

Delirium induced by tigecycline treatment for *Acinetobacter baumannii* infection

A case report

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Abstract

Rationale: Tigecycline is a broad-spectrum antimicrobial agent structurally belong to tetracyclines and covers against many multidrug-resistant organisms. Arising clinical cases reporting its adverse drug reactions have emerged alongside with the increasing off label use globally. By literature review, delirium caused by tigecycline has not been reported yet. We present what we believe to be the first case of tigecycline-induced delirium.

Patient concerns: A 77-year-old male patient with end-stage renal disease was hospitalized due to acute exacerbation of chronic obstructive pulmonary disease.

Diagnosis: The patient developed delirium after infused with a loading dose of tigecycline for pulmonary infection.

Interventions: All potential causes inducing delirium were evaluated and the symptoms improved soon after discontinuation of tigecycline. He experienced delirium once again after reusing tigecycline for the exacerbation of the pulmonary infection even without a loading dose. Tigecycline was discontinued and the symptoms quickly relieved.

Outcomes: According to the Naranjo adverse drug reaction probability scale, tigecycline was the probable cause of his delirium.

Lessons: Clinicians should be aware of this potential adverse effect of tigecycline. We recommend that clinicians monitor patients for signs and symptoms of delirium during treatment with tigecycline.

Abbreviations: ADRs = adverse drug reactions, CNS = central nervous system, CRP = C-reactive protein, cSSSIs = complicated skin and skin-structure infections, CT = computed tomography, DSM-V = the Diagnostic and Statistical Manual of Mental Disorders fifth edition, ESRD = end-stage renal disease, FDA = the US Food and Drug Administration, MDR = multiple drug resistance, P-gp = p-glycoprotein, procalcitonin, WBC = white blood cell count.

Keywords: adverse drug reactions, delirium, tigecycline

1. Introduction

Tigecycline (Tygacil, Wyeth Carolina), is the first member of glycylycylone class bacteriostatic agent which is structurally derived from tetracyclines. It was approved by the US Food and Drug Administration (FDA) in 2005 for the treatment of complicated skin and skin-structure infections (cSSSIs), complicated intra-abdominal infections and community-acquired bacterial pneumonia caused by susceptible Gram-positive, Gram-negative, anaerobic, and atypical bacteria organisms.^[1] Because of its broad-

spectrum antibiotic activity against multiple drug resistant (MDR) organisms, for example, *Enterobacter cloacae*, *Acinetobacter baumannii*, *K pneumoniae*, the use of tigecycline has expanded to treatment of nosocomial pneumonia, osteitis, and other infections not yet approved for.^[2] Arising clinical cases reporting its adverse drug reactions (ADRs) have emerged alongside with the increasing off label use globally, for example, nausea, vomiting, pancreatitis, and some other ADRs less often reported like hypoglycemia, hepatic failure, and increased plasma gamma-glutamyltransferase level.^[2,3] Except for headache, dizziness, and chills, other adverse reactions concerning central nervous system are not listed in the manufacture's prescribing information. Notably, delirium is among the most common mental disorders encountered in patients in hospitals, and drug toxicity accounts for approximately 30% of all cases.^[4] However, to our best knowledge, delirium has never been reported as an ADR induced by tigecycline so far.

Clinicians must be aware that delirium can occur even with "therapeutic" levels of agents, and earlier identification of the disorder and comprehensive intervention to treat underlying causes can prevent subsequent complications such as immobility, aspiration, and skin breakdown. Herein, we report a first known case of tigecycline causing delirium.

2. Method

The study was approved by the Research Ethics Committee of the First Affiliated Hospital of Chongqing Medical University.

Editor: N/A.

The authors have no conflicts of interest to disclose.

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Medicine (2019) 98:19(e15399)

Received: 21 November 2018 / Received in final form: 23 March 2019 /

Accepted: 2 April 2019

<http://dx.doi.org/10.1097/MD.00000000000015399>

“Written” informed consent was obtained from the patient for the publication of the report.

3. Case presentation

A 77-year-old, Asian male patient (weight: 60 kg, height: 165 cm) with end-stage renal disease (ESRD) undergoing periodic hemodialysis, was hospitalized due to acute exacerbation of chronic obstructive pulmonary disease. He had no known history of psychosis prior to admission to the hospital. His social history was positive for alcohol consumption (25 mL a day for 10 years) and smoking (40 cigarettes a day for 30 years).

