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A Case Report on Faropenem Induced Focal Seizures

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***Abstract*---- Faropenem, an orally active Carbapenem, showcases a distinctive molecular structure characterized by a beta-lactam ring accompanied by a chiral tetrahydrofuran substitution at the C2 position. This structural modification serves a dual purpose: it enhances the compound's chemical stability while also diminishing the potential for adverse effects within the central nervous system (CNS) [1]. Consequently, Faropenem emerges as a notably safer therapeutic choice in comparison to other compounds within its pharmacological class. However, it is essential to highlight that the current body of literature remains notably lacking in substantial evidence linking Faropenem usage to triggering of seizures. In light of this, we present a case report featuring a 48-year-old woman who, subsequent to receiving the Faropenem antibiotic, presented with a series of recurrent focal seizures.**

Keywords:- *Adverse Drug Reaction; Carbapenem; Faropenem; Seizure.*

I. INTRODUCTION

Faropenem received approval for usage in India back in 2005. More recently, in 2021, its suspension variant was granted approval for pediatric usage. India and China are the leading consumers of faropenem [2]. Like other beta-lactam antibiotics, Faropenem works against bacteria by disrupting their cell wall formation. It achieves this by attaching to penicillin-binding proteins (PBPs), rendering them ineffective. This disruption prevents the proper cross-linking of peptidoglycan, leading to the rupture of bacterial cells. Moreover, faropenem's efficacy is maintained as it is resistant to degradation by multiple beta-lactamases. With a potent -cidal action, faropenem exhibits a wide-ranging antimicrobial effect, effective against diverse strains of both gram-positive, gram-negative bacteria, including aerobic and anaerobic strains. It has shown an impressive safety record, with a minimal occurrence of diarrhea, nausea, or vomiting. Furthermore, there have been no reported instances of cardiotoxicity or seizures associated with the use of this medication [1,3]. During the period from 2010 to 2014, faropenem consumption surged by 154% in India, resulting in a heightened risk of antimicrobial resistance [2]. This situation emphasizes the need to limit and use such antibiotics cautiously.

II. CASE REPORT

A 48-year-old woman visited the OPD with complaints of burning micturition in the past 7 days, reduced appetite, generalized fatigue in the past 3 days, and increased PV bleeding even during the 8th day of menstruation. She was a known case of type 2 DM, focal seizures, and a history of neurocysticercosis for which she was treated 5 years back. The patient was seizure free for the past one year. She was on regular medications for her co-morbid conditions (Tab. Sitagliptin+ metformin 50/500mg BD, Tab. Levetiracetam500mg BD, and Tab. dexamethasone 2mg BD). During the physical examination, the patient's vitals were found to be Temperature: 103°F, BP:130/80 mm Hg, RBS: 352 mg/dL, and pulse rate: 120 beats/min, given these findings, the patient was admitted to the hospital. On further examinations HbA1c was 12.8%, a urine routine test showed greenish-yellow color for sugar, and positive for urine acetone. WBC total count was 10,300 cells/µL. CT of the brain showed no significant abnormality, the EEG suggested a normal wake record. HRCT chest showed linear atelectasis and subtle ground glass densities, suggestive of infective etiology. The urine culture showed presence of organism E.coli which was resistant to cephalosporins. Her final diagnoses encompassed uncontrolled type 2 diabetes mellitus (DM), lower respiratory tract infection (LRTI), and urinary tract infection (UTI). During hospitalization, the patient was initially treated with antimicrobials like Inj. Ceftriaxone 2g BD then switched over to Inj. piperacillin+ tazobactam 4.5g TID, Tab. Azithromycin500mg OD, Inj.Fluconazole200mg OD, cap. Oseltamivir 75mg BD along with Tab. Levetiracetam 500 mg BD, vitamin supplements, and insulin.

The patient was symptomatically better and was discharged on day 6 with the following discharge medications; Tab. Faropenem 200mg BD x 7days, Tab. fluconazole 200 mg OD x 2days, Cap. Oseltamivir 75mg BD x 4days, Tab. tranexamic acid 500mg TID x 5 days, Tab. Montelukast 10mg OD x 10 days, Tab. Levetiracetam 500mg BD x to continue, multivitamins & insulin.

The patient was back to the hospital 5 days after discharge with complaints of multiple episodes of involuntary movement of the left lower quadrant of the face in the past 2 days, each episode lasting for about 1 min without loss of control. On physical examination the patient's temperature was normal, BP: 150/90 mm Hg, RBS: 345 mg/dL, and pulse rate: 110beats/min. The patient was admitted to the hospital again and initially received the same treatment. Later she

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developed 2 episodes of focal seizures lasting for about 1 min in the hospital for which Inj. Levetiracetam 750 mg BD was administered. The following day the patient's temperature was normal, BP: 120/70 mm Hg, and she further developed multiple episodes of focal seizures for which Tab. Clobazam10 mg OD and Tab. Oxcarbazepine 150mg BD was added to the therapy. The next day, Tab. Faropenem was stopped & Inj. Amikacin 750mg OD was added to the treatment plan. The patient was observed closely for 3 more days, she was symptomatically better and had no further episodes of seizure, therefore, she was discharged with the medications: Tab. Levetiracetam 750mg BD, Tab. Clobazam 10mg OD, Tab Oxcarbazepine 150mg BD, multivitamins & insulin.

The patient was followed up for 1 month after discharge, and she had not developed any further episodes of seizure.

