https://africanjournalofbiomedicalresearch.com/index.php/AJBR
Afr. J. Biomed. Res. Vol. 27(4s) (December 2024); 15650-15654
Research Article

Phenytoin Toxicity Due To Fluconazole Interaction in Epilepsy and Oropharyngeal Candidiasis: A Case Study with Therapeutic Drug Monitoring

Akshaya. G[1], Dr. Dheenadhayalan. M[2*], Dr. Sundar Sri Mk[3], Sreelakshmi S[4], B Shreesha[5], Dr P Monika[6], J Kabilan[7]

[1]Pharm D Intern, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies, Pallavaram, Chennai-600117, India. Email: ganeakshaya007@gmail.com
[2*]Assistant Professor, Department of Pharmacy Practice, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies, Pallavaram, Chennai-600117, India. Email: drdheenadhavalanap@email.com
[3]Assistant Professor, Department of Pharmacy Practice, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies, Pallavaram, Chennai-600117, India. Email: sundarsri.sps@vistas.ac.in
[4]Pharm D Intern, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies, Pallavaram, Chennai-600117, India. Email: Sreemasree677@gmail.com
[5]Pharm D Intern, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies, Pallavaram, Chennai-600117, India. Email: bshreesha112001@gmail.com
[6]Assistant Professor, Department of Pharmacy Practice, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies, Pallavaram, Chennai – 600117, India. Email: monikapeter750@gmail.com
[7]Assistant Professor, Department of Pharmacy Practice, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies, Pallavaram, Chennai – 600117, India. Email: kabilan276@gmail.com

Abstract
In a patient suffering from both epilepsy and oropharyngeal candidiasis, this case report brings forth a clinically relevant drug-drug interaction between phenytoin, an antiepileptic drug-and fluconazole, an antifungal drug. Interaction between the two drugs elevated the serum phenytoin levels, leading to toxicities manifested by neurological and systemic symptoms, which were ataxia, nausea, and dizziness. This was greatly remedied by prompt action that included putting the patient off phenytoin for a while, undertaking therapeutic drug monitoring (TDM), and substituting fluconazole with itraconazole, which was effective in managing the toxicity. This case demonstrates the importance of vigilance in prescribing therapy, therapeutic drug monitoring, and multidisciplinary teamwork in preventing and managing drug-drug interactions. Such safety would not have been achievable without patient education and the integration of clinical decision-support systems.

Keywords: Phenytoin, Fluconazole, Drug-Drug Interaction, Therapeutic Drug Monitoring

Received: 2024/09/25 *Accepted: 2024/10/10*
DOI: https://doi.org/10.53555/AJBR.v27i4S.7828

INTRODUCTION

Drug-drug interactions are one of the major issues to be taken into account in medical practice, particularly in patients suffering with chronic diseases, as they require treatment with more than one drug. These changes dramatically alter either the pharmacokinetics or the pharmacodynamics of a drug, resulting in reduced therapeutic efficacy and side effects. Antiepileptic drugs (AEDs) like phenytoin are otherwise the most commonly prescribed AEDs for controlling seizures. Most of the drugs usually prescribe for patients with epilepsy falls under narrow therapeutic index drugs, highly subject to DDIs and represent extensive hepatic metabolism. Fluconazole is a well-known and widely used antifungal drug that inhibits cytochrome P450 enzymes and especially CYP2C9 and CYP2C19, which are indispensable for phenytoin metabolism. Co-administration of these two is high-risk combination, elevating levels of phenytoin and causing potential toxicity. [1,2,3]

Therapeutic Drug Monitoring (TDM) is the measurement of the concentration of drugs in the bloodstream of the patient over specified intervals in order to maintain them within a predetermined therapeutic range. TDM aims to optimize drug therapy by adjusting drug dosages-from-the desired therapeutic effect ignoring the toxic effects. TDM is of utmost importance for the drugs with a narrow therapeutic window, where a small change in drug levels results in a significant change in efficacy or safety. [4,5]