On admission, the patient was conscious and oriented to person, time, and place. Complete neurological examination including mental state was normal. The patient was in shortness of breath with the following vital signs: temperature 36.2 °C, blood pressure 156/91 mmHg, pulse 98 beats/min, and respiratory rate 20 per minute. He reported progressively worsening cough productive of yellow purulent sputum. Bilateral moist crackles were heard in both lungs on auscultation but with no wheezing. Markers of systemic inflammation were elevated (white blood cell count [WBC] $10.25 \times 10^3/\mu\text{L}$, C-reactive protein [CRP] 57.50 mg/L, procalcitonin [PCT] 0.49 ng/mL). Laboratory analysis revealed increased baseline serum creatinine (10.63 mg/dL, estimated creatinine clearance 4.94 mL/min). His liver function was moderately impaired and classified into Child-Pugh class B. Chest computed tomography (CT) scan showed diffuse inflammation and interstitial change and a small amount of pleural effusion in bilateral lungs.

Intravenous moxifloxacin was initiated 400 mg daily as empiric treatment for pulmonary infection on hospital day 1. A sputum sample was collected for microbiological culture before initiation of antibiotics and the result came back negative. On day 12, the patient was feeling tired and weak with hyperthermia (38.1 °C), hypertension (184/91 mmHg), and worsened shortness of breath (26 beats/min). Plasma indicators for infection were elevated (WBC $11.50 \times 10^9/\text{L}$, neutrophils 97.1%, PCT 22.10 ng/mL). On the 13th day, moxifloxacin was switched to meropenem 500 mg intravenous every 8 hours. On 16th day, sputum culture revealed multidrug-resistant (MDR) *A baumannii* (resistant to carbapenem but sensitive to tetracycline). Then intravenous tigecycline was added to the regimen at a loading dose of 100 mg followed by 50 mg every 12 hours.

Fourteen hours after tigecycline initiation, the patient became confused, disoriented to location, and the time. He had difficulty understanding instructions and was clearly disturbed in attention during the conversation. He was agitated, fearing that people around him were trying to harm him. Then he became verbally aggressive toward his family members and medical staff. His mental disorder worsened in the next 2 to 3 hours then he began having hallucinations, seeing a huge ball in the ceiling and asking the nurse to take it down so he could eat it. He asked other people to gather together and said he had important things to announce. His Confusion Assessment Method, which is a valid tool for the detection of delirium, was negative prior to the initiation of tigecycline, but became positive after it was started. His clinical manifestations also met the key features listed by the Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-V) criteria from the American Psychiatric Association that characterizes delirium.^[5]

No focal neurological disease was noted after neurological examination. A computerized tomographic scan of the head was

Table 1

Medications administered from admission to delirium.

Hospital day	Medication
d1–d18	Alprostadil
d1–d26	Left carnitine
d1–d28	insulin
d1–d12	Moxifloxacin
d1–d28	Clopidogrel
d1–d28	Ambroxol
d1–d18	Levamlodipine
d1–d18	Ferrous sulfate
d1–d18	Folic acid
d3–d26	Aminophylline
d3–d28	Trimetazidine
d3–d20	Isosorbide mononitrate
d13–d15	Meropenem
d16–d16	Tigecycline

then performed, and no abnormalities were identified. Oxygen supplementation (4 L/min via nasal cannulae) was initiated after the arterial blood gas analysis showed hypoxemia (pH 7.41; PaCO₂ 25 mmHg; PaO₂ 68 mmHg; Na⁺ 132 mEq/L; K⁺ 5.5 mEq/L). The patient did not have any prior history of mental illness. Drug-induced delirium was suspected and tigecycline was speculated to be the most likely offending agent after medication review (Table 1). Since his delirium was treated with little success with olanzapine, tigecycline therapy was discontinued the next morning after the patient stayed awake the whole night. During the following day after discontinuation of tigecycline, the patient’s mental state improved and delirium cleared slowly. He restored the ability of focus and orientation. Perceptual disturbances disappeared, and no visual illusions or vague delusions of harm were noted again.

Meanwhile, markers of systemic inflammation were elevated (WBC $43.91 \times 10^9/\text{L}$, neutrophils 98.2%, PCT 34.04 ng/mL, CRP 89.09 mg/L). On Day 19, antibiotic therapy was switched to meropenem (i.v., 500 mg q8h) combined with minocycline (p.o., 400 mg q12h), and amikacin (i.v., 200 mg qd). The regimen continued for 5 days but the patient did not respond well, showing even higher systemic inflammation markers and exacerbated dyspnea. Antibiotic therapy was switched to meropenem 500 mg every 8 hours, and he started again on tigecycline 50 mg every 12 hours on 24th day with no loading dose.

