Case Report
Volume 13:01, 2023

Clinical Case Reports

ISSN: 2165-7920 Open Access

Tigecycline-Induced Triad of Adverse Effects: Acute Pancreatitis, Drug Reaction with Eosinophilia and Systemic Symptoms and Thrombocytopenia – A Rare Case Report

Khalil Zahalka* and Tsvi Gregory Avishai

Department of Clinical Pharmacy, Tel-Aviv Sourasky Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Abstract

Reports about Tigecycline-induced acute pancreatitis are raising, Tigecycline-induced thrombocytopenia and hypersensitivity reactions are also fairly reported leading to severe clinical complications. We report a rare case of a triad adverse effects associated with Tigecycline treatment in a 5-year-old boy who received Tigecycline for treatment of disseminated mycobacterium abscessus within three months. Tigecycline was a leading cause for all three adverse effects especially acute pancreatitis based on the Naranjo adverse drug reaction probability scale, adverse effects were addressed by a multidisciplinary team and even discontinuation of Tigecycline was done twice with a desensitization re-challenge protocol. Clinicians should be aware of these possible adverse effects especially acute pancreatitis and mainly in high-risk patients.

Keywords: Tigecycline • Pancreatitis • Thrombocytopenia • DRESS • Adverse effects • Adverse reactions

Introduction

Assessing, monitoring and preventing of adverse drug reactions and drug-induced diseases is the cornerstone of the pharmacovigilance field of practice [1].

Clinical assessment of drug-induced diseases is challenging for healthcare providers since management tools are limited and better understanding of the mechanisms responsible for induction such reactions is important, side by side with reviewing medical history, imaging, physical manifestation and laboratory tests [2].

Acute pancreatitis is a common gastrointestinal complication caused mainly by gallstones, excessive alcohol intake, hypertriglyceridemia and rarely by medications, approximately 0.1 -2% of total cases [3].

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a hypersensitivity reaction manifested mainly by a wide-scale skin rash and fever [4] with involvement of visceral organs, lymphadenopathy, eosinophilia and atypical lymphocytosis [5,6]. The clinical presentation is diverse, characterized by lengthy latency of approximately two to eight weeks post exposure to the provoking drug [7]. Its incidence is more likely seen in children compared to adult population [8].

Compared to drug-induced acute pancreatitis and DRESS, drug-induced thrombocytopenia is a common complication and it can be a continuation of bone marrow suppression or immune-mediated destruction [9].

Tigecycline is a bacteriostatic antibacterial related to tetracycline's class and it is mainly for the treatment of polymicrobial multidrug-resistant infections or extensively drug-resistant bacterial pathogens [10].

***Address for Correspondence:** Dr. Khalil Zahalka, Department of Clinical Pharmacy, Tel-Aviv Sourasky Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, Tel: 972527719673; Email: zakhaleel@gmail.com; khalilz@tlvmc.gov.il*

Received: 16 January, 2023; Manuscript No. jccr-23-87191; **Editor Assigned:** 17 January, 2023; PreQC No. P-87191; **Reviewed:** 24 January, 2023; QC No. Q-87191; **Revised:** 27 January, 2023, Manuscript No. R-87191; **Published:** 30 January, 2023, DOI: 10.37421/2165-7920.2023.13.1545

Its pharmacokinetic doesn't altered by age, sex and renal function but it does by hepatic function. The main elimination is through biliary excretion in the feces, approximately 59% [11]. Its main side effects are gastrointestinal symptoms [12] and a significant high rate of pancreatitis including fatalities was reported [13]. Cases have been reported in patients without known risk factors for pancreatitis [14].

Thrombocytopenia reported in less than 2% of the patients who received Tigecycline in clinical trials [14] but a recent retrospective study demonstrated a significantly higher rate, about 12.3% [15].

Multiple cases were reported about tetracycline-induced DRESS, most are related to Minocycline but a possibility of tetracycline cross-reactivity with DRESS is plausible [16]. One case described Tigecycline-induced coagulopathy and DRESS which resolved after Tigecycline cessation [17].

We report and discuss a rare clinical case for the first time in medical literature of Tigecycline-induced acute pancreatitis, DRESS and thrombocytopenia. Three heterogeneous adverse reactions in one patient during hospitalization period of three months.

Case Report

A 5-year-old boy whom diagnosed with a background of acute myeloid leukemia after B-cell acute lymphoblastic leukemia was treated with accepted chemotherapy protocols and an allogeneic hematopoietic stem cell transplantation (HSCT) after that.

On September 2022, the patient was transferred from the intensive care unit after a bronchoscopy and bronchoalveolar lavage due to suspected pulmonary findings to the pediatric Hematology and Oncology department in Tel-Aviv SOURASKY medical center.

A decision for a second HSCT was made and he received a proper preparation. A week after transplantation acceptance, the patient was feverish with noticeable skin lesions, a biopsy from the lesion returned negative for microorganism cultivation and growth.

A Magnetic resonance imaging was performed, arthritis and osteomyelitis were demonstrated which approved a wide-scale infectious process in the left elbow along with synovitis, disseminated mycobacterium was approved according to positive blood cultures.

Due to these findings, Tigecycline was added to the anti-infectious

treatment combination which included Imipenem, Amikacin, Isavuconazole, Linezolid and Maribavir.

A week after Tigecycline initiation, a diffused eczematous rash appeared which was reviewed by an infectious specialist, a dermatologist and an allergist, they recommended treatment with anti-histamine and a topical corticosteroid.

Three days after that, eosinophilia was observed and eosinophils levels were 1.1x10^3/μL (normal levels = 0 – 0.6 x10^3/μL) along with elevated hepatocellular functions by laboratory tests. Aspartate aminotransferase and Gamma glutamyltransferase were measured, 49 U/L (normal levels = 7 – 40 U/L) and 57 U/L (normal levels = 6 – 42 U/L) respectively.

Alkaline phosphatase was also elevated, 458 U/L (normal levels = 141.80 – 336.40). Thrombocytopenia also apparent, platelets count was 88 x10^3/μL (normal levels = 150 – 450 x10^3/μL).

Inguinal lymph nodes in the groin were also enlarged and DRESS was suspected, Tigecycline treatment was stopped and replaced with Clofazimine.

Five days after that, laboratory values of Aspartate aminotransferase, Gamma glutamyltransferase and eosinophils returned to normal levels and the rash area was narrowed proportionally. The platelets count was elevated and the thrombocytopenia resolved.

Three months after these findings, a culture rich with disseminated mycobacterium was still evident, uncontrolled with worsening symptoms.

A decision to renew treatment with Tigecycline was made according to a desensitization protocol and the re-challenge was successful, Clofazimine treatment was stopped.

Nearly a month after renewing a treatment with Tetracycline, the patient presented gastrointestinal discomfort, nausea, recurrent diarrheic episodes and acute pancreatitis diagnosis was suspected.

Sample for Cytolethal distending toxins, Rotavirus and bacteria was tested and abdominal Computed Tomography imaging showed a mild infiltration around the pancreas without pathological biliary involvement.

Laboratory findings showed a remarkable elevation in lipase levels 1160 U/L (normal levels = 12 – 51 U/L) and amylase levels 559 U/L (normal levels = 20 – 104 U/L) and recurrent thrombocytopenia with platelets count of 88 x10^3/μL (normal levels = 150 – 450 x10^3/μL).

A clinical pharmacist consultation was made regarding the possibility of Tigecycline-induced acute pancreatitis and a rigorous screening of primary literature led to conclusion that Tigecycline could be a paramount cause and an infectious disease specialist opinion is needed again to make an informed decision.

An infectious disease specialist decided to stop treatment with Tigecycline without replacement to any medication. Less than two days after discontinuation of Tigecycline, lipase and amylase levels dropped significantly to 65 U/L each and normalized, thrombocytopenia subsided.