This report will discuss the clinical implications of the phenytoin-fluconazole interaction, the role of TDM in preventing and managing toxicity, and the strategies used to safely manage the patient's condition while ensuring effective treatment for both epilepsy and oropharyngeal candidiasis. [6,7]

CASE PRESENTATION

Patient Information

- **Demographics:**
  - **Age:** 46 years
  - **Gender:** Male
  - **Weight:** 69.5 kg
  - **Height:** 172 cm
  - **BMI:** 23.5 kg/m²
- **Medical History:**
  - **Primary Condition:** Epilepsy diagnosed at age 22, currently under treatment with phenytoin alone (300 mg/day)
  - **Past Medical History:** No major comorbidities or hospitalizations noted
  - **Allergies:** No known drug or food allergies
  - **Family History:** No familial history of epilepsy or major chronic diseases
- **Lifestyle Factors:**
  - Non-smoker
  - Occasional alcohol intake (1-2 drinks per week)
  - Moderate physical activity (walking 30 minutes daily)
- **Current Condition:**
  - Presented with oropharyngeal candidiasis diagnosed 2 weeks before hospital admission
  - No history of recurrent fungal infections
- **Medication History:**
  - Phenytoin: 300 mg/day (maintained for over 20 years with stable therapeutic levels)
  - No recent changes in dosage or formulation
  - No concurrent use of over-the-counter medications, supplements, or herbal remedies
- **Social and Occupational History:**
  - Employed as an office worker with no occupational exposure to hazardous substances. Lives with family; supportive home environment

Presenting Complaint

The patient came into the emergency department with the following complaints:

- Drowsy and confused for the past 48 hours
- Trouble keeping balance and trouble with walking
- Slurred speech noted by family members
- Persistent nausea along with intermittent vomiting
- Diplopia (double vision) reported upon visual focus attempts
- Generalized fatigue and a sense of malaise

History of Present Illness

Approximately 14 days before the hospitalization, the patient reported that he was diagnosed with oropharyngeal candidiasis and has taken oral fluconazole (200 mg/day) treatment. Prior to this, the patient was stable on phenytoin monotherapy (300 mg/day) with more than a decade free from reported side effects and breakthrough seizures. Ten days after fluconazole therapy, the patient started to experience neurological symptoms of lightheadedness combined with lack of balance while walking. Over several subsequent days, the symptoms progressed. Family members noticed lethargy with speech difficulties and improper balance. These symptoms had seen a significant increase in severity two days prior to presentation with vomiting and worsening balance problem culminating in near-fall. Concerned about the rapid progression of these symptoms, the family sought immediate medical attention.

Clinical Examination

- **General Appearance:**
  - Patient appears drowsy and is arousable with verbal stimuli.
  - No acute distress observed.
- **Neurological Examination:**
  - **Mental Status:** Alert but disoriented to time and place.
  - **Speech:** Slurred and difficult to comprehend.
  - **Cranial Nerves:** Bilateral cranial nerves intact; mild diplopia noted during eye movement testing.
  - **Motor System:** Normal muscle bulk and tone; no focal motor deficits.
  - **Coordination:** Marked ataxia with difficulty performing finger-to-nose and heel-to-shin tests.
  - **Gait:** Unsteady and wide-based; unable to perform tandem walking.

- **Reflexes:** Deep tendon reflexes were 2+ bilaterally.

• **Cardiovascular Examination:**
- Heart rate: 78 beats/min, regular rhythm
- Blood pressure: 130/80 mmHg
- No murmurs or abnormal heart sounds detected.

• **Respiratory Examination:**
- Respiratory rate: 18 breaths/min
- Lungs clear to auscultation bilaterally.

• **Gastrointestinal Examination:**
- Abdomen soft and non-tender and no organomegaly or masses detected.

