## Case Report

# Suspected Tigecycline and Levetiracetam induced raised Creatine Kinase (CK) and Rhabdomyolysis

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Drug induced skeletal muscle toxicities are rare adverse effects which are often under reported. Rhabdomyolysis involves breakdown of skeletal muscle fibers leading to release of its cellular contents like Creatine Kinase (CK) and myoglobin into the bloodstream. Tigecycline (TG) has rarely been observed to cause elevated CK levels, but there are some published reports of Levetiracetam (LEV) associated Rhabdomyolysis.

We report a case of intracerebral haemorrhage and sepsis who developed Rhabdomyolysis suspected to be due to tigecycline and levetiracetam. This case report intends to sensitize clinicians of a rare and potentially life threatening Adverse Drug Reactions (ADR) of Rhabdomyolysis suspected to TG and LEV. Timely diagnosis and prompt management averted fatality.

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***Key words*** **: Tigecycline, Levetiracetam, Rhabdomyolysis, Creatine Kinase (CK), Adverse Drug Reaction.**

Drug induced skeletal muscle toxicities are rare adverse effects which are often under reported. The spectrum of such Adverse Drug Reactions (ADR) vary from mild myalgia, muscle weakness to potentially fatal rhabdomyolysis.

Rhabdomyolysis involves breakdown of skeletal muscle fibers leading to release of its cellular contents like Creatine Kinase (CK) and myoglobin into the bloodstream. Elevated serum CK level is the most commonly used laboratory parameter to substantiate the clinical diagnosis of rhabdomyolysis.

Tigecycline (TG) is a broad spectrum parenteral antibiotic. It is chemically a tetracycline derivative (glycylcycline)[1-3]. The approved indications are complicated skin and soft tissue infections, intra abdominal infections and bacterial pneumonia in adults and children[2,3]. The listed ADR are anaphylaxis, anaphylactoid reaction, raised liver enzymes, jaundice and rarely hepatic failure[2,3].

Levetiracetam (LEV) is an anti seizure drug approved as adjunctive therapy for myoclonic, focal onset and primary generalized tonic clonic seizures in adults and children above 4 years of age. The common ADRs include fatigue, somnolence, ataxia, dizziness, behavioral abnormalities and psychotic symptoms[4,5].

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***Editor's Comment :***

- TG has rarely been observed to cause elevated CK levels.
- A patient with ICH and sepsis treated conservatively with Tigecycline showed marked elevation of serum CK level [nearly a 30 fold rise of upper limit of normal].
- After discontinuation, though significant decrease in CK level, but did not normalize.
- Levetiracetam was replaced with Lacosamide and CK level came to normal.

TG has rarely been reported to cause elevated CK levels, but LEV associated rhabdomyolysis has been reported. We narrate a rare case of rise of CK level with Rhabdomyolysis induced by tigecycline (TG) and Levetiracetam (LEV) in a patient of Cerebrovascular Accident (CVA) with sepsis.

### Case Report

A 69-year-old male patient was admitted to a Critical Care Unit of Tertiary Care Neurosciences hospital in Kolkata with right sided hemiplegia. Imaging studies confirmed it as left sided Intracerebral Hemorrhage (ICH) with midline shift. Patient was hypertensive with Type 2 Diabetes adequately controlled by oral medications. His baseline biochemical, serological and hematological parameters were within normal range (Table 1). There was no history of convulsions, rigorous exercises or any musculo- skeletal disorders prior to admission. No significant abnormalities were noted in baseline EEG and ECG.

Patient received conservative management for ICH. He was hemodynamically stable and baseline tracheostomy was done and after 3 days he was successfully weaned off from mechanical ventilation. He

Table 1 — *Baseline parameters*

| Parameter | Result |
|---|---|
| Hemoglobin (g/dl) | 11.2 |
| Serum Potassium (mEq/L) | 3.5 |
| Serum Sodium (mEq/L) | 137 |
| Serum Calcium (mg/dl) | 7.8 |
| Serum Magnesium (mg/dl) | 1.96 |
| Serum Creatinine (mg/dl) | 0.9 |
| AST (IU/L) | 164 |
| ALT (IU/L) | 138 |
| ALK (IU/L) | 82 |
| LDH (IU/L) | 493 |
| GGT (IU/L) | 17 |
| Total protein (g/dl) | 4.66 |
| Albumin (g/dl) | 2.01 |
| SARS CoV2 RT PCR | negative |

AST- Aspartate Transaminase; ALT- Alanine Transaminase; Alk Alkaline Phosphatase; LDH- Lactate Dehydrogenase; GGT- Gamma Glutamyl Transaminase; RT PCR- Reverse Transcriptase Polymerase Chain Reaction

developed fever with raised CRP levels and was given injection meropenem from 18/4/22 to 26/4/2022 and injection teicoplanin 18/4/2022 to 23/4/2022. As his CRP levels remained high, injection tigecycline (100 mg loading dose followed by 50 mg twice daily) was added from 27/4/22. After receiving four doses of TG (100mg IV loading dose followed 50mg IV twice daily), his urine colour changed to dark brown.

