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Tigecycline Treatment Causes a Decrease in Fibrinogen Levels

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The objective of this study was to assess the impact of tigecycline treatment on coagulation parameters, specifically fibrinogen, in patients with severe infections. We examined 20 cases of tigecycline-treated patients with severe infections, including hospital-acquired pneumonia, complicated intra-abdominal infections, complicated skin and soft tissue infections, and bloodstream infections. We monitored the relative markers of coagulation and renal and liver function before, during, and after treatment. Fibrinogen (FIB) levels decreased significantly after the use of tigecycline and normalized after the cessation of treatment. FIB levels significantly decreased in the patients treated with the recommended dose or a higher treatment dose. The FIB levels decreased more in the higher-treatment-dose group. There was no difference in the decrease in FIB levels or the FIB level recovery by age. Prothrombin time (PT), activated partial thromboplastin time (APTT), and thrombin time (TT) were prolonged after tigecycline use. The TT decreased after the cessation of treatment, and the PT and APTT also decreased but not to a significant level. There was no change in platelet, alanine aminotransferase (ALT), or creatinine (Cr) levels associated with treatment. The use of tigecycline was associated with decreased FIB levels, which returned to normal after the cessation of treatment. A high-dose treatment group showed greater decreases in FIB levels than did patients treated with the recommended dose. The decline in FIB was not related to patient age. The use of tigecycline was associated with prolonged PT, APTT, and TT.

Tigecycline is a novel broad-spectrum intravenous antibiotic that inhibits bacterial protein synthesis. Tigecycline functions by binding to the 30S ribosomal subunit and preventing aminoacylated tRNA molecules from entering the ribosomal A site. Tigecycline contains a glycylamino group substituted for the 9-minocycline group, a substitution rarely seen in any natural or semisynthetic tetracycline compound, which gives tigecycline unique microbiological properties. Tigecycline is not affected by the two major bacterial tetracycline resistance mechanisms, efflux and ribosomal protection mechanisms (1). Tigecycline has a very broad spectrum of antibacterial activity, with Gram-positive cocci (including methicillin-resistant *Staphylococcus aureus*, [MRSA] and vancomycin-resistant enterococci [VRE]) (2), Gram-negative bacilli (including *Acinetobacter* spp. and *Stenotrophomonas maltophilia*) (3), and anaerobic bacteria (4) having relatively high sensitivities. Kadoyama et al. (5) summarized a total of 248 tigecycline-related adverse reactions, the most common being nausea, vomiting, elevated levels of alanine aminotransferase, bilirubin, alkaline phosphatase, and aspartate aminotransferase, and hepatic dysfunction. In a number of studies, patients showed good tolerance of tigecycline, indicating that it is safe (6–7). However, there were two case reports that tigecycline can induce decreases in fibrinogen (FIB) levels (8–9). Fibrinogen clotting factor I is a glycosylated acute-phase protein with a half-life of 3 to 4 days. It is synthesized by liver parenchymal cells. Fibrinogen concentrations in normal plasma are 2 g/liter to 4 g/liter, with slight increases during acute severe infections. The most important physiological function of fibrinogen is coagulation. The conformation of fibrinogen changes after catalysis by thrombin to an aggregate of insoluble fibrin matrix (10). Severe reductions in fibrinogen cause coagulation dysfunction, which leads to further severe hemorrhagic disease. We carried out a retrospective analysis of the use of tigecycline to treat severe infections in 20 patients in order to better characterize its effect on coagulation and plasma fibrinogen levels, as well as to provide reference information for the clinical use of tigecycline.

MATERIALS AND METHODS

Data. Sixty patients with severe infections were treated with tigecycline from December 2012 to April 2014 at the First Affiliated Hospital of Nanjing Medical University. Of these, 40 were excluded due to incomplete clinical documents, but no one was excluded because of medication. In the present study, 20 patients presented with a normal or higher level of fibrinogen before tigecycline treatment. Concomitant drug use is listed in Table 1. Twenty-one patients treated with cefoperazone and sulbactam served as a control group, with a dose of 1.5 g every 6 h (q6h) to 3 g q8h.

Observation. Coagulation, liver, and kidney function were evaluated before, during, and after treatment. Fibrinogen (FIB) levels, prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), platelet count (PLT), alanine aminotransferase (ALT) levels, and creatinine (Cr) levels were determined to measure the effects of treatment.

