

# Phenytoin Delayed Excretion because of Esomeprazole Co-administration

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## Abstract:

**Background:** Drug Interaction between Phenytoin and Esomeprazole is not commonly reported or widely recognized. A case of Phenytoin toxicity post prolonged administration of phenytoin and esomeprazole is reported.

**Case Summary:** A 22 years old female diagnosed with MELAS (Mitochondrial myopathy, Encephalopathy, Lactic Acidosis, stroke like symptoms). She was maintained on Phenytoin 100 mg suspension via nasogastric tube every 8 hours as anticonvulsant for 3 years and esomeprazole 40 mg via nasogastric tube every 24 hours for hyperacidity. After 7 months from co-administration of phenytoin and esomeprazole the patient developed bradycardia, hypotension with nystagmus so upon checking the phenytoin trough serum level it was found to be 163 µmole/L, phenytoin was suspended and serum level monitored daily but it was found to be increasing to 167 µmole/L and the patient laboratory results showed leukopenia, thrombocytopenia and elevated liver enzymes, upon suspending Esomeprazole it was noticed that the Phenytoin serum level decreased dramatically by 10-20 µmole/L/day so the toxicity symptoms and abnormal laboratory results resolved upon normalization the Phenytoin serum level.

**Conclusion:** Esomeprazole may competitively inhibit the CYP2C19 mediated Phenytoin metabolism which leads to prolonged exposure to high serum level and toxicities.

**Keywords:** Phenytoin; Esomeprazole; Phenytoin toxicity; CYP2C19

## Introduction

Phenytoin is a Hydantoin anticonvulsant used to manage generalized tonic-clonic (grand mal) and complex partial seizures and the prevention of seizures following head trauma/neurosurgery; it has also been used for simple partial seizures management [1,2]. Esomeprazole is a Proton pump inhibitor that inhibits gastric acid secretion by blocking the hydrogen-potassium adenosine triphosphatase enzyme system (the 'proton pump') of the gastric parietal cell [3,4]. Both Phenytoin and Esomeprazole are major substrates for CYP2C19 isoenzymes [1,3,4].

Despite of being a weak CYP2C19 inhibitor [3], Esomeprazole was reported to increase the Phenytoin trough serum level by 13% in epileptic patients [4,5]. So it is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn [5,6] and further investigated about this drug interaction.

## Patient information and treatment course

A 22 years old female, diagnosed with MELAS (Mitochondrial myopathy, Encephalopathy, Lactic Acidosis, stroke like symptoms), admitted initially with encephalopathy and lactic acidosis, shifted to ICU due to progressive worsening of respiratory symptoms. Elective tracheostomy was done and patient is maintained on mechanical ventilator, then the patient was transferred to long term care unit.

During her hospital stay, she developed generalized tonic clonic seizures so she was initiated on Phenytoin and maintained on it with a

dose of 100 mg suspension via Nasogastric tube once daily then increased gradually to 100 mg suspension *via* Nasogastric tube three times daily, she was also maintained on clonazepam 0.5 mg *via* nasogastric tube twice daily increased to 1 mg twice daily, levetiracetam syrup 700 mg twice daily, creatin monohydrate powder 3 gm twice daily, esomeprazole 40 mg *via* nasogastric tube once daily.

During the phenytoin course, the phenytoin trough serum level was maintained between 40-80 µmol/L, and Albumin level was maintained between (35-50 g/L).

3 years after starting phenytoin, 7 months after starting esomeprazole the patient started to have nystagmus, bradycardia and hypotension so immediate phenytoin level was ordered and the result was 163 µmol/L (Normal range : 40-80 µmol/L) so the plan was to suspend Phenytoin, do phenytoin level daily until lowering to the therapeutic range again as shown in Table 2.

Parameter	Pre-event Values	Event values	Post event values	Reference range
Total WBC	4900 white blood cells/µL	3500 white blood cells/µL	6200 white blood cells /µL	4000 -10000 white blood cells /µL
Platelets	223 x 10 <sup>3</sup> platelets /µL	115 x 10 <sup>3</sup> platelets /µL	133 x 10 <sup>3</sup> platelets /µL	150 – 400 x 10 <sup>3</sup> platelets /µL
ALT	19 U /L	38 U /L	39 U /L	0 – 30 U /L

**Table 1:** Laboratory parameters monitored.

Days in number	Phenytoin level in (µmole/L)
1	163
2	167
3	157
4	148
5	138
6	126
7	100
8	67

**Table 2:** Phenytoin therapeutic drug monitoring.

Laboratory investigations were done and thrombocytopenia, leukopenia and elevated ALT were found as shown in Table 1.

## Discussion

This case report is adding more data to the previous little data [4,5] about the esomeprazole-phenytoin drug interaction. The role of CYP2C19 competitive enzyme inhibition by esomeprazole was studied and documented in other drug interactions like esomeprazole-clopidogrel [7] drug interaction. It was noticed in this case that esomeprazole postponed the phenytoin excretion *via* CYP 2C19 competitive inhibition.

Limitation of this case report is the lack of the genetic profile of the patient so it is not known if the patient has CYP2C19 deficiency.

Drug interaction probability scale introduced in 2007 by Horn et al. is used to assess the drug interaction causation of elevated serum level of phenytoin. The Drug Interaction Probability Scale (DIPS) uses a series of 10 questions to assess the probability that a causal relationship exists between an event observed in a patient and the administration of 2 drugs. Each question is answered with a "yes," "no," or "unknown/not applicable" response. For each question, a numeric score is assigned to the answer, and the scores from all 10 questions are tallied. The total score is used to estimate the probability that the

interaction is causally related to the patient event. Probability is assigned as doubtful, possible, probable, or highly probable. Two pharmacists with profound knowledge of the two interaction drugs independently used the scale to assign probability to encountered interaction. There was a significant high agreement between the two pharmacists ( $\kappa=0.8$ ,  $P\text{-value}=0.04$ ) for a "Probable" interaction between esomeprazole and phenytoin to cause elevated phenytoin serum level. Analysis was performed using Stata software (version 14.2).

## Conclusion

It is concluded that esomeprazole is affecting the phenytoin excretion so it is recommended to closely monitor phenytoin serum trough level upon initiation, discontinuation or esomeprazole dose adjustment, also it is recommended to suspend esomeprazole in case of phenytoin toxicity, and finally it is recommended to further investigate in the significance of this drug interaction.

## Acknowledgements

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## Competing Interest

We declare that we have no personal interests that might have influenced the performance of the work described in this case report.

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