There was marked elevation of serum Creatine Kinase level [approximately 30 fold rise of upper limit of normal- (ULN <308 IU/L in males]. The rise was nearly 90 fold from his admission CK level (103 IU/L to 9410 IU/L) and urine myoglobin was also raised (>30000µg/L). A transient elevation of serum potassium (6.1 mEq/L) was noted but other electrolytes and creatinine were within the ULN. EEG was also done to rule out non-convulsive seizures and CK -MB cardiac enzymes were also normal. His liver function parameters were normal and due to early interventions he did not develop acute kidney injury. Concomitant medications included-leviteracetam, metoprolol, metformin, ivabradine, pantoprazole, salbutamol with ipratropium and lactulose.

In the absence of other non-drug related causes like seizures, hypothermia, muscle trauma, cardiac injury, dyskinesia, vigorous exercise and hypothyroidism a detailed review of the prescribed medications was undertaken. Absence of drug exposure with known myotoxicity potential other than tigecycline and levetiracetam led to a clinical suspicion that TG as the primary suspect drug due to its closest temporal association. TG was discontinued but LEV was continued though were several published reports of LEV induced raised Creatine Kinase levels. The justification for such decision was based on the fact that we first wanted to discontinue the suspect medications one at a time. He was promptly treated with intravenous fluids, forced

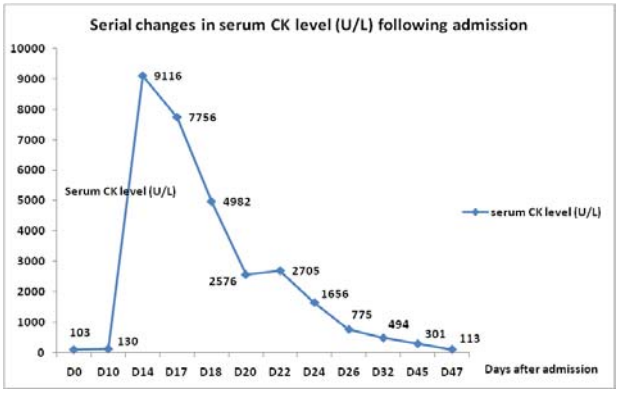


Fig 1 — Serial changes in serum creatine kinase (CK) levels

alkaline diuresis for management of rhabdomyolysis. The serial changes of Creatine Kinase levels are depicted in Fig 1.

Though there was a significant decline in the CK levels after TG discontinuation but it did not normalize even after 5 days so we suspected that LEV could also be additionally implicated. Hence, LEV was stopped LEV and replaced with lacosamide. Within 4 days of LEV withdrawal, the CK levels normalized. However, CK estimation was done only on admission and thereafter when the patient passed high colored urine. Therefore, we cannot rule out the possibility of any rise of CK levels after levetiracetam initiation and whether it was an additive ADR following TG administration. As the lag period between TG initiation and passage of high colored urine was the shortest so TG was considered as primary suspect drug but LEV was also implicated in the causation as CK levels reduced but did not normalize after TG withdrawal. Therefore, we suspect that concomitant administration of TG and levetiracetam may have increased the risk of the ADR.

A diagnosis of tigecycline and levetiracetam induced elevated CK was made on the basis of temporal association, exclusion of other known causes of raised CK levels and positive dechallenge outcome. Causality assessment as per Naranjo's[6] and the WHO-UMC causality assessment[7] scales categorized it as "Probable" for TG and LEV.

## Discussion

A literature search of drug induced elevated CK and rhabdomyolysis was undertaken and summarized in Table 2. A review article [8] on drug induced myo-toxicties has suggested some underlying mechanisms - (a) direct damage to muscle cell organelles like the myofibrillar proteins, lysosomes and mitochondria, (b) immunologically mediated inflammatory damage, (c) alteration of muscle function secondary to drug induced changes in electrolytes, substrate availability and oxygen/blood supply to muscles. However, the mechanism of TG and LEV induced skeletal muscle toxicity has not been

explicitly stated in any published literature.

The WHO global spontaneous drug safety database (*Vigibase*)[9] as on July 16th 2022, showed 6 reports globally of TG and 420 reports of LEV induced rhabdomyolysis. A recently published review article [10] on LEV induced rhabdomyolysis has highlighted several cases.

Table 2 — *List of some drugs which may cause elevated creatine kinase (CK) and/or rhabdomyolysis*[8,10-14]

| Groups | Drug |
|---|---|
| Lipid lowering drugs | statins, fibrates, niacin |
| Rheumatological drugs | D-penicillamine, chloroquine, hydroxychloroquine, |
| Antimicrobials | zidovudine, abacavir (especially when given with protease inhibitors), clarithromycin, ketoconazole |
| Dermatological | systemic retinoids |
| Antipsychotics | clozapine, olanzapine |
| Oncologic/ Immunomodulatory drugs | |
| • BRAF inhibitors | binimetinib |
| • Tyrosine Kinase inhibitors | dasatinib, nilitinib, bosutinib |
| • Immune check point inhibitors | pembrolizumab, avelumab, nivolumab |
| Others | colchicine, cocaine, MDMA (3,4-methylenedioxy-methamphetamine), amphetamines, alcohol, labetolol, pindolol nebivolol, leviteracetam |

## Conclusion

Patients in critical care setting require therapy with multiple drugs so careful monitoring of their safety is relevant. This case report sensitizes clinicians of a rare and potentially life threatening ADR of Rhabdomyolysis suspected to TG and LEV. Timely diagnosis and prompt management averted fatality.

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