Statistical analysis. All data were analyzed using SPSS 18.0. The missing data were completed using multiple imputations. The imputed variables include age, gender, and other indicators related to coagulation and blood biochemistry. The FIB, APTT, PT, TT, PLT, ALT, and Cr measurement data were expressed as the median and 25% to 75% range, as these data were not normally distributed. A rank sum test was used to compare the APTT, FIB, PT, and TT levels at different time points. When checking if FIB was associated with age or dose regimen, the pretreatment, treatment, and posttreatment differences were first calculated, and the rank sum test was then carried out. A PLT decrease of 30% was considered

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TABLE 1 Characteristics and treatment information of 20 patients given tigecycline

Patient	Infection type(s)[a]	Pathogen(s) isolated (sample type)[b]	Comorbidity	Concomitant drugs	Renal failure (undergoing hemodialysis)	Hepatic impairment (Child-Pugh class)	Dosage (mg)	Duration of treatment (days)	Hemorrhage (site)	Blood transfusion	Treatment outcome
1	Pneumonia, cIAIs	*A. baumannii* (sputum), *Enterococcus faecium* (ascites)	Hepatitis B, post-liver transplantation	Cyclosporine/voriconazole/ caspofungin/entecavir/ piperacillin-tazobactam	No	Yes (A)	50 q8h	21	Yes (airway)	No	Completion
2	cIAIs	Negative	Diabetes	Imipenem-cilastatin/cefoperazone-sulbactam/fluconazole/aspirin/ low-molecular-weight heparin	Yes (Yes)	No	50 q12h	27	Yes (alimentary tract)	Yes	Completion
3	Pneumonia	*A. baumannii* (sputum)	Diabetes	Cefoperazone -sulbactam/caspofungin/ linezolid	Yes (No)	No	50 q12h	14	No	No	Completion
4	Pneumonia	*A. baumannii*、KPCs (sputum)	Diabetes	Voriconazole/piperacillin-tazobactam/linezolid	Yes (Yes)	No	50 q12h	14	No	No	Death
5	Bacteremia, pneumonia	*A. baumannii* (blood、sputum)	Trauma, amputation	Cefoperazone-sulbactam/ fluconazole	No	No	50 q12h	15	Yes (surgical wound、alimentary tract)	Yes	Completion
6	Pneumonia	*A. baumannii* (sputum)	Subarachnoid hemorrhage, hypertension, diabetes, hepatitis C	Fluconazole/clopidogrel	No	No	50 q12h	14	No	No	Completion
7	Pneumonia	*A. baumannii* (sputum)	Hypertension	Ceftazidime/voriconazole	Yes (Yes)	No	50 q12h	24	Yes (incision wound)	Yes	Completion
8	Pneumonia	*A. baumannii* (sputum)	Dermatitis medicaments, hypertension	Fluconazole	No	No	50 q12h	14	No	No	Death
9	Bacteremia	ESBLs-*K. pneumoniae*, *E. faecium* (blood)	Portal thrombosis	Imipenem-cilastatin/amikacin/ piperacillin-tazobactam/low-molecular-weight heparin	No	No	50 q12h	14	No	No	Completion
10	Pneumonia	*A. baumannii* (sputum)	Lung cancer	Voriconazole/vancomycin/ imipenem-cilastatin/ cefoperazone-sulbactam	No	No	50 q12h	15	No	No	Death
11	cIAIs	Negative	Gastric cancer	Piperacillin-tazobactam/ fluconazole	No	No	50 q12h	8	Yes (alimentary tract)	Yes	Completion
12	Pneumonia, cSSSIs	*A. baumannii* (sputum), *E. coli* (wound secretion)	Trauma	Cefoperazone-sulbactam/ vancomycin/micafungin/ levofloxacin	No	No	50 q12h	14	No	Yes	Death
13	Pneumonia, septic shock	None	Diabetes, rheumatoid arthritis	Low-molecular-weight heparin/imipenem-cilastatin	No	Yes (B)	50 q12h	7	No	No	Death
14	Pneumonia	Negative	Myelodysplastic syndrome, posthematopoietic stem cell transplantation	Piperacillin-tazobactam/ cyclosporine/caspofungin/ fluconazole/methylprednisolone	No	No	50 q12h	21	No	No	Completion
15	Pneumonia	*A. baumannii* (sputum)	Percutaneous aortic valve replacement, COPD[c]	Ceftazidime/clopidogrel	No	No	100 q12h	9	Yes (airway, subcutaneous)	Yes	Death
16	Bacteremia	None	Hematopoietic function exhaustion	Piperacillin-tazobactam	No	Yes (C)	50 q12h	6	No	Yes	Completion
17	Bacteremia, pneumonia	MRSA, *A. baumannii* (blood、sputum)	Trauma: paraplegia, hepatitis B	Ceftazidime/clopidogrel/ voriconazole/cefoperazone-sulbactam	No	Yes (B)	50 q12h	14	No	No	Completion
18	cIAIs	Negative	Acute lymphoblastic leukemia, hypertension	Itraconazole/imipenem-cilastatin	No	No	50 q12h	8	No	Yes	Completion
19	Pneumonia	MRSA (sputum)	COPD, hypertension	Methylprednisolone/imipenem-cilastatin	No	No	50 q12h	10	No	No	Death
20	Pneumonia	*A. baumannii* (sputum)		A amikacin/cefoperazone-sulbactam/cefoselis/low-molecular-weight heparin	No	No	50 q12h	24	No	No	Completion

