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ORIGINAL RESEARCH

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Tigecycline versus INR increase; more than expected?

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ABSTRACT

Objectives: The aim of the study was to investigate the frequency of tigecycline-associated INR abnormality.
Methods: Patients who were hospitalized between June and September 2016 and treated with tigecycline including therapy were extracted from hospital database and retrospectively reviewed. INR values at the beginning and end of treatment were compared.
Results: A total of 79 patients who received tigecycline were identified by analyzing the hospital database. Nineteen patients were excluded from the study since INR was not measured at the beginning and/or end of treatment. In 55 of the 60 patients, INR levels were within normal limits (0.9–1.2) at the beginning of treatment while 19 of these 55 (34,5%) had prolonged INR after treatment. Prolongation was found to be mild (1.01–1.25 x ULN-upper limit of normal) in 12 of 19 patients, moderate (1.26–1.5 x ULN) in six and severe (1.51–3.0 x ULN) in one. In 10 of 19 patients, tigecycline was stopped, and the INR values normalized. There was no difference in INR abnormality rate between tigecycline monotherapy versus combination therapy receiving cases (19/27–33% vs. 10/33–30% p:1).
Conclusion: These data show that INR prolongation may develop as common as 34.6% during tigecycline therapy. Regular INR follow-up may be beneficial in cases receiving tigecycline.

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Tigecycline; adverse events; INR; coagulation disorder; prothrombin time

1. Introduction

Tigecycline, which is a tetracycline derivative, is the first example of the glycylcycline group antibiotics. It has a wide antibacterial spectrum including multidrug-resistant (MDR) infections such as methicillin-resistant *S. aureus*, vancomycin-resistant Enterococci, and *Acinetobacter* spp. United States Food and Drug Administration (FDA) approved its use for the treatment of complicated skin and soft tissue infections, complicated intraabdominal infections, and community-acquired bacterial pneumonia. However, it is used in off label indications commonly such as nosocomial pneumonia, meningitis, bacteremia, and spondylodiscitis due to its pharmacological and microbiological efficacy [1–3]. The frequency of tigecycline use has also increased over the last years [4].

Side effects associated with gastrointestinal system, especially nausea and vomiting are common during tigecycline therapy (>% 10) [5]. Increased prothrombin time/INR (international normalized ratio) and partial thromboplastin time are considered as rare side effects (<2%). However, there are case reports showing that tigecycline can induce coagulopathy by disrupting coagulation parameters [6–10]. In our daily clinical practice, the effect of tigecycline on INR prolongation was observed to be higher than 2% and this study was planned. Herein, we aimed to investigate the frequency of coagulation disorder side effect of tigecycline.

2. Patients and methods

The patients who received standard dose (after 100-mg loading dose, 50 mg, every 12 h) tigecycline treatment with different indications in the Oncology, Neurosurgery, and Infectious Diseases Clinics of our hospital between June and September 2016 were retrospectively analyzed. INR values at the start and end of tigecycline therapy were compared.

Patients who were aged over 18 years and treated with the original molecule (Tygacil, Pfizer) at the standard dose (100 mg loading dose after 50 mg, 12-h interval) were included in the study. Prolongation of INR was evaluated according to American National Institute of Allergy and Infectious Diseases Division of Microbiology and Infectious Diseases (DMID) criteria [11] and 1.01–1.25-fold increase in the upper limit of normal was considered as mild, 1.26–1.5-fold increase as moderate and 1.51–3-fold increase as severe degree. Patients with prolongation of INR according to baseline value were evaluated for impairment of liver function tests, underlying liver disease, concurrent use of other antibiotics and/or hepatotoxic drugs, and improvement in INR when tigecycline was discontinued.

Chi-square test was used for statistical comparison and a p-value <0.05 was considered to be significant.

3. Results

A total of 79 patients who received any tigecycline including treatment in accordance with the study criteria were identified. Nineteen patients were excluded from the study since they had no INR data at the beginning and/or the end of their treatment.

Of the remaining 60 cases, 27 received tigecycline monotherapy while 33 received tigecycline including combination

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therapy. In 55 of the 60 patients, INR levels were within normal limits (0.9–1.2) at the beginning of treatment while 19 of 55 (34,5%) had prolonged INR after tigecycline treatment. Of these 19 patients, 7 (36.84%) were female. Twelve of 19 patients had mild (1.01–1.25 x ULN), while 6 of them had moderate (1.26–1.5 x ULN), and one had severe (1.51–3.0 x ULN) INR prolongation. In 10 of 19 patients, tigecycline was stopped, and the INR values returned to normal. One of the patients with prolonged INR was found to have a co-morbid disease (liver neoplasm). In two patients, rifampicin was used concurrently with tigecycline. None of the cases developed clinically manifesting bleeding.

There was no significant difference between the rates of INR prolongation in patients receiving tigecycline monotherapy (9/27–33%) and multiple antibiotics (10/33–30%) (p: 1).

4. Discussion

Prothrombin time/INR tests are being used for evaluating the functions of plasma proteins involved in the coagulation pathway. These tests mainly detect deficiencies of the extrinsic and common pathway factors 1 (fibrinogen), 2 (prothrombin), 5, 7, 10, and to monitor vitamin K antagonist drug therapies. In clinical practice, PTZ/INR may prolong due to the lack of coagulation factors' synthesis (liver disease), proteolytic depletion (disseminated intravascular coagulopathy), and the presence of enhanced antibodies to coagulation factors or phospholipids [12]. However, to our knowledge, there are no data illuminating the cause of tigecycline-induced coagulation disorder.

Side effects of tigecycline use are quite common but data evaluating its effect on coagulation are inadequate. It was reported by the FDA that the prolongation in INR is one of the rare tigecycline-associated side effects [4]. In a meta-analysis by Shen et al., 12 randomized controlled trials with a total of 6292 patients were investigated. In studies that compared tigecycline with a control drug, the rate of side effects was significantly higher in the tigecycline group (OR = 1.49, 95% CI = 1.23 to 1.80, $P < 0.0001$). In side effect subgroup analysis, while metabolic, hematological, and lymphatic system-associated side effects were not significantly more common, the digestive-system-associated side effects were statistically more frequent [13]. Coagulation disorder was reported as a side effect in only one study and the INR prolongation rate was 4.8% in the tigecycline group and 1.8% in the control group (p not specified) [14]. In a systematic review by Yahav et al., bleeding disorder was observed in 9 of 1279 patients receiving tigecycline, while it was seen in 14 of the 1284 patients in the comparison arm. However, the cause of bleeding disorder was not reported in this study and it is not clear whether this was the cause of the coagulation disorder or not [15].

Leng et al. analyzed 50 patients retrospectively to evaluate the effect of tigecycline on coagulation. They reported that tigecycline treatment decreased fibrinogen and increased APTZ and PZ mean values compared to the beginning of treatment. This difference was found to be statistically significant ($p < 0.001$, $p = 0.002$ and $p = 0.004$, respectively). In that study, 36.72% decrease in mean fibrinogen level, 11.29% and 6.51% increase, respectively, in aPTT and PT mean values were reported, whereas in our study, the rate of INR prolongation was 34.5% [16]. In our cohort cases were not checked in terms of fibrinogen levels.

In the literature, there are also few case reports with tigecycline-related coagulation disorder. Wu et al. presented a case, who was treated high dose tigecycline for treatment of severe acute cholangitis and septic shock and developed coagulation disorder and hypofibrinogenemia at the second day of treatment [17]. In the same paper, the authors discussed three other case reports presenting the same adverse reactions associated with tigecycline [6–8]. Considering these case reports, it was emphasized that female sex, renal failure, and high dose tigecycline use may be risk factors for these adverse reactions. But, in our cohort, the majority of patients (12/19) were male, and only one patient had renal failure. In addition, only patients who were treated with standard dose tigecycline were included in the study. We believe that this difference is due to the sample size and the risk factors may be defined more accurately by newer randomized controlled studies including larger cohorts or analyzing deeply the already performed ones.

In the presented study, cases were evaluated in terms of co-morbidities that may cause INR prolongation, and those whose initial INR level was above normal were excluded from the study. None of the cases had a diffuse bleeding disorder. One of the patients had comorbidity (liver malignancy/disease) that could cause prolonged INR and two had concurrent use of rifampicin with tigecycline. There was no difference in INR abnormality rate between tigecycline monotherapy and combination therapy receiving cases. Similarly, in the study of Leng et al., patients receiving tigecycline and cefoperazone/sulbactam combination therapy and patients receiving monotherapy were compared and the changes in fibrinogen, APTZ, and PZ levels were reported to be similar in both groups [15]. These findings support that coagulation disorder is highly probably caused by tigecycline.

4.1. Limitations

Our study is a well-defined cohort treated with standard doses of the original tigecycline molecule but has several limitations. Importantly, it was a retrospective analysis and only the INR was included in the evaluation for the coagulation disorder. At the same time, the cohort's overall comorbidities and indications for tigecycline use and duration of the treatment were not standardized. Furthermore, there were co-therapy treatments that could affect the physiological parameters evaluated, although they did not make coagulopathy. However, due to lack of adequate data in the literature, we believe that our study is important and may be a guide for larger prospective cohort analysis, or subgroup analysis of available data in the tigecycline randomized controlled studies to further clarify the possible importance of tigecycline-related coagulopathy.

5. Conclusion

Although tigecycline is a preferred antibiotic in daily practice, coagulopathy side effects can be ignored. Our data show that the side effect of INR prolongation may be as high as 34,6%. Our findings suggest that regular INR follow-up may be beneficial in cases receiving tigecycline.

Author contributions

D Akdag and OR Sipahi were involved in the conception and design, analysis and interpretation of the data and writing manuscript. H Sipahi contributed to data analysis, data interpretation. MI Taşbakan and H Pullukçu contributed to study patients and critical revisions in the manuscript for important intellectual content. All authors provided the final approval of the manuscript for submission.

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Declaration of interest

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• **This is report of a case with coagulopathy and hyperfibirinogenemia**