In the morning of Day 25, the patient showed reduced psychomotor activity, decreased speech, but no obvious hallucinations. He had no idea of the time of day, nor where he was, although the day before he was fully orientated. The patient experienced a hypoactive state of delirium. CT examination of the chest showed increased inflammatory pulmonary lesions in bilateral lungs. Blood gas analysis revealed hypoxemia without carbon dioxide retention, and the electrolytes were found to be within range. Also, no significant changes in blood profile like levels of liver enzymes or serum creatinine was observed compared with the last test taken before the delirium appeared again. Tigecycline was discontinued and delirium resolved in the afternoon. Antibiotic treatment was then switched to levofloxacin (i.v., 600 mg qd) and minocycline (p.o., 100 mg q12h). But the patient did not respond well to the present antibiotic therapy and his dyspnea exacerbated. He was transferred to the intensive

care unit 6 days later as mechanical ventilation was required. Unfortunately, the patient died of recurrent attacks of left heart failure probably caused by uncontrolled serious infections on 33th day.

4. Discussion

We present a patient with end-stage renal disease and pulmonary infection that developed delirium after infused with a loading dose of tigecycline. The symptoms quickly relieved after intravenous tigecycline was discontinued and appeared again once he was on this medication even without a loading dose. Delirium is a multifactorial disorder. The most commonly identified risk factors are underlying brain diseases such as dementia, stroke, or Parkinson disease. Other factors that may increase the vulnerability to delirium or precipitate the disease include advanced age, sensory impairment, polypharmacy, infection, dehydration, immobility, etc. Drug toxicity represents the second leading cause of delirium after infections and the “worst offenders” are opioids, antipsychotics, benzodiazepines, anticholinergics, and antidepressants.^[4,6] For our patient, no common causes of neuropsychological disorders, such as trauma, alcoholism, or metabolic encephalopathy were identified.

Delirium may have a single cause or more than one cause, such as a combination of a medical condition and drug toxicity. For our patient, medical conditions and other medications apart from tigecycline may have increased the risk of delirium, but was probably not the main cause triggered it. First, our patient were suffering from fever and infection, which are indeed those leading medical conditions causing delirium. However, his symptoms like cognitive impairment, behavioral changes quickly relieved after discontinuation of tigecycline, while the infection itself gradually worsen with time. Second, it’s true that other medications could have caused the delirium (Table 1), but the patient had been on these medications for many days, and he quickly recovered despite continuance of all other drugs used. The time sequence of tigecycline infusion, the onset of delirium and the prompt recovery after discontinuation of the medication, reoccurrence of delirium when the drug was readministered suggest a cause-and-effect relationship. The manufacture’s instructions^[1] revealed that tigecycline is a substrate for p-glycoprotein (P-gp), although the potential role of P-gp-mediated transport in the treatment of tigecycline is currently unclear. Combination with P-gp inhibitors (such as ketoconazole or cyclosporine) or P-gp inducers (such as

rifampicin) may affect the pharmacokinetics of tigecycline. Fortunately, these drugs were not used by patient. Moreover, tigecycline does not interfere with common cytochrome P450 enzymes, making pharmacokinetic drug interactions uncommon. Because tigecycline does not undergo extensive metabolism and works independently of the cytochrome P-450 isoenzyme system.^[7] So it’s unlikely the delirium could have been caused by the drug interactions between tigecycline and other medications used at the same time. Furthermore, blood gas analysis revealed the electrolytes were found within the range, therefore, the delirium caused by electrolyte disturbances can be also excluded. The Naranjo method^[8] yielded a probability score of +7 for tigecycline (Table 2), suggesting that it was the probable cause of delirium.

The pathophysiology of delirium is poorly understood. Published data addressing this issue have made implications in disrupted arousal and attention, impairment of cortical as well as subcortical structures,^[8] and neurotransmitter deficiency. The last one is considered to be an important mechanism for drug induced delirium. Anticholinergic drugs can cause delirium by blocking acetylcholine which plays a key role in the pathogenesis of delirium. This effect can be reversed with cholinesterase inhibitors such as physostigmine. This also explains why psychotropic drugs are also offenders in inducing delirium, as they interfere with the serum anticholinergic activity. Drugs^[7,9] that are agonists or antagonists of other neurotransmitters, such as somatostatin, endorphins, serotonin, norepinephrine, and γ -aminobutyric acid can produce delirium-like effects. Other drugs, which can cross the blood–brain barrier and are concentrated in brain tissue, such as propranolol and imipenem,^[10] may also increase the incidence of central nervous system (CNS) side effects including delirium.