[a] cIAIs, complicated intra-abdominal infections; cSSSIs, complicated skin and skin structure infections.

[b] KPCs, *K. pneumoniae* carbapenemases; ESBLs, extended-spectrum β-lactamases; MRSA, methicillin-resistant *S. aureus*.

[c] COPD, chronic obstructive pulmonary disease.

TABLE 2 Differences between cefoperazone-sulbactam group and tigecycline group

Characteristic	Cefoperazone-sulbactam group	Tigecycline group	*P*
Age (mean [SD]) (yr)	62.9 ± 24.4	62.5 ± 22.1	0.822
Sex (no. of females/no. of males)	6/15	7/15	0.817
APACHE II score (mean [SD])	15.33 ± 7.49	13.08 ± 5.41	0.353
Median (pretreatment to posttreatment) difference in:			
FIB (g/liter)	0.49 (−0.09 to ~1.06)	−1.27 (−2.28 to ~−0.21)	<0.001
PT (s)	0.60 (−0.30 to ~2.40)	0.36 (−1.70 to ~2.90)	<0.001
APTT (s)	3.30 (0.20 to ~6.30)	6.70 (−4.00 to ~19.25)	<0.001
TT (s)	−0.20 (−1.20 to ~1.80)	2.16 (−0.23 to ~4.75)	<0.001

significant, as was a doubling of the ALT level. A 1.5-fold increase in the Cr level was considered significant. A chi-square test was used to compare the PLT, ALT, and Cr levels between the groups. A *P* value of ≤0.05 was considered statistically significant.

RESULTS

Patient characteristics. The 20 patients who were treated with tigecycline showed no statistically significant differences from those in the cefoperazone and sulbactam group with respect to age, gender, or acute physiology and chronic health evaluation (APACHE) II score (Table 2). Among these 20 patients, 15 were treated in the intensive care unit (ICU) (75%), 3 in the hematology division, 1 in the infectious disease division, and 1 in the gastroenterology division. The mean patient age was 62.5 ± 22.1 (standard deviation [SD]) years (range, 22 to 95 years). There were 10 patients ≥65 years of age (50%), including 6 who were ≥75 years of age (30%). There were 16 male and 4 female patients. Four out of 20 patients presented with hepatic dysfunction (Child-Pugh score, class A, 1 patient; class B, 2 patients; class C, 1 patient). At presentation, 4 patients had renal failure, and 3 of these patients required dialysis. Special patients included 1 liver transplant case (mentioned above, liver function Child-Pugh class A), 1 hematopoietic dysfunction case, 1 myelodysplastic syndrome case treated with allogeneic hematopoietic stem cell transplantation, and 1 acute lymphoblastic leukemia case. The fibrinogen levels in the 3 patients with blood diseases were normal before tigecycline treatment.

Four of the 20 cases had complicated intra-abdominal infections (including 1 patient with a pulmonary infection), 1 had a complicated skin and soft tissue infection and pulmonary infection, 4 patients had bloodstream infections (including 2 patients with pulmonary infection), and 11 patients had pulmonary infections. There were 22 specimens cultured from sputum, blood, ascites, and secretion samples. Fourteen of these specimens were multidrug-resistant *Acinetobacter baumannii*, 3 were MRSA, 2 were *Enterococcus* spp., 1 was *Escherichia coli*, 1 was *Klebsiella pneumoniae* producing extended-spectrum β-lactamase, and 1 was *K. pneumoniae* producing carbapenemase.

