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Case Report

Tigecycline Induced Disseminated Intravascular Coagulation

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ABSTRACT

Tigecycline is a broad-spectrum antibiotic with good activity against multidrug resistant pathogens, thus being commonly used in the intensive care units (ICU). However, tigecycline can cause adverse drug reactions ranging from nausea, vomiting to rarest events like disseminated intravascular coagulopathy (DIC). Tigecycline induced DIC occurs hours to days after starting the drug and is more common in patients with hepatic or renal impairment. Here we report one such rare case where DIC occurred within hours after initiating tigecycline. A 42years old man with chronic obstructive pulmonary disease was admitted to the respiratory ICU with community acquired pneumonia. He developed thrombocytopenia and DIC subsequent to tigecycline which subsided only after stoppage of the drug. One should keep in mind these life-threatening adverse effects which when recognized and treated on time can give good outcomes.

Keywords: Tigecycline; Coagulopathy; Adverse drug reaction

Case Presentation

A 42 years old man, known case of chronic obstructive pulmonary disease (COPD), was admitted to the respiratory intensive care unit (ICU) with complaints of high-grade fever, cough with mucopurulent expectoration and increased dyspnea for 5 days. He was an active smoker for the last 15 years and a farmer by occupation. On admission, he was febrile with temperature of 103 °F, pulse rate was 130/minute and respiratory rate was 28/minute. He was in shock with blood pressure of 80/50 mm of Hg. The auscultation of the chest revealed bilateral normal vesicular breath sounds with bilateral rhonchi and crepitations over left infraclavicular and mammary areas. His chest radiograph in antero-posterior projection showed left upper zone consolidation. His blood investigation reports before starting antibiotics are enlisted in **(Table 1)**. His initial platelet counts were 1.1 lakhs/cumm. His liver function tests revealed slightly raised bilirubin with normal enzyme levels and kidney function tests were also altered (no previous history of renal disease) possibly due to sepsis. A working diagnosis of left upper lobe community acquired pneumonia with hypoxemic respiratory failure and septic shock was made. He was started on empiric antibiotics: amoxycillin and clavulanate at a dose of 1.2 gm intravenous thrice daily and oral azithromycin 500mg once daily. Other supportive treatment was given for respiratory failure and shock as per the ICU protocol. The patient continued running high grade fever 48 hours past antibiotic therapy. The sputum

and blood culture results were non-contributory. Also, there was further clinical deterioration hence his antibiotics were stepped-up to piperacillin and tazobactam 4.5 gm intravenous thrice daily and tigecycline 100mg intravenous stat dose followed by 50 mg twice daily. After 6 hours when the blood investigations were repeated during monitoring, his complete blood counts revealed a decline in his platelet counts to 18,000/cumm, then to 7000/cumm during the next 24 hours **(Table 2)**. However, there was clinical improvement as the fever gradually subsided over next 24 hours and shock also improved. Noradrenaline injection was tapered off over 12 hours. There were no bleeding complications or rash. The cause for worsening thrombocytopenia was searched. His Dengue serology came out to be negative. His liver enzymes were raised, there was prolongation in his prothrombin time (PT) and activated partial thromboplastin time (APTT) along with raised D-Dimer levels **(Table 2)** indicating the development of disseminated intravascular coagulation (DIC). Meanwhile multiple platelet transfusions were given which failed to raise his platelet counts. Tigecycline was suspected as the culprit drug for DIC after ruling out other causes. After reviewing the literature on tigecycline induced DIC, the drug was stopped, following which all the blood parameters improved over the next 24-48 hours. His platelet counts started to improve from 7000/cumm to 69,000/cumm over next 2 days and were completely normal by the time he got discharged from the hospital **(Table 2)**. During all this time, he never had any bleeding complications.

Table 1: Laboratory parameters of the patient on admission.

