

# Phenytoin Induced Psychosis: A Case Report

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## ABSTRACT

An adverse drug reaction is a causal relationship between a drug and an event. Alcohol consumption remains a huge threat to the global health. A seizure is an event accompanied with loss of motor activity and alterations in the patients EEG. Phenytoin is one of the most commonly employed anti-seizure medications. Manifestations of chronic phenytoin use may induce phenytoin toxicity and psychosis. Here we report a case of a 45 year old male patient with probable phenytoin induced psychosis while being treated for seizures in the in-patient ward. The long term use of phenytoin may manifest psychotic symptoms in certain population. There is a definite need of more evidence in this field and proper diagnostic and management approaches.

**Key words:** Adverse drug reaction, Alcohol, Phenytoin, Probable, Psychosis, Seizures.

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## INTRODUCTION

An adverse drug reaction (ADR) is an injury caused due to a drug. A causal relationship between the drug and the event signifies an ADR, which can also be due to an interaction of the drug and the events usually are unexpected with resultant toxic effects.<sup>1</sup> Based on the severity and the outcome of an ADR, it may require a change in therapy, admission to a hospital, prolonged hospital stay that may even result in disability, coma or death.<sup>2</sup>

Alcohol use has lead to a huge burden on the global health. Alcohol withdrawal syndrome refers to a set of outcomes following reduction or abstinence from alcohol use. Such outcomes usually occur in individuals with alcohol dependency and the pathophysiology behind this generally involves a decreased responsiveness of the Gama aminobutyric acid (GABA) receptors and abnormalities in the glutamate receptors.<sup>3</sup>

Seizures can be defined as an event characterized by an altered state of consciousness that may be accompanied with loss of motor activity or abnormal motor activity with alterations in the patients electroencephalogram (EEG).<sup>4</sup> The induction of the abnormal discharge potentiates from the neurons in the cortical or subcortical regions, that can also be triggered by minute stimuli such as fever, drug induced and biochemical-physiological disturbances.<sup>5</sup>

Phenytoin acts via the direct action on the sodium channels receptors regulating the movement of the sodium ions resulting into net control of the action potential and neuronal firing.<sup>6</sup> However, long-term use of anti-seizure drugs has been reported to produce psychosis in various patients.<sup>7</sup>

Psychosis can be defined as a mental health problem leading to the inability of the patient to perceive the reality (hallucinations and delusions).<sup>8</sup> The incidence of psychosis in India ranges up to 58.2 per thousand populations.<sup>9</sup> The descriptions of drug-induced psychosis as complications of long-term therapy of anti-seizure drugs is still non conclusive as the number of evidential reviews are less.

## CASE HISTORY

A 45 year old male patient was presented to the intensive care unit (ICU) with complaints of seizures and altered behavior. On examination his physical and vitals were normal, Central nervous system (CNS) with bilateral postural tenderness was also found to be normal, Cardio vascular sounds (CVS) S1S2 normal, Respiratory system (RS) with bilateral air entry positive and per abdomen soft. Blood pressure (BP) was measured at 110/70mmHg and Pulse Rate (PR) was 88beats/minute. His past medical history found him to be a chronic alcoholic and with occasional seizure episodes since ten years. His medication history includes Phenytoin 100mg BD.

At the day of admission, his partial oxygen was measured 95% in room air with fluid input and output being 1500/1000ml. The patient was prescribed with IV Ringer Lactate (RL) 2 pints, Normal Saline (NS) 2 pints, Inj Diazepam 1mg diluted in 10ml of NS IV SOS, Inj Phenytoin 600mg in 1pint of NS infused for 1hour, Inj Ranitidine 50mg BD, IV Ondansetron 10mg SOS, Inj Vitamin B<sub>12</sub> 100mg IM OD, Inj Thiamine 100mg in 1pint Normal Saline over one hour and Inj Dexamethasone 8mg BD.

On the second day since admission, the BP was measured at 110/60mmHg, PR-78/minute, Respiratory rate (RR)-22/minute and his partial oxygen (SPO<sub>2</sub>) was 95% in room air with fluid input and output chart being 2400/1600 ml. He was prescribed with Inj Ranitidine 50mg BD, Inj Vitamin B<sub>12</sub> 100mg IM OD, Inj Dexamethasone 8mg BD, Tab Phenytoin 100mg, Tab Calcium 300mg OD, Tab B-Complex BD, Tab Diazepam 5mg 3-3-4, Inj Phenergan 12.5mg IM BD and Tab Haloperidol 1.5mg BD.

The next day, the patient was found to be restless and non-cooperative. Diazepam was withheld with continuation of the other therapies. On the fourth day, the patient presented with complaints of sleep disturbances and progressive muscular atrophy (PMT). BP was measured at 120/80mmHg, PR-80/min, RR-20/Min, Fasting blood Sugar (FBS)-

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110mg%, Post Prandial Blood Sugar (PPBS)-120mg % and his partial oxygen was 95% in room air with fluid input and output being 1250/900 ml. The patient was prescribed with IVF NS one pint, 10% DNS 1 pint, Inj Thiamine 100mg in 100ml of normal saline, Inj Ranitidine 50mg BD, Tab Diazepam 5mg 3-3-4, Inj Phenergan 12.5mg IM BD, Tab Haloperidol 1.5mg BD and Tab B-Complex 2-2-2.

On the fifth day, the patient had complaints of bed-wetting and was not willing for catheterization. The patient was transferred to a tertiary care hospital for further treatment.