The suggested first dose of tigecycline is 100 mg (also for renal failure patients requiring dialysis and Child-Pugh class A and B hepatic dysfunction patients), followed by 50 mg q12h. For Child-Pugh class C patients, the dose is decreased to 25 mg q12h. This regimen is normally administered for 5 to 14 days (11). Eleven patients were administered the suggested dose, and 3 patients received a higher dose (Table 1, patients 1, 15, and 16). Seven cases were treated for >14 days (including 1 higher-dose case).

Among the 20 patients, 19 showed decreased FIB levels, with 16 having levels of <2.0 g/liter. Six (20%) patients developed active bleeding during treatment. All of the 6 patients were treated with supportive plasma, fibrinogen treatment, or both. Another 2 patients with FIB levels of <1.5 g/liter were given cryoprecipitate infusion. In this study, 13 (65%) patients responded to treatment and 7 (35%) died. All of the 7 deaths were due to severe infection and not related to hemorrhage.

Tigecycline effects on coagulation. The FIB levels decreased with tigecycline treatment from 3.660 g/liter (2.450 to 4.670 g/liter) to 2.155 g/liter (1.371 to 3.212 g/liter) ($P < 0.001$). This is a significant difference from the levels of the control group (Table 2). After the cessation of treatment, the FIB levels rebounded from 2.155 g/liter (1.371 to 3.212 g/liter) to 2.353 g/liter (1.580 to 3.234 g/liter) ($P < 0.001$) (Fig. 1).

The FIB levels dropped significantly in both the suggested-dose and higher-dose groups. Among the 11 patients in the suggested-dose group, one (9%) developed active bleeding. Among the 9 patients in the higher-dose group, 5 (55.6%) developed active bleeding. The respective medians (25th quartile [Q25] to Q75) of the FIB levels before and after treatment were 3.220 g/liter (2.298 to 4.640 g/liter) and 2.201 g/liter (1.358 to 3.189 g/liter) ($P < 0.001$), and 3.745 g/liter (3.270 to 4.680 g/liter) and 2.119 g/liter (1.400 to 3.239 g/liter) ($P < 0.001$). The higher-dose group had a more pronounced decline than the recommended-dose group, at −1.032 g/liter (−1.979 to −0.084 g/liter) and −1.505 g/liter (−2.851 to −0.465 g/liter) for the suggested-dose and higher-dose groups, respectively ($P < 0.001$). After the cessation of treatment, the FIB levels of both groups rebounded significantly. The FIB levels in the suggested-dose group increased from 2.201 g/liter (1.358 to 3.189 g/liter) to 2.321 g/liter (1.576 to 3.347 g/liter) ($P = 0.02$) and in the higher-dose group from 2.119 g/liter (1.400 to 3.239 g/liter) to 2.410 g/liter (1.594 to 3.181 g/liter) ($P = 0.006$). There was no difference in the improvement of FIB levels of the two treatment groups after the cessation of tigecycline (0.174 g/liter [0.458 to 0.883 g/liter] for the suggested-dose group versus 0.322 g/liter [0.408 to 0.898 g/liter] for the higher-dose group) ($P = 0.168$) (Fig. 2).

Both the <65 and ≥65 years age groups had significant decreases in FIB levels, with the FIB levels before and after treatment being 3.550 g/liter (2.410 to 4.550 g/liter) and 1.980 g/liter (1.288 to 3.011 g/liter) ($P < 0.001$), respectively, in the <65 year age group, and 4.430 g/liter (3.700 to 4.680 g/liter) and 2.608 g/liter (1.678 to 3.682 g/liter) ($P < 0.001$), respectively, in the ≥65 age group. There was no difference in the FIB levels by age group. The FIB levels increased after the cessation of treatment back to nor-