Investigations

1. **Laboratory Investigations:**
- **Complete Blood Count (CBC):**
  - Hemoglobin: 13.8 g/dL (normal)
  - White Blood Cell Count: 7,800/µL (normal)
  - Platelets: 259,000/µL (normal)
- **Liver Function Tests (LFTs):**
  - ALT: 23 IU/L (normal)
  - AST: 24 IU/L (normal)
  - Total Bilirubin: 0.7 mg/dL (normal)
- **Renal Function Tests (RFTs):**
  - Blood Urea Nitrogen: 15 mg/dL (normal)
  - Creatinine: 0.8 mg/dL (normal)
  - Estimated GFR: >90 mL/min (normal)
- **Serum Electrolytes:**
  - Sodium: 142 mEq/L (normal)
  - Potassium: 4.4 mEq/L (normal)
  - Calcium: 9.6 mg/dL (normal)

2. **Serum Phenytoin Levels:**
- 34 µg/mL (toxic range; therapeutic range: 10-20 µg/mL)

3. **Imaging:**
- **CT Brain (Non-Contrast):** No acute infarcts, hemorrhages, or structural abnormalities detected.

4. **Electrocardiogram (ECG):**
- Normal sinus rhythm; no QT prolongation or other abnormalities.

5. **Electroencephalogram (EEG):**
- Normal background activity; no epileptiform discharges noted.

6. **Fungal Culture and Sensitivity:**
- Candida species isolated; susceptible to fluconazole.

Diagnosis

Phenytoin toxicity has been diagnosed in the patient due to interaction of drugs fluconazole. The ultimately confirmed diagnosis was based on raised serum levels of phenytoin in conjunction with the presentation of neurological symptoms that followed the further initiation of fluconazole therapy. Additional exclusionary criteria ruling out other diagnoses include:
• No evidence of structural abnormality, nor acute neurological events were observed on imaging.
• EEG findings were normal and excluded seizures.
• Lack of evidence of any other systemic infections or metabolic derangements.

Management

Day 1

• **Immediate Interventions:**
- Temporarily stopped phenytoin to prevent further toxicity.
- Discontinued fluconazole to prevent the inhibitory effect on phenytoin metabolism.
- Patient admitted to general ward for close monitoring.

• **Supportive Care:**
- Intravenous fluids initiated (0.9% saline) for hydration and maintenance.
- Symptomatic treatment for nausea with ondansetron (4 mg IV)

• **Therapeutic Drug Monitoring (TDM):**
- Baseline serum phenytoin level measured (34 µg/mL).

Day 2

• **Symptom Management:**
- Slight improvement in ataxia and drowsiness.
- IV Dexamethasone (4 mg) for reducing possible cerebral effects of toxicity.

• **TDM:**
- Repeat serum phenytoin level: 25 µg/mL.

Day 3

• **Continuation of Monitoring:**
- Further drop in the level of phenytoin to 22 µg/mL.
- Clinical symptoms improved significantly, drowsiness much reduced, and coordination better.

• **Alternative Antifungal Therapy:**
- Started oral itraconazole (200 mg/day) as alternative antifungal agent with lesser interaction potential.

Day 4

• **Clinical Stabilization:**
- Neurological symptoms of the patient lessened significantly; balance and gait were improved.
- Continued measurement of serum phenytoin level and symptom resolution.

Day 5-7

• **Transition to Maintenance:**
- Reintroduction of phenytoin therapy but at a lower dose (200 mg/day) under close monitoring.
- Serum phenytoin levels normalized to therapeutic range (15 µg/mL).

• **Completion of Antifungal Therapy:**
- Itraconazole was well tolerated by the patient; oropharyngeal candidiasis resolved with no recurrent episodes.

Follow-Up:

• The patient was discharged with instructions for proper regular follow-up in outpatient care. Advised for periodic TDM of phenytoin levels and vigilance for any recurrence of symptoms. Counseling provided regarding possible DDIs and the importance of reporting new medications.

Outcome of the Case

In this case, early intervention has salvaged phenytoin toxicity through normalization of serum phenytoin levels and complete resolution of neurological symptoms, notably ataxia and drowsiness. The alternative antifungal regimen of itraconazole was effective against oropharyngeal candidiasis with no apparent recurrence. The patient was discharged in

stable condition without residual effects or complications. Follow-up outpatient therapy and practical drug monitoring were recommended only to avert possible drug-drug interactions but will further reassure comprehensive care and guarantee safety for continued benefit.

DISCUSSION

It is an important example of how significant the pharmacokinetic interaction is between phenytoin and fluconazole, and should definitely serve as a lesson for clinicians managing patients on multiple drugs. Phenytoin, the very widely used antiepileptic drug, undergoes hepatic metabolism predominantly via the CYP2C9 and CYP2C19 enzymes. Administration along with fluconazole, a very potent CYP450 inhibitor, caused drastic reduction in phenytoin clearance, resulting in high levels of serum concentration that reached toxic levels. Neurological symptoms ataxia and dizziness, as well as nausea and drowsiness, have systemic effects.[8,9]

The management of this case proved that therapeutic drug monitoring (TDM) would be a cornerstone. Serum phenytoin levels would enable early recognition of toxicity while guiding appropriate interventions. Temporary discontinuation of phenytoin brought serum levels to a range where further complications were avoided. Reintroduction of phenytoin at a lower dose kept seizures controlled while avoiding recurrence of toxicity. The current case study illustrates how TDM helps in individualizing therapy according to specific pharmacokinetic profiles, especially in the face of DDIs.[10,11]

In replacing fluconazole with itraconazole, the necessity of alternative treatments with lesser interaction potential is emphasized. The patient had good antifungal therapy using itraconazole on oropharyngeal candidiasis without increasing phenytoin toxicity. This decision underlines the need for a multidisciplinary approach to optimize patient outcomes that carefully selects drug regimens that balance efficacy and safety.

Patient counseling is the other very important part of management in this case. Informing the patient about the adverse effects of polypharmacy coupled with DDIs would strengthen the cause for adherence to the prescribed treatment and regular observation. Reporting all concomitant medications including non-prescription ones and herbal supplements is laid significant to minimize future risks.

The case again reminds us of the very important aspect of clinical decision-support systems (CDSS), which are essential in identifying potential DDIs during prescribing. The combination of electronic health records (EHRs) with integrated CDSS would sound alarms for those known interactions that would require the clinician to consider an alternative therapy or better monitoring regimens.[12,13]

In short, the effective management of this case could be attributed to integrated and combined approaches involving the timely identification of the problem, therapeutic drug monitoring, judicious drug substitution, and extensive patient counseling. It demonstrates how complex the management of polypharmacy becomes in patients with chronic diseases and shows how much practice vigilance is needed in the prevention and management of DDIs. Proactive measures and using knowledge-based systems will make health systems much better in terms of safe and effective pharmacotherapy and therefore in patient outcomes.[14,15]

CONCLUSION

This case looks at the important healthcare drug interaction case of phenytoin and fluconazole on a patient with epilepsy and oropharyngeal candidiasis, which resulted in increased serum phenytoin levels and toxicity as symptoms of ataxia, nausea, and dizziness. The patient's condition was treated by a few quick interventions, such as the temporary discontinuation of phenytoin, therapeutic drug supervision, and the use of itraconazole as the alternative antifungal agent. This case emphasizes the vigilance in prescribing early recognition of possibly occurring drug interactions and the contribution of a multidisciplinary approach toward safe patient outcomes. Regular monitoring and patient education were essential in preventing complications and optimizing long-term therapy.