## DISCUSSION

Alcohol use remains the fourth leading cause of preventable deaths in the World. The global scenario dictated excessive alcohol use linked with approximately 3.3 million deaths in the year of 2015. Moreover, alcohol consumption has been attributed to 5.1 % of the global disease burden, which can be measured as in disability adjusted life years (DALYs).<sup>10</sup> The incidence of death and disability occur relatively in the early ages in life. Similarly, an approximate of 25 % of the total deaths in people from the age group 20 – 39 years were attributable to alcohol.<sup>11</sup> Moreover, alcoholism may associate with Wernicke encephalopathy, Korsakoff syndrome and hepatic encephalopathy.<sup>12</sup> Alcohol affects virtually every organ system in the body and several neurotransmitter systems in the brain, including opiates, GABA, glutamate, serotonin and dopamine. However, chronic alcohol consumption leads to the blockade of glutamate receptors with resultant follow of complex biological pathway that ultimately leads to the over expression of glutamate receptors. Therefore, on withdrawal, the central nervous system experiences increased excitability.<sup>13</sup> Alcohol dependence is regarded as the final phase of habitual alcohol consumption. Benzodiazepines are usually the first line choice of drug for the symptomatic reliefs, which may include an add on anticonvulsant therapy with or without supportive care depending upon the biological assay of the patients blood.<sup>14</sup>

Consumption of alcohol promotes seizure threshold, cessation of alcohol decreases the seizure threshold. The increase in seizure threshold may be mediated through the calcium and chloride flux through the ion-gated glutamate, N-methyl-D-aspartate (NMDA) and Gamma-Aminobutyric Acid (GABA) receptors. Daily alcohol intake has been reportedly linked with hyponatremia and hypomagnesaemia.<sup>15</sup> Approach generally includes one or all of the following. Intravenous (IV) line of 5% dextrose and saline with Inj thiamine, dextrose and Inj naloxone. Lorazepam is usually first line choice for symptomatic seizures.<sup>16</sup>

A seizure is a sudden and uncontrolled electrical disturbance induced due to imbalance in the excitatory and inhibitory forces with excessive excitation or loss of inhibition within the cortical neurons.<sup>17</sup> Recent evidence on epileptic medications witness patients with drug induced neurological disorders. Commonly used anti-seizure medications were reported to cause antiepileptic drug induced psychotic disorder (AIPD).<sup>18</sup> A need that arises, now is the need of more prominent evidence and regular Psychosis screening as well. However, the confirmation of the phenytoin-induced psychosis is a debatable issue and the most commonly used ways for confirmation include drug de-challenge and re-challenge.

Phenytoin is one of the most commonly used anti-seizure drug and also been reported with antiarrhythmic and muscle relaxant properties as well.<sup>19</sup> In the year 2015, the American National Poison Data system reported 1601 patients bearing single exposures to phenytoin and moreover, 543 of them were reported with adverse reactions.<sup>20</sup> Other indications of phenytoin include as first-line or an adjunctive therapy for partial and generalized seizures, status epilepticus, Lennox-Gastaut syndrome and childhood epileptic syndromes. Phenytoin has a very partial gastro intestinal (GI) absorption. Moreover, phenytoin, when

administered intravenously at a rate higher than 50 mg/min may lead to cardiac toxicity and hypotension. The volume of distribution reported for phenytoin is 0.6 L/kg and is also reported with 90% extensive binding to plasma proteins.<sup>21</sup>

Psychosis is a socio-economical problem associated with situations that are not real and imaginary, which affects one's personal life, social status and the people around them. Psychosis can be classified into two sub categories. Episodic psychosis of epilepsy and non-episodic psychosis of epilepsy. Episodic psychosis of epilepsy is correlated to the seizure episodes or events and vice versa.<sup>22</sup> Patients with chronic epilepsy may or may not display psychosis related to treatment with Phenytoin. The pathophysiology rendering the relation between psychosis and phenytoin have always hypothesized with Vitamin B12 deficiency and folic acid deficiency.<sup>23</sup> However, there are still reports of phenytoin induced psychosis non attributable to the above. Moreover one hypotheses also remains with the susceptibility linked to the neuro-anatomical anomalies that may potentiate an drug induced psychosis.<sup>24</sup> And a pathophysiology concerned with vitamin B deficiency in phenytoin use.<sup>25</sup> This case signifies the long-term use of phenytoin and resultant psychosis. The psychotic symptoms were controlled upon de-challenge of the suspected drug. On the basis of Naranjo Causality assessment, the reaction was found to be a probable reaction. The data for re-challenge was not attained because of patient transfer to a tertiary care hospital.

## CONCLUSION

The following case signifies the occurrence of unexpected ADRs that might follow phenytoin use. More updated evidence and directive management approaches are a required goal in such circumstances.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ABBREVIATIONS

**ADR:** Adverse drug reaction; **AIPD:** Antiepileptic drug Induced Psychotic Disorder; **CVS:** Cardio vascular sounds; **CNS:** Central nervous system; **DALYs:** Disability adjusted life years; **EEG:** Electroencephalogram; **FBS:** Fasting blood Sugar; **GABA:** Gama aminobutyric acid; **GI:** Gastro intestinal; **ICU:** Intensive care unit; **IV:** Intravenous; **NMDA:** N-methyl-D-aspartate; **NS:** Normal Saline; **PPBS:** Post Prandial Blood Sugar. **PMT:** Progressive muscular atrophy; **RS:** Respiratory system; **RL:** Ringer Lactate.

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