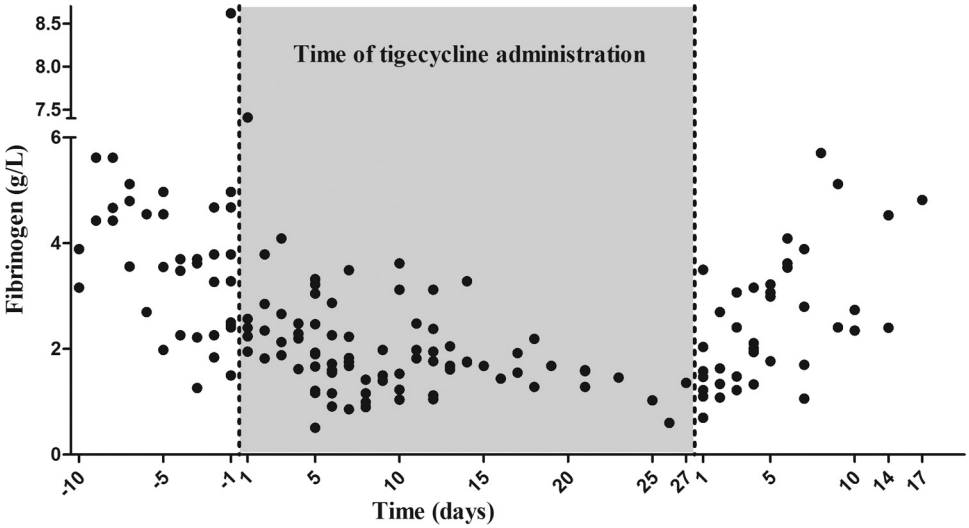

FIG 1 Fibrinogen levels of 20 severe infection cases treated with tigecycline (FIB normal values, 2 to 4 g/liter). The FIB levels decreased significantly after tigecycline treatment, but FIB levels returned to normal after the cessation of tigecycline.

mal levels (<65 year age group, 1.980 g/liter [1.288 to 3.011 g/liter] versus 2.220 g/liter [1.480 to 2.990 g/liter] [$P = 0.002$]; ≥65 age group, 2.608 g/liter [1.678 to 3.682 g/liter] versus 2.813 g/liter [1.801 to 3.894 g/liter] [$P = 0.051$]). The changes in FIB levels from during to after treatment were not different by age group (0.229 g/liter [−0.421 to 0.879 g/liter] and 0.244g/liter [−0.546 to 0.930 g/liter] [$P = 0.551$]) (Fig. 3).

The PT, APTT, and TT were all longer in patients who had undergone tigecycline treatment than those in the control patients ($P < 0.001$, Table 2). The pretreatment and treatment median values (Q25 to Q75) for PT were 13.500 s (12.600 to 15.800 s) and 15.099 s (12.809 to 17.848 s) ($P < 0.001$), respectively; for APTT, these were 33.750 s (27.900 to 45.900 s) and 43.985 s (31.290 to 59.413 s) ($P < 0.001$), respectively; for TT, these were 17.950 s (17.100 to 18.700 s) and 19.900 s (17.433 to 22.444 s) ($P < 0.001$), respectively. No change in platelet levels was seen with treatment. TT shortened after the cessation of tigecycline treatment, from 19.483 s (17.400 to 21.528 s) to 19.900 s (17.433 to 22.444 s) ($P = 0.003$). PT and APTT did not vary after the cessation of treatment ($P = 0.071$ and 0.056, respectively).

Tigecycline effects on liver and kidney function. There were no significant changes in ALT and Cr levels, by our definition, associated with treatment.

DISCUSSION

Bacterial resistance is an increasing health threat (12). Tigecycline is the first glycyl tetracycline drug. It was approved by the FDA in June 2005 and entered the Chinese market at the end of 2011. The main indications for tigecycline are complicated intra-abdominal infections, complicated skin and skin and soft tissue infections, and community-acquired pneumonia caused by sensitive bacteria. Its antibacterial spectrum comprises drug-resistant *S. aureus*, *Enterobacteriaceae*, and *A. baumannii*. Multidrug-resistant *Enterobacteriaceae* also have shown high sensitivity *in vitro* against tigecycline, including penicillinase-producing strains, such as the

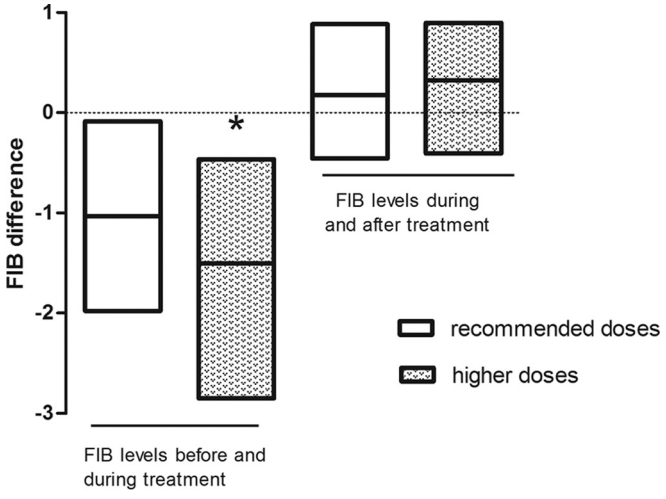

FIG 2 FIB levels (medians and 25th and 75th quartiles) associated with recommended and higher treatment doses. The FIB levels were significantly lower in patients treated with the recommended dose or higher. The FIB levels decreased more in the higher-dose group. *, significant difference from recommended-dose group, $P < 0.001$.