It is also worth noting that a feces sample after that returned positive for cryptosporidium antigen. Our case in not considered as a clinical trial or medical research but rather a procedure description without sharing identifying data and the institutional ethical committee exempted us from the need to review after presenting the case report to them.

Discussion

Our case we describe required a multidisciplinary intervention by a pediatric Hematology oncologist, an infectious specialist, an allergist, a dermatologist, an immunologist, a toxicologist, a pediatric surgeon and a clinical pharmacist. Each teamed to make an informed decision regarding the progression of the patient's situation and due to a high-risk defined patient, who was also immunocompromised.

Acute pancreatitis etiology includes mainly gallstone in 40 - 70% of documented cases [18], chronic alcohol use accounts for approximately 25% to 35% of cases in the United States [19], hypertriglyceridemia and hypercalcemia [20]. None of them was relevant in the mentioned case and all were ruled out, it is slightly probable that this acute pancreatitis case is associated to parasitic infection with Cryptosporidium since such infections can elaborate the findings but limited data regarding the frequency these infections leading to acute pancreatitis [21].

Moreover, using the Naranjo adverse drug reaction probability scale [22], a high score is recorded (score=9) which indicates definite cause and relation although taking Cryptosporidium infection as a cause for acute pancreatitis into consideration. Also, the significant drop seen in lipase and amylase levels on laboratory tests only within less than two days after stopping treatment with Tigecycline strengthens the causality contrary to other case reports in medical literature which describes longer periods for acute pancreatitis markers to normalize.

Hung, et al. [23] demonstrated normalization of lipase levels after 36 days of discontinuation of Tigecycline while Lipshitz, et al. [24] showed decline in lipase and amylase concentration on day 5 after discontinuation.

A recent study by Wolfe, et al. [25] classified Tigecycline with a Class 1A in drug classification system for assessment of association with drug induced pancreatitis which means that there is at least one case report in humans, with positive re-challenge and all other causes including other drugs are ruled out.

Ten cases were reported by Wolfe, et al. [25] and we screened them all [23-24, 26-31], all of them were case reports in adults with ages ranging from 22 to 70 years old and onset of symptoms of acute pancreatitis ranging from 6 days to 4 weeks. In conclusion, we assume that Tigecycline-induced pancreatitis can strike both genders with non-uniformity of onset and symptoms.

Only one case of drug induced pancreatitis was reported in the pediatric population, a 9-year-old with a background of sickle-cell anemia and cholecystectomy who was fed by parenteral nutrition [32] that may contributed to the reaction as declared by authors.

The mechanisms interpret the pathophysiology of Tigecycline-induced pancreatitis suggested to be due to high bile concentrations, hypertriglyceridemia and producing toxic metabolites [33]. Accumulation of unidentified toxic metabolite due to hepatotoxic agents that can provoke idiosyncratic reactions and cause acute but not chronic pancreatitis [34].

The bacteriostatic activity of Tigecycline is described by inhibiting the 30S ribosomal subunit that could result in accumulation of damaged proteins in the liver which leads to inhibition of triglycerides release and eventually pancreatitis [23].

As mentioned earlier, the main elimination route of Tigecycline is by biliary excretion [11] and high bile concentration may be associated with acute pancreatitis, it is observed that bile concentration of Minocycline is 10 times higher than concurrent serum concentrations after a loading dose and a maintenance dose after that [23]. Due to similarity in chemical structure of Minocycline and Tigecycline, an extrapolation was made regarding high bile concentration of Tigecycline also [23].

Upon these findings, monitoring and expecting acute pancreatitis symptoms and markers is pivotal when planning treatment with Tigecycline.

It is noteworthy that acute pancreatitis is a well-known complication after HSCT and is related to high rate of morbidity and mortality (overall rate of 14.9%) either due to use of conditioning chemotherapeutic medications which leads to acinar cell injury and acute pancreatitis or high propensity of infection by opportunistic microorganisms. Also, the development of graft-versus-host disease and increased length of survival post-transplant can contribute to the emergence of acute pancreatitis in such population [35].