REFERENCES

1. Palleria C, Di Paolo A, Giofrè C, Caglioti C, Leuzzi G, Siniscalchi A, De Sarro G, Gallelli L. Pharmacokinetic drug-drug interaction and their implication in clinical management. J Res Med Sci. 2013 Jul;18(7):601-10 https://pmc.ncbi.nlm.nih.gov/articles/PMC3897029/
2. Lee J, Beers JL, Geffert RM, Jackson KD. A Review of CYP-Mediated Drug Interactions: Mechanisms and In Vitro Drug-Drug Interaction Assessment. *Biomolecules*. 2024; 14(1):99. https://pubmed.ncbi.nlm.nih.gov/38254699/
3. Perucca E. Clinically relevant drug interactions with antiepileptic drugs. Br J Clin Pharmacol. 2006 Mar;61(3):246-55. https://pubmed.ncbi.nlm.nih.gov/16487217/
4. Kang JS, Lee MH. Overview of therapeutic drug monitoring. Korean J Intern Med. 2009 Mar;24(1):1-10. https://www.kjim.org/m/journal/view.php?doi=10.3904/kjim.2009.24.1.1
5. Jacob S, Nair AB. An Updated Overview on Therapeutic Drug Monitoring of Recent Antiepileptic Drugs. Drugs R D. 2016 Dec;16(4):303-316. https://pubmed.ncbi.nlm.nih.gov/27766590/
6. Cadle RM, Zenon GJ 3rd, Rodriguez-Barradas MC, Hamill RJ. Fluconazole-induced symptomatic phenytoin toxicity. Ann Pharmacother. 1994 Feb;28(2):191-5.
7. Blum RA, Wilton JH, Hilligoss DM, Gardner MJ, Henry EB, Harrison NJ, Schentag JJ. Effect of fluconazole on the disposition of phenytoin. Clin Pharmacol Ther. 1991 Apr;49(4):420-5 https://pubmed.ncbi.nlm.nih.gov/2015731/

8. Helldén A, Bergman U, Engström Hellgren K, Masquelier M, Nilsson Remahl I, Odar-Cederlöf I, Ramsjö M, Bertilsson L. Fluconazole-induced intoxication with phenytoin in a patient with ultra-high activity of CYP2C9. Eur J Clin Pharmacol. 2010 Aug;66(8):791-5.
9. Blum, Robert & Wilton, John & Hilligoss, Donald & Gardner, Mark & Henry, Eugenia & Harrison, Nedra & Schentag, Jerome. Effect of fluconazole on the disposition of phenytoin. Clinical pharmacology and therapeutics.1991; 49: 420-5. https://www.researchgate.net/publication/21139742_Effect_of_fluconazole_on_the_disposition_of_phenytoin
10. von Winckelmann SL, Spriet I, Willems L. Therapeutic drug monitoring of phenytoin in critically ill patients. Pharmacotherapy. 2008 Nov;28(11):1391-400.
11. Howitt KM, Oziemski MA. Phenytoin toxicity induced by fluconazole. *Med J Aust.* 1989; 151(10):603-604.
12. Tucker RM, Denning DW, Hanson LH, et al. Interaction of azoles with rifampin, phenytoin, and carbamazepine: in vitro and clinical observations. *Clin Infect Dis.* 1992;14(1):165-174. https://pubmed.ncbi.nlm.nih.gov/1315160/
13. Sutton RT, Pincock D, Baumgart DC, Sadowski DC, Fedorak RN, Kroeker KI. An overview of clinical decision support systems: benefits, risks, and strategies for success. NPJ Digit Med. 2020 Feb 6;3:17.
14. Mitchell AS, Holland JT. Fluconazole and phenytoin: A predictable interaction (letter). *Br Med J* 1989; 298: 1315.
15. GianMario Tiboni, Franca Giampietro, Stefania A ngelucci, Pasquale Moio, Umberto Bellati, Carmi ne D. Additional investigation on the potentiation of phenytoin teratogenicity by fluconazole. Toxicology Letters. 2003;145(3):219-229.