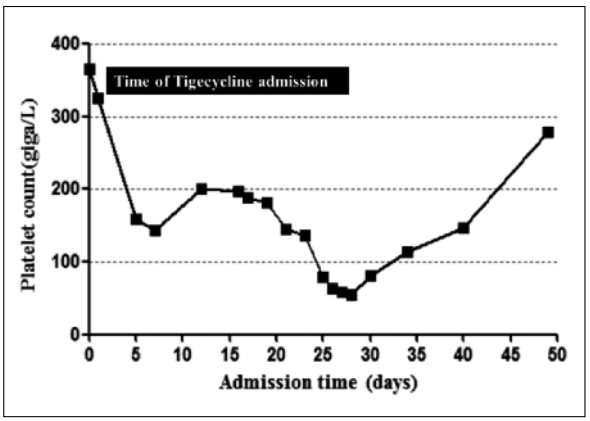

Figure 1. Platelet counts fluctuated in the normal range.

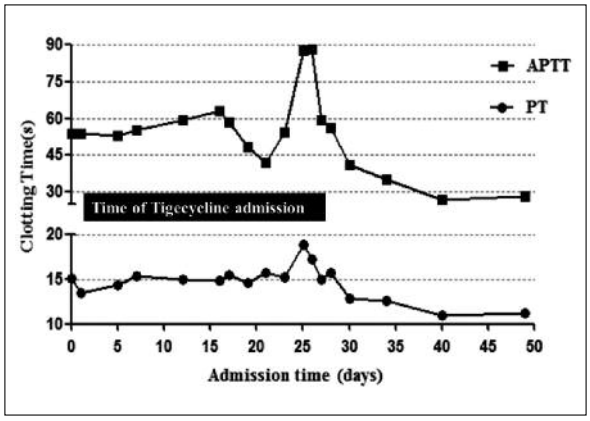

Figure 2. The prothrombin time remained in the normal range.

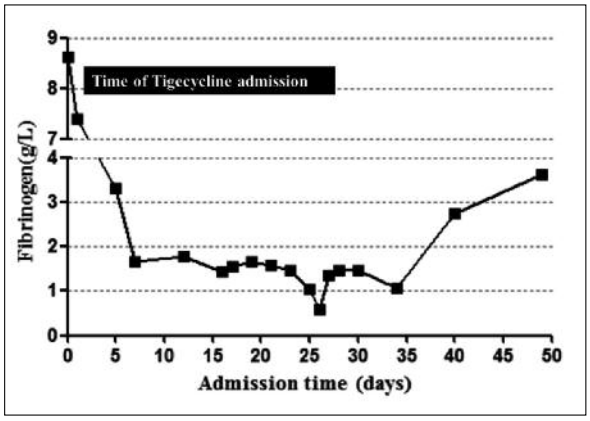

Figure 3. Fibrinogen levels were significantly reduced.

The recommended dosage of tigecycline[1] is 100 mg IV as a loading dose, followed by 50 mg IV q12h. Korth-Bradley et al[6] reported that the pharmacokinetic properties of tigecycline did not change in patients with impaired renal function and that Tigecycline was not cleared by dialysis. Patients with renal impairment or undergoing hemodialysis do not need any dose adjustments. The patient presented here had renal failure and an abdominal infection. The patient responded to treatment, but also developed a coagulopathy. The patient developed a prolonged APTT, decreased platelet count, decreased fibrinogen levels, and active bleeding. These all resolved after discontinu-

ing the tigecycline and supportive treatment. No previous cases of bleeding disorders associated with Tigecycline have been reported. Clinicians should be aware of this risk and coagulation parameters should be monitored during treatment. If coagulation disorders or active bleeding occurs, tigecycline treatment should be immediately stopped.

Acknowledgements

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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