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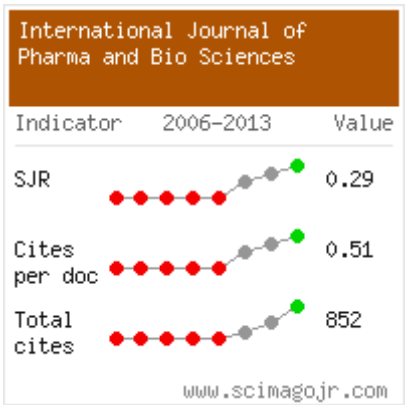

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Case Report **Pharamacology**

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A RARE CASE OF PHENYTOIN INDUCED CHOREA & PHENYTOIN HYPERSENSITIVITY SYNDROME

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ABSTRACT

Phenytoin is widely prescribed anticonvulsant for seizure disorder.However, it is associated with a lot of side effects of which chorea and Anticonvulsant hypersensitivity syndrome(AHS) are rare. Occurence of Phenytoin induced chorea and AHS at the same time is a very rare phenomenon .Hereby we are presenting a case where both occurred at same time.CASE:57 yrs old female presented to outpatient department with complaints of abnormal facial and limb movements, fever ,rash. She was on phenytoin for one month.She developed phenytoin induced chorea and AHS at the same time. Phenytoin was immediately withdrawn from the patient and started on levetiracetam .Patient's chorea and AHS recovered in 1 week. Conclusion: phenytoin induced chorea and AHS presenting in same time in the same patient is very rare.The early recognition of multi organ involvement is important as stopping the drug results in complete recovery. Anticonvulsant Hypersensitivity Syndrome should be considered in any patient treated with phenytoin, carbamazepine or phenobarbitone who presents with fever, rash or lymphadenopathy. The medication should be immediately discontinued pending investigation. Although the syndrome is rare, recognition is essential to avoid considerable morbidity and possible fatal outcome.

KEYWORDS: **phenytoin, chorea, anticonvulsant hypersensitivity syndrome.**

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INTRODUCTION

Phenytoin is widely prescribed Anticonvulsant for seizure disorder. However it is associated with myriad of side effects both idiosyncratic and dose related .we are presenting a rare case of Anticonvulsant hypersensitivity syndrome and Chorea presenting at same time within one month of starting Phenytoin.

CASE

A 57 years old female patient weighs 50 kg came to OP with complaints of fever not associated with chills,rash, involuntary movements of face, tongue and limbs of two days duration. She was diagnosed to have seizure disorder one month back and was taking phenytoin 300 mg per day daily. There was no history of fresh seizure ,altered sensorium. On examination pulse rate 76 per minute, regular. Blood pressure was 110/70 mm of hg,There was no pallor,cyanosis,clubbing,edema but lymphadenopathy was present.Maculo papular erythematous rash on face ,ears,trunk was present.Cental nervous system examination was normal except for involuntary movements involving face,tongue,upper extremities.The patient had repeated twitching and grimacing movements of face that changed constantly in character and location.There was abnormal vocalization and difficