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Usual Erratic Phenomenon, Dramatic Outcome: A Case Report of Phenytoin Toxicity

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ÖZET:

Değişken fenomen, dramatik sonuç: Fenitoin toksisitesi olan bir olgu

Fenitoin birçok ülkede hala yaygın olarak kullanılan bir antiepileptik ilaçtır. Fenitoin'in olağan yan etkileri arasında horizontal nistagmus, ataksi ve bilişsel işlev bozukluğu bildirilmiştir. Bu yazıda, fenitoinin klinik olarak gözden kaçmış yan etkilerine bağlı olarak ortaya çıkan ve davranım bozukluğu şeklinde görülen nadir rastlanan bir fenitoin toksisitesi olgusu sunulmuştur. Fenitoin dozunun azaltılmasıyla yan etkiler ve ikincil davranışsal bulgular düzelmiştir.

Anahtar sözcükler: Fenitoin, toksisite, yan etkiler

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ABSTRACT:

Usual erratic phenomenon, dramatic outcome: a case report of phenytoin toxicity

Phenytoin is still one of the most commonly used antiepileptic drugs in clinical practice in many countries. It has a range of usual deleterious and erratic side effects, which have been reported previously including horizontal nystagmus, ataxia and cognitive dysfunctions amongst others. Here we report a rare case of phenytoin toxicity presenting dramatically as a behavioral disorder resulting from two underlying primary adverse effects of phenytoin, which were clinically overlooked. Reduction in the dose of phenytoin resulted in remission of side effects as well as the secondary behavioral manifestations.

Key words: Phenytoin, toxicity, adverse effect

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INTRODUCTION

Phenytoin seems to be the most commonly used and studied antiepileptic agent and its side effects and toxicity symptoms are well documented (1). It is a well-known fact that phenytoin may commonly cause central nervous system side effects like sedation, blurring of vision, nystagmus, ataxia, hyperkinesia, psychosis and phenytoin encephalopathy in addition to other noted side effects such as megaloblastic anemia, decreased serum folate level, decreased bone mineral content, liver disease, Immunoglobulin A deficiency, gingival hyperplasia, and a lupus-like hypersensitivity syndrome. Research has shown that neurological and cognitive adverse effects are more common and more deleterious with phenytoin and other older antiepileptic drugs than with the newer antiepileptics (1,2,3). Moreover these usual erratic neurological and cognitive adverse effects can be more troublesome in young, physically active cases and those patients with active cognitive lifestyles, resulting in a variety of problems ranging from poor performance in studies to impairment in the work place.

Furthermore these side effects if overlooked, which is rather common as has been reported earlier (4), can lead to behavioral changes ranging from irritability and low mood to suicidality especially in patients with active cognitive lifestyles including school-aged children and adolescents. Here we report a rare case of phenytoin toxicity in

an adolescent male presenting dramatically as poor scholastic performance with behavioral changes.

CASE REPORT

An 18 year old male, single Hindu patient, a student of the 12th class and belonging to the middle socio-economic level was referred to the Out Patient Clinics of Psychiatry of Vardhman Mahavir Medical College & Safdarjang Hospital, New Delhi with a note mentioning examination phobia, abnormal behavior and suiciderisk.

The patient was accompanied by his mother and presented with a complaint of performance anxiety in the ongoing 12th class board examinations manifested as episodic blurring of vision bilaterally at approximately 10 am and 10 pm, which lasted about 1-2 hours. These spells were associated with giddiness and difficulty maintaining balance while walking. The symptoms of irritability, feeling low and subsequent aggression were also present along with death wishes. Further questioning revealed that he had previously been diagnosed with generalized tonic clonic seizures (GTCS) and had been on phenytoin 300 m/day with folic acid 5 mg / day for the past two and a half years and was seizure free and stable on treatment. However following two recent episodes in a day, phenytoin had been increased to 400 mg (200 mg twice a day). After about six weeks of increased dosage, the patient gradually started having blurring of vision with giddiness, which happened about 2 to 2.5 hours after the of intake of phenytoin in the morning and night. The symptoms gradually increased further with comorbid loss of balance while walking. He started falling back in his studies and hence performed very poorly in examinations to the extent that in one paper he wrote nothing because of the blurred vision and gait problems. Consequently, he started feeling low and helpless, became irritable and abusive from time to time, to the extent of expressing death wishes which was culminated in an intent to commit suicide. The treating physician and family members linked these symptoms to academic performance anxiety due to the dramatic presentation and episodic nature of the symptoms. On the Hamilton depression rating scale (HDRS) his score was 20. His routine blood and urine tests and Brain Magnetic Resonance Imaging (MRI) findings were normal; but post-episode Electro-Encephalography (EEG) observations suggested interictal epileptiform activity.