Table 1 The patient was followed up for 1 month after discharge

DIAGNOSTIC TESTS	VALUE	UNIT
28-09-2022		
Albumin	3.7	g/dL
ALP (alkaline phosphatase)	92	IU/L
ALT (alanine aminotransferase)	36	IU/L
AST (aspartate aminotransferase)	26	IU/L
BUN (blood urea nitrogen)	8	mg/dL
Chloride	99	mEq/L
Creatinine	0.69	mg/dL
HbA1C (hemoglobin A1C)	12.8	%
Potassium	5.2	mEq/L
Protein, total	6.9	g/dL
Sodium	132	mEq/L
29-09-2022		
Urine culture	positive	
02-10-2022		
Lymphocytes	24	%
Monocytes	10	%
Neutrophils	64	%
WBC (total white blood cells)	10300	cells/µL
09-10-2022		
BUN (blood urea nitrogen)	6	mg/dL
Chloride	101	mEq/L
Creatinine	0.69	mg/dL
Hb (hemoglobin)	9.8	g/dL
Potassium	3.9	mEq/L
Sodium	133	mEq/L

Table 2 TIMELINE

28-09-2022	Patient came to the OPD with complaints of burning micturition since7 days, reduced appetite, generalized fatigue in the past 3 days, and increased PV bleeding even during the 8th day of menstruation. She was admitted to the hospital
29-09-2022	Patient was diagnosed with UTI, LRTI and was treated with antibiotics like Inj. Ceftriaxone 2g BD then switched over to Inj. Piperacillin+ Tazobactam 4.5g TID, Tab. Azithromycin500mg OD
03-10-2022	Patient was symptomatically better and was discharged from the hospital with Tab. Faropenem 200mg BD x 7days
05-10-2022	Patient experienced one episode of involuntary movement of the lower quadrant of the face.
07-10-2022	Patient experienced multiple episodes of involuntary movement of the lower quadrant of the face.
08-10-2022	Patient was re-admitted to the hospital for focal seizures.
09-10-2022	Patient further developed multiple episodes of seizures in the hospital. clobazam and oxcarbazepine were added to the treatment.
10-10-2022	Faropenem was withheld.
13-10-2022	No further episodes of seizures were experienced, the patient was discharged.
15-10-2022	Patient didn't develop any further episodes of seizures.

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III. DISCUSSION

Focal seizures are the transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain originating within networks limited to one hemisphere [4]. Certain antibiotics like fluoroquinolones and beta-lactams have potential CNS toxicity and neurological side effects. Most drug-induced seizures are self-limited. However, prolonged or recurrent seizures can lead to serious complications and require vigorous supportive care and anticonvulsant drugs [5].

Carbapenems, such as imipenem-cilastatin, have been linked to seizures, with rates ranging from 3% to 33%. Other carbapenems like meropenem, doripenem, faropenem, and ertapenem have seizure rates below 1% [6]. Carbapenem use is mostly associated with generalized tonic-clonic seizures and, less commonly, with focal seizures [7]. These antibiotics induce seizures through mechanisms like GABA antagonism by binding to GABA A receptors and interacting with the NMDA receptor complex, disrupting the equilibrium between excitatory and inhibitory neurotransmitters. Patients with risk factors like renal/hepatic issues, neurological disorders, epilepsy history, critical illness, or advanced age are more vulnerable to antibiotic-induced seizures [8]. Concurrent use of antibiotics and anti-seizure drugs can heighten seizure risk due to interactions affecting drug metabolism and efficacy. Carbapenems can also interact with antiepileptic agents, leading to fluctuations in their plasma concentrations, potentially causing seizures or neurotoxicity [9]. Following the discontinuation of Faropenem, the patient returned for a one-month follow-up and did not encounter any additional seizure episodes. In order to assess the potential link between the drug and the adverse reaction, a causality assessment was done using Naranjo's algorithm and the WHO scale sanctioned by the Uppsala Monitoring Centre. This analysis yielded a score of 7, indicating a high probability of the adverse reaction being associated with the drug. According to the WHO-UMC scale, the adverse reaction was classified as a probable ADR. This determination stems from the fact that the development of seizures subsequent to Faropenem administration aligns with the criteria for a probable ADR. Importantly, no re-challenge was undertaken. This ADR was then reported to the Pharmacovigilance Programme of India (PvPI) through the spontaneous reporting system, contributing to the expansion of the knowledge base.

IV. CONCLUSION

This case illustrates a rare adverse event where focal seizures were induced by Faropenem, a relatively new carbapenem that has not been associated with risk of CNS toxicity so far. This emphasizes the importance of careful consideration when prescribing antibiotics like faropenem, especially for patients with a history of CNS abnormalities. Healthcare providers should exercise caution and remain vigilant regarding the possibility of seizures triggered by faropenem, ensuring thoughtful decision-making regarding the choice and dosage of antimicrobial treatments.

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ABBREVEATIONS

ADR: adverse drug reaction, **BD:** bis in die (twice daily)**,** **BP:** blood pressure, **CNS:** central nervous system, **CT:** computed tomography, **DM:** Diabetes mellitus, **EEG:** electroencephalogram, **GABA:** Gamma-amino butyric acid, **HbA1C:** hemoglobin A1C, **HRCT:** high-resolution computed tomography, **INJ:** injection, **NMDA:** N-methyl-D-aspartate, **OD**: omne in die (once daily)**, OPD:** out-patient department, **PV:** per vaginum, **RBS:** Random blood sugar**,** **TAB:** tablet, **TID:** ter in die (three times a day), **UMC:** Uppsala monitoring center, **WBC:** white blood cells, **WHO:** World Health Organization

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