By literature review, delirium caused by tigecycline has not been reported yet. We present what we believe to be the first case of tigecycline-induced delirium. According to the drug information provided by the manufacture, tigecycline is the 9-t-butylglycylamido derivative of minocycline and may have similar adverse effects. CNS effects such as dizziness, fatigue, malaise were among the frequent (1%–10%) reported ADRs of the major representatives in the tetracycline class, including minocycline and doxycycline. These drugs exert pleiotropic psychotropic activity, which has yet to be fully elucidated.^[11] In a case series reported by Atigari et al,^[12] 3 patients with no history of mental disorder who were treated for skin conditions with doxycycline, developed suicidal ideation with an outcome of suicide in 2 of the cases. For 1 patient,

Table 2
Naranjo scale for likelihood of tigecycline-induced delirium.

Question	Yes	No	Don't know	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 reaction reappear when the drug was re-administered?	+2	-1	0	+2
5. Are there possible alternative causes that could have caused the reaction? Are there alternate causes (other than the drug) that could have solely caused the reaction?	-1	+2	0	+2
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the drug detected in the 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	0
Total score				+7

a discontinuation of doxycycline has led to the resolution of symptoms without the need for psychotropic medications.

Although the exact cause of tetracyclines induced mental disorders remains unknown, there have been at least 3 mechanisms implicated, including inhibiting microglial activation^[13] and retinoid catabolism,^[14] blockade of mitochondrial Ca²⁺ channels,^[15] and interaction with N-methyl-D-aspartate receptors or intracellular messengers consequent to glutamate receptor activation.^[16] Moreover, Inta et al^[17] suggested that inhibition of microglia activation by minocycline was shown to induce extensive neuronal cell death thus impair subventricular zone neurogenesis and synaptic pruning in the early postnatal and adolescent rodent brain. However, further researches are needed before postulating these mechanisms to tigecycline induced mental disorders.

As drug toxicity causes or contributes to approximately 30% of all cases of delirium, delirium can occur even with “therapeutic” levels of such agents as digoxin or lithium, particularly in at risk patients. In this case we present, it should be noted that 2 reasons may increase the drug concentration. First, tigecycline is not extensively metabolized in human body, 59% of the dose is eliminated by biliary/fecal excretion, and 33% is excreted in urine. Overall, the primary route of elimination for tigecycline is biliary excretion of unchanged tigecycline and its metabolites. Systemic clearance of tigecycline was reduced by 25% and the half-life of it was prolonged by 23% in patients with moderate hepatic impairment (Child-Pugh B). Although no dosage adjustment is warranted according to the manufacturer’s instructions, the profile of pharmacokinetics of tigecycline will probably be changed significantly for patients who suffered from end-stage renal disease. Meagher et al^[18] suggested that tigecycline clearance was reduced by approximately 20%, and area under the tigecycline concentration–time curve was increased by approximately 30% in subjects with severe renal impairment. These outcomes were in agreement with Troy study^[19] in which the mean tigecycline C_{max} was observed to be 60% higher in subjects with ESRD than in age-matched, healthy subjects, and the area under curve was 20% higher in subjects with ESRD. Unfortunately, the blood concentration of tigecycline was not measured in this patient because such technics for tigecycline was not readily available in our hospital. Second, the in vitro plasma protein binding of tigecycline ranges from approximately 71% to 89%.^[20] As the plasma albumin concentration has dropped to 25 g/L in our patient, the free (unbound) tigecycline level may be increased. The above 2 reasons may have contributed to the adverse effect induced by tigecycline in the case we reported, however, drug concentration monitoring and further clinical investigations are needed to confirm these speculations and their clinical relevance.

The major limitation of this study is that the blood levels of tigecycline were not be able to be measured to confirm the speculations we made. But such a case is quite indicative of our future study. Methods for tigecycline blood concentrations analysis should be developed so the exact data could be obtained to further explain the causes of those rare adverse effects.

5. Conclusion

Clinicians should be aware that tigecycline, a derivative from tetracyclines with broad-spectrum antibiotic activity against MDR organisms, may rarely cause delirium. Based on the case presented here, we recommend special attention with this

possible adverse reaction to patients with hepatic and/or renal impairment that are treated with tigecycline. Decreased serum albumin level could also be an important predisposing factor. Tigecycline induced delirium could be present as both hyperactive and hypoactive, the latter one is often unrecognized and misdiagnosed. Thorough evaluation and a supportive antipsychotic therapy are needed, especially under circumstances when withdrawal of tigecycline is controversial with antibiotic therapy against severe infections.

Author contributions

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