He was empirically treated with escitalopram 10 mg per day, while his blood sample was sent for serum phenytoin and folic acid assays. Serum phenytoin and folic acid levels were found to be 28.3 mcg/ml and 22 ng/ml, respectively. Opthlamologic examination revealed horizontal nystagmus and macular edema bilaterally while his visual acuity was normal. The phenytoin dose was reduced to 350 mg/day with a careful watch for any seizure activity.

Within 15 days of the dose reduction, the visual blurring episodes as well as giddiness and gait problems reduced both in intensity and duration while his mood improved dramatically, with his HDRS score dropping to 5. The repeat opthalmologic examination gave no evidence of diplopia or macular edema with foveal contour being maintained. The serum phenytoin level decreased to 15.3 mcg/ml within a month. The antidepressant dose was tapered and subsequently discontinued. During the next two months of follow-up, patient did not report any seizures.

DISCUSSION

The symptoms experienced by the patient in question are understandable in terms of the complex pharmacokinetics, narrow therapeutic index and individual variability in the metabolism and elimination of phenytoin. The patient developed exaggerated side effects gradually over a period of 6 weeks after the dosage increase, which can be explained by the gradual build up of the drug over the time as the pharmacokinetics of phenytoin follows a nonlinear path changing from first order kinetics to zero order; hence, even minor dosage changes can result in variable concentrations as the elimination is saturated (5).

Furthermore the patient experienced episodic toxic effects about 2 to 2.5 hours after drug intake;

peak plasma concentration is reached in 2.5 to 12 hours after the oral intake of phenytoin and even earlier peaks have been reported (6). Previous research has reported these types of transient neurotoxic and ophthalmic side effects as occurred in this case during the first few hours of drug ingestion due to excessive fluctuation in plasma concentration of phenytoin between intake and time to peak plasma concentration (5).

Moreover toxic side effects may develop in some patients even at therapeutic concentrations as the relationship between serum level of antiepileptic drugs and their side effects has always been found to be somewhat erratic (5,7,8). What is important here is to understand the deleterious effect of these side effects on the scholastic performance and the consequent development of dramatic behavioral symptoms, even suicidality, when the primary side effect cluster was overlooked (9).

The initial presentation of this case was indeed dramatic in nature and hence the treating physicians were mislead into considering the possibility of stress induced psychiatric disorders or aggravation of the underlying seizure disorder. However careful history taking and supporting scientific evidence ruled out such disorders.

Hence, this case report serves to alert clinicians to remain clinically vigilant for such manifestation in patients with active cognitive lifestyles who are on long term phenytoin therapy. Caution needs to be exercised when making dosage changes as we saw that even a small change can precipitate or mitigate the side effects. There is a need to keep in mind the erratic association of serum levels and toxic effects especially in case of phenytoin so that the progression to such possibly hazardous behavioral changes and the dramatic consequences thereof can be prevented.

References:

1. Livanainen M, Savolainen H. Side effects of phenobarbital and phenytoin during long-term treatment of epilepsy. Acta Neurol Scand Suppl 1983; 97:49-67.
2. Larsen JR, Larsen LS. Clinical features and management of poisoning due to phenytoin. Med Toxicol Adverse Drug Exp 1989; 4(4):229-45.
3. Cohen AF, Ashby L, Crowley D, Land G, Peck AW, Miller AA. Lamotrigine (BW430C), a potential anticonvulsant. Effects on the central nervous system in comparison with phenytoin and diazepam. Br J Clin Pharmacol 1985; 20(6):619-29.
4. Hwang WJ, Tsai JJ. Acute phenytoin intoxication: causes, symptoms, misdiagnoses, and outcomes. Kaohsiung J Med Sci 2004; 20(12):580-5.
5. Hussein A, Abdulgalil A, Omer F, Eltoum H, Hamad A, El-Adil O, et al. Correlation between Serum Level of Antiepileptic Drugs and their Side Effects. Oman Med J 2010; 25(1):17-21.
6. Robinson JD, Morris BA, Aherne GW, Marks V. Pharmacokinetics of a single dose of phenytoin in man measured by radioimmunoassay. Br J Clin Pharmacol 1975; 2(4):345-49.
7. Lüders H, Acharya J, Baumgartner C, Benbadis S, Bleasel A, Burgess R, et al. Semiological seizure classification. Epilepsia 1998; 39(9):1006-13.
8. Engel J Jr. Classifications of the International League Against Epilepsy: time for reappraisal. Epilepsia 1998; 39(9):1014-17.
9. Pandey AK, Gupta S. Biological correlates of mental disorders psychiatric symptomatology, scholastics and phenytoin: A case report Posters. Indian J Psychiatry [serial online] 2011 [cited 2012 May 6];53:73-109. Available from: http://www.indianjpsychiatry.org/text.asp?2011/53/5/73/94536 accessed online on 20th may 2012.