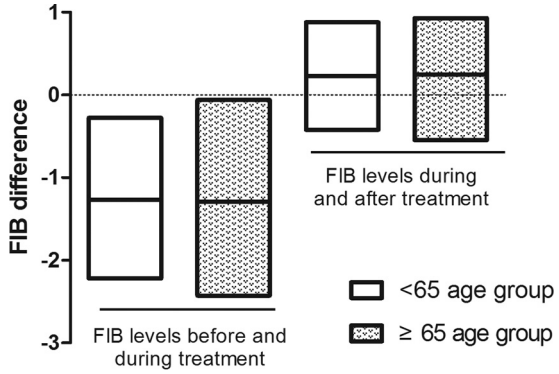

FIG 3 Both <65 and ≥65 year age groups had significant decreases in FIB levels (medians and 25th and 75th quartiles). There was no difference in the decreases in FIB levels or the FIB level recoveries by age.

New Delhi-β-lactamase (13). Tigecycline has not been approved for *A. baumannii* infections or ventilator-associated pneumonia treatment, but the global scope of its off-label use is expanding (14–15). We evaluated 20 patients treated with tigecycline for severe infections and after failure or intolerance of other antibiotic treatments, particularly for the treatment of pan-drug-resistant *A. baumannii*.

The manufacturer lists the most common adverse reactions to tigecycline as being gastrointestinal symptoms, which usually occur 1 to days 2 after treatment and include mild to moderate nausea and vomiting (11). Uncommon adverse reactions can involve the blood and lymphatic system (incidence, <2%), the prolongation of APTT and PT, an increase in eosinophils, an increase in the international normalized ratio (INR), and a decrease in blood platelets. We found that patients with severe infections treated with tigecycline experienced a reduction in fibrinogen levels that was proportional to the dose. Among these 20 patients, 7 days after treatment, there was an 80% incidence of FIB reduction with a magnitude of >30%. Our results suggest that dose increases or/and regimen prolongation may cause greater decreases in FIB levels. These levels normalized after the cessation of treatment. The manufacturer's instructions state that out of 2,514 patients in a phase III clinical trial, there were 664 patients ≥65 years old and 288 patients ≥75 years old. These patients were not at increased risk for adverse events related to tigecycline. We found no difference in the FIB decrease in patients <65 and ≥65 years of age, suggesting that it is not dependent on age. We found no change in ALT levels associated with treatment. The factors that can affect the metabolism of fibrinogen include liver dysfunction, active bleeding, fibrinogen degradation accelerated by acidosis, and fibrinogen inhibition caused by low body temperature (16). The mechanism for the decrease found with tigecycline is unclear.

Ten patients with mild hepatic impairment (Child-Pugh class A), 10 patients with moderate hepatic impairment (Child-Pugh class B), 5 patients with severe hepatic impairment (Child-Pugh class C), and 23 healthy control subjects were reported to be treated with tigecycline (11). The single-dose pharmacokinetics of tigecycline did not change in the patients with mild hepatic impairment. However, the drug clearance rates were reduced by 25% and 55%, respectively, in patients with moderate and severe hepatic impairment, leading to coagulation disorders. The use of tigecycline in patients with more severe reductions in fibrinogen may put patients at an increased risk of bleeding. Tigecycline dose reduction, monitoring of coagulation markers, cessation of tigecycline treatment, and cryoprecipitate or fibrinogen infusion should be performed.

Our patients did not have alterations in creatinine levels with treatment. Two studies (17–18) found no significant change in the tigecycline pharmacokinetics in patients with impaired renal function, and tigecycline was not cleared by dialysis. There is no need to adjust the dose in patients with impaired renal function or in patients undergoing hemodialysis treatment (11).

The recommended dose of tigecycline can result in a reduction in plasma fibrinogen levels. This can occur within a few days of tigecycline treatment. Fibrinogen decreases, combined with prolongation of clotting time or/and platelet decreases, can cause severe bleeding, increased hospitalization, and mortality. The monitoring of coagulation during tigecycline treatment should be routine. Fibrinogen levels of <1.2 g/liter should be treated with cryoprecipitate, or fibrinogen infusion should be given. If active bleeding begins, the drug should be withdrawn, and the patient should be observed. The patient should be also infused with fresh-frozen plasma to supply blood coagulation factors.

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