Base line investigations	Result
Haemoglobin	12.7 g/dl
Total leukocytes	2100 cells/cumm
Platelets	1,10,000/cumm
Random blood sugar	119 mg/dl
Liver function tests: Bilirubin SGOT SGPT Alkaline Phosphatase (ALP)	 1.5 mg/dl 66 U/L 46 U/L 54 U/L
Kidney function tests: Blood Urea Creatinine	 83 mg/dl 2.8 mg/dl
Proteins: Total Albumin	 6.3 g/dl 3.2 g/dl
Electrolytes: Sodium Potassium Chloride	 142 mmol/l 4.1 mmol/l 102 mmol/l
Serum Procalcitonin	>100 ng/ml

Discussion

Tigecycline induced DIC is one of the rarest and life-threatening complications which occurs hours to days after starting the drug. Bleeding is the most severe adverse effect but it is of rare occurrence. This adverse effect may present with prolongation of coagulation parameters or raised D-Dimer levels or with decreased platelet counts and fibrinogen levels[1]. Tigecycline induced coagulopathy is either due to direct inhibition of coagulation factor synthesis or due to the effect on the coagulation cascade. It presents as slow and progressive deterioration of the coagulation parameters. In our case stoppage of tigecycline led to improvement in the patient's coagulation parameters thus confirming it as tigecycline induced DIC. Our timely recognition of tigecycline as the culprit drug and its discontinuation led to save the patient from life threatening bleeding complications.

Table 2: Alteration of laboratory parameters indicating DIC after initiation of tigecycline and reversal to normal after drug discontinuation.

Laboratory parameter	After 12 hours	After 1 day	After 2 days	After stopping the drug
Total platelet count (cells/cumm)	18,000	7,000	7,000	35,000 on day1 69,000 on day2 1,26,000 on discharge
Liver enzymes SGOT (U/L) SGPT (U/L) ALP (U/L)		 235 157 149	 257 207 204	 55 60 55
Coagulation parameters PT (sec) APTT (sec) INR		 18.6 58 1.40		 13.7 40 0.95
D-Dimer (mcg/mL)		6.5		2.1

Tigecycline induced coagulopathy and thrombocytopenia is rarely reported in literature. To the best of our knowledge, till date a total of 13 case reports and four retrospective studies have been published regarding the same. Our case is unique as tigecycline induced coagulopathy presented within hours after starting the drug. Also, we found even with very low counts of platelets (7000/cumm.), the patient did not present with any bleeding complications.

The coagulopathy can occur while using tigecycline alone or in combination with other drugs. Tigecycline induced coagulopathy is both time and dose dependent. The higher doses and longer duration of tigecycline use increases the severity of this adverse event[2-5]. Tigecycline induced coagulopathy can present from day 1 till 39 days after initiation of the drug. Our patient developed the complication within hours of starting the drug.

Tigecycline induced DIC occurs more in patients with hepatic and renal impairment as the drug clearance is delayed in them. Tigecycline is mainly metabolized in the liver and is secreted in bile along with its metabolites[6,7]. The plasma clearance of tigecycline gets reduced by 25% and 55% respectively in moderate and severe hepatic impairment. Hence the dose adjustment is needed in severe hepatic impairment but not in moderate impairment. In our patient, only total bilirubin was mildly elevated with normal enzyme levels before initiating tigecycline, but the enzyme levels raised after initiation of tigecycline. Tigecycline dosage need not be adjusted in case of renal impairment[8,9]. Tigecycline have no action on renal function but the renal impairment prolongs the clearance time of the drug and the duration of drug activity leading to increased risk of tigecycline induced coagulopathy. In our patient, both the bilirubin levels and renal function tests were impaired initially which probably increased the risk of DIC.

Vitamin K administration does not show to improve the coagulopathy[10,11]. The abnormal coagulation parameters resolve

spontaneously after the discontinuation of the drug. If bleeding complications occur during the drug therapy, best measure is to stop the drug immediately and to infuse blood products. The timely action in our case prevented the development of bleeding complications even with severe thrombocytopenia and the patient discharged safely after resolution of DIC and pneumonia.

Conclusion

Tigecycline induced DIC is a rare adverse event that can occur within hours of starting the drug. This adverse effect is seen mostly in patients with hepatic and renal impairment. The stoppage of the drug helps in recovery. It is important to keep in mind the possible adverse effects drugs can cause, even if they are rare and act timely which can prevent life threatening complications.

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