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*Case Report*

# Severe hypoglycemia induced by Tigecycline in a diabetic and hemodialysis patient

Entela Puca[1,2], Edmond Puca[3], Klei Vrekaj[4], Dea Puca[5]

[1] *Department of Internal Medicine, Service of Endocrinology, American Hospital, Tirane, Albania*
[2] *Western Balkans University, Tirane, Albania*
[3] *Service of Infection Diseases, University Hospital Center, Tirane, Albania*
[4] *Service of Intern Medicine, American Hospital, Tirane, Albania*
[5] *Catholic University "Our Lady of Good Counsel" Tirane, Albania*

## Abstract

Introduction: Tigecycline has a broad spectrum of activity, including activity against drug-resistant Gram-positive and -negative microorganisms. Its side effects are significant, but hypoglycemia is a rare finding during treatment. We aim to present an event of severe hypoglycemia in a patient with type 2 diabetes mellitus with replacement renal therapy, and hemodialysis after initiating tigecycline.

Case presentation: A 54-year-old female diagnosed with type 2 diabetes mellitus was under treatment with basal-bolus insulin therapy and oral antihypertensive drugs. She started hemodialysis 24 months ago. She complained of recurrent fever for the last seven months and was treated with several antibiotics. In two separate blood cultures, she tested positive for methicillin-resistant *Staphylococcus epidermidis* (MRSE). Based on the antibiogram, we started treatment with tigecycline 100 mg/day. After 6-8 hours from the first dose, the patient is complicated with events of hypoglycemia and then continues with severe hypoglycemia (40-47 mg/dL). The patient continued to have hypoglycemia for about 16-18 hours after the last dose. We didn't find any reasons to explain the cause of episodes of hypoglycemia. She did not have high blood insulin levels (insulin 4.11 mIU/L [range 2.6-24.9]). We followed her for six months and the patient did not experience episodes of hypoglycemia.

Conclusions: The association of severe hypoglycemia with tigecycline treatment is a very rare event and published papers on this topic are limited. Clinicians should be aware of this rare event when administering tigecycline and should routinely check blood glucose level during the treatment.

**Key words:** Tigecycline; Staphylococcus epidermidis; antibiotic resistance; hemodialysis; severe hypoglycemia.

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## Introduction

Tigecycline, a derivative of minocycline, is a broad-spectrum antibiotic belonging to the glycylcycline class that inhibits protein synthesis by binding to the 30S ribosomal subunit of bacteria. This prevents the incorporation of amino acid residues into elongating peptide chains [1,2]. Tigecycline should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. It has activity against resistant strains of gram-positive bacteria like methicillin-resistant *Staphylococcus aureus* (MRSA), *Staphylococcus epidermidis* (MRSE), vancomycin-resistant *Enterococcus faecalis and faecium* (VRE), penicillin-resistant *Streptococcus pneumoniae*, and gram-negative bacteria like *Escherichia coli*, *Klebsiella pneumonia, Acinetobacter*, and *Enterobacter cloacae* [3,4]. The primary route of elimination of unchanged tigecycline is biliary excretion whereas glucuronidation and renal excretion are the secondary routes. No dosage adjustment is required in patients with renal impairment or hemodialysis patients because tigecycline is not removed by hemodialysis [2]. Adverse effects reported in VigiAccess, from 6342 reports with the use of tigecycline are: gastrointestinal disorders (23%) led by nausea/vomiting and diarrhea; general disorders and administration site conditions (10%) led by ineffectively and pyrexia; skin and subcutaneous tissue disorders (8%) led by rush and pruritis; hepatobiliary disorders in 7% and other side effects. Hypoglycemia is a rare adverse effect, with only 47 such events reported in this

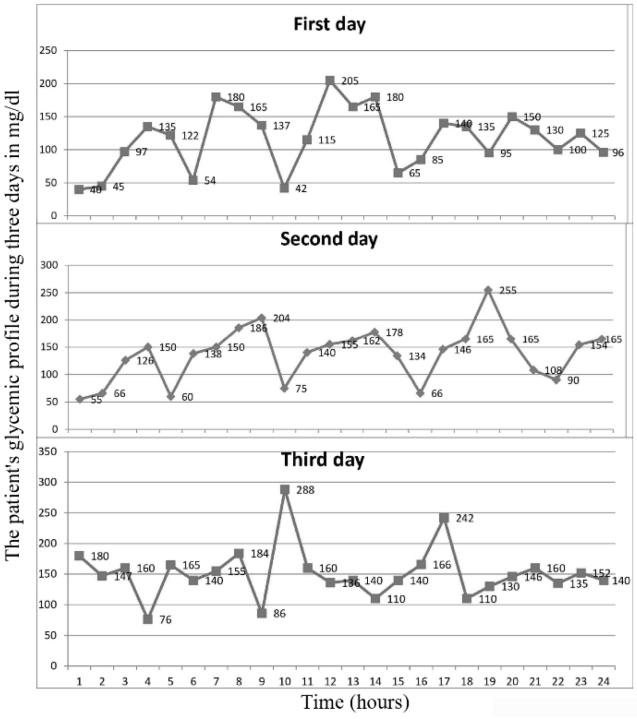
database to date (Uppsala Monitoring Centre VigiAccess™) [5–7]. Even though hypoglycemia is a known adverse effect of some antibiotics, severe hypoglycemia is a very rare adverse effect [8–12]. It is defined by glycemia < 70 mg/dL and inability to function, because of mental or physical changes and requires assistance [13,14].

We report a case of severe hypoglycemia in a diabetic hemodialysis patient treated with tigecycline for a *Staphylococcus epidermidis* (MRSE) infection.

## Case presentation

A 54-year-old female complained of intermittent fever for more than seven months. She was diagnosed with type 2 diabetes mellitus and hypertension for over 15 years. In the last years, her health was complicated with end-stage renal disease and hemodialysis too. She had access to thrice-weekly scheduled hemodialysis. During the last seven months, the patient was treated with several antibiotics (cephalosporins of third and fourth generation, vancomycin, clindamycin, fluoroquinolones, etc.) but no pathogen was isolated. Firstly, we started ceftriaxone 2 g/day for seven days, followed by cefepime 2 g/day. The patient continued to have fever. At that time vancomycin 1 gram after every dialysis session was used for ten days. After that clindamycin and ciprofloxacin were used separately for another ten days. Except for fever the patient did not have any other complains. Laboratory test results showed:

**Figure 1.** Episodes of hypoglycemia day by day for three days.




hemoglobin level was 10 g/dL (range 13.0-16.5 g/dL); total WBCs were 14.68 × $10^9$/L (range 4-10.5 × $10^9$/L) [neutrophils 82%, lymphocytes 17%]; platelet count was 230 K/μL (range 150-400 K/μL); blood urea was 277.83 mg/dL (range 0-50 mg/dL); serum creatinine was 12.0 mg/dL (range 0.57-1.11 mg/dL); serum sodium 140.00 mEq/L (range 136 – 148 mEq/L); potassium 6.6 mEq/L (range 3.7-5.5 mEq/L); calcium 9.14 mg/dL (range 8.4-10.2 mg/dL); HbA1c was 6.5% and procalcitonin level was 2.01 ng/mL (range 0-0.5 ng/mL = no sepsis; >

**Table 1.** Naranjo algorithm score

| | Question | YES | NO | Do Not Know | Patient score |
|---|---|---|---|---|---|
| 1 | Are there previous conclusive reports on this reaction? | +1 | 0 | 0 | 0 |
| 2 | Did the adverse event appear after the suspected drug was administered? | +2 | -1 | 0 | +2 |
| 3 | Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered? | +1 | 0 | 0 | +1 |
| 4 | Did the adverse event reappear when the drug was re-administered? | +2 | -1 | 0 | 0 |
| 5 | Are there alternative causes (other than the drug) that could on their own have caused the reaction? | -1 | +2 | 0 | +2 |
| 6 | Did the reaction reappear when a placebo was given? | -1 | +1 | 0 | +1 |
| 7 | Was the drug detected in blood (or other fluids) in concentrations known to be toxic? | +1 | 0 | 0 | 0 |
| 8 | Was the reaction more severe when the dose was increased or less severe when the dose was decreased? | +1 | 0 | 0 | 0 |
| 9 | Did the patient have a similar reaction to the same or similar drugs in any previous exposure? | +1 | 0 | 0 | 0 |
| 10 | Was the adverse event confirmed by any objective evidence? | +1 | 0 | 0 | +1 |
| | Total patient score | | | | +7 |

2 ng/mL = sepsis). Parameters of liver function were normal. Based on our radiologic investigation (total body CT scan, transthoracic, and transesophageal echocardiography) we excluded a connection between fever and any abscess. However, in two separate blood cultures, *Staphylococcus epidermidis* (MRSE) sensitive to tigecycline was isolated. After 6-8 hours from the first dose, the patient's condition worsened with events of hypoglycemia followed by severe hypoglycemia (40-47 mg/dL). On the next day, the patient was afebrile. She experienced other episodes of severe hypoglycemia in the following days (Figure 1).

Treatment with tigecycline lasted for three days. The patient had hypoglycemic events almost all the time. Based on our investigation, we didn't find any reasons to explain the cause of episodes of hypoglycemia. Her insulin-like growth factor (IGF-1) was normal at 206.0 nmol/L (range 49.6–204 nmol/L), C peptid level was 1.82 ng/mL (< 5.19 ng/mL), cortisol level was 724 nmol/L (range 68.2-327 nmol/L) and ACTH level was 25.70 pg/mL (range 7.2-63.3 pg/mL). The patient did not have a high level of insulin in the blood (insulin 4.11 mIU/L [range 2.6-24.9 mIU/L]). The patient continued to have hypoglycemia episodes for about 16-18 hours after the last dose. Gradually her condition started improving. We followed her for six months and the patient did not experience episodes of hypoglycemia.

## Discussion

Fever in hemodialysis patients must be investigated properly. The chances of contamination from the apparatus and the hemodialysis procedure are high. In patients who develop fevers it is important to obtain blood cultures from different sites and to repeat the analysis afterwards [15]. In this case, we insisted on blood culture and isolated a pathogen. VigiAccess is a WHO web application that allows anyone to access information and report adverse effects from medicinal products [5]. As mentioned above, there are reported several cases of hypoglycemia after antibiotics use (doxycycline, clarithromycin, fluoroquinolones, trimethoprim/sulfamethoxazole), but severe hypoglycemia connected with tigecycline is a rare event [7–10,12]. The first episode of hypoglycemia in this patient happened 6-8 hours after the first dose of tigecycline. These hypoglycemia episodes persisted for 16-18 hours after cessation of the antibiotic despite supportive care, which matches the antibiotic half-life. Her glucose level was normal before tigecycline administration, fell after administration, and was persistently low for the whole duration of therapy, trending up after tigecycline cessation. Our patient was not on insulin therapy since starting tigecycline, however, she was on rapid and basal insulin before tigecycline administration. On the other hand, the insulin level was normal. We did not confirm any drug-to-drug reaction to explain hypoglycemic events. The patient was classified between 5-8 on the Naranjo algorithm score (Table 1).

A score of 7 indicated that a "probable" relationship exists between tigecycline administration and severe hypoglycemia. None of the other medications co-administered (antihypertensive drugs) with tigecycline during treatment were known to cause hypoglycemia. The patient continued with the same therapy after tigecycline treatment. All these factors suggest that tigecycline was the only drug that caused episodes of severe hypoglycemia.

Ray *et al.* hypothesized that the cause of hypoglycemia is a release of insulin from the islet beta cells of the pancreas, suppression of alpha-glucosidase and alpha-amylase and/or increase of insulin sensitivity [11]. Another approach that we did not pursue would have been to re-initiate the treatment with tigecycline and monitor for further hypoglycemia episodes.

## Conclusions

We report a case of a diabetic patient with end-stage renal disease on hemodialysis that experienced severe hypoglycemia episodes induced by tigecycline. To our knowledge, this is one of the few cases of sustained severe hypoglycemia due to tigecycline. Severe hypoglycemia is a serious event and immediate intervention is needed to correct it otherwise the outcome can be fatal. The reason why we are presenting is to bring awareness to other clinicians.

Further investigations are needed to clarify the underlying reactions caused by tigecycline.

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## Corresponding author


Edmond Puca, MD, PhD
Service of Infection Diseases,
University Hospital Center, Rruga e Dibres no 370.
Postal code 1007. Tirane, Albania
Tel: +355684062820
Email Address: edmond_puca@yahoo.com


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