In our case we report, the patient didn't undergo acute pancreatitis due to the transplantation process, he was transplanted twice due to graft failure, according to imaging, physical examination and laboratory tests. Acute pancreatitis occurred after the second transplantation and aggravated adjacent to Tigecycline initiation and blatantly resolved after discontinuation.

Likewise, HSCT is associated with high rate of prolonged isolated thrombocytopenia (5-20%) [36], suspected Tigecycline-induced thrombocytopenia in our case was prominent twice adjacent to two courses of Tigecycline treatment. Moreover, international normalized ratio was prolonged (result = 1.23) overlapping with decreased platelets count.

A possible mechanism for international normalized ratio prolongation by Tigecycline is decreasing the synthesis of vitamin K due to gastrointestinal flora alteration [37]. Hypofibrinogenemia can also occur when administrating Tigecycline because it can reduce the levels of interleukin-6 and tumor necrosis factor-alpha and interfere with interleukin enhanced biosynthesis of fibrinogen resulting in reduced production of blood clots [38].

Using the Naranjo adverse drug reaction probability scale [22] for estimating Tigecycline-induced thrombocytopenia resulted in a score of 8, which indicated a probable relation and causality, we took into consideration that thrombocytopenia is a common complication of HSCT in the estimation.

Tigecycline hypersensitivity reactions can be Immunoglobulin-E mediated and non-Immunoglobulin-E mediated, both mechanisms are described and DRESS is referred to as non-Immunoglobulin-E mediated reaction [39].

Tigecycline is a tetracycline antibiotic and a cross-reactivity resulting in DRESS is possible, forming a complex with Melanin is another explanation for such reactions etiology [40]. Even though tetracycline-induced DRESS occurs generally with Fitzpatrick skin phototypes V and VI [16], the patient mentioned in our report was not with such a phototype.

The Naranjo adverse drug reaction probability scale [22] for estimating Tigecycline-induced DRESS resulted in a score of 5 which indicated a probable relation, we considered that the patient received multiple antibiotics and antivirals in the estimation.

After the first observation with Tigecycline-induced diffused eczematous rash, a decision was made by a multidisciplinary consensus not to stop treatment with Tigecycline or any other antibiotics, antivirals and antifungals in the treatment plan even though it is suspected as a drug-induced reaction because it was crucial and life-saving and to rely on symptomatic treatment.

The observation of suspected DRESS led to a multidisciplinary decision to stop treatment with Tigecycline, ruling out a herpetic viral cause of DRESS was made because the patient has a cytomegalovirus reactivation much longer before appearance.

To our best knowledge, this is the second case reported about Tigecycline-induced acute pancreatitis in children but the first included DRESS and thrombocytopenia performing a triad and resolving after discontinuation.

Conclusion

Reports regarding Tigecycline-induced acute pancreatitis are increasing. No enough data are available about specific markers to predict it in clinical management neither for the exact mechanism to explain it, same for Tigecycline-induced DRESS and thrombocytopenia. Future studies are needed for a detailed description of the mechanisms of how Tigecycline causes such adverse effects. Knowledge of these adverse effects and addressing them appropriately by a multidisciplinary approach is important. For Tigecycline-induced acute pancreatitis, we agree that diagnosis of acute pancreatitis should be considered in patients taking Tigecycline who develop clinical symptoms, signs, or laboratory abnormalities suggestive of acute pancreatitis.

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How to cite this article: Zahalka, Khalil and Tsvi Gregory Avishai. "Tigecycline-Induced Triad of Adverse Effects: Acute Pancreatitis, Drug Reaction with Eosinophilia and Systemic Symptoms and Thrombocytopenia – A Rare Case Report." *Clin Case Rep* 13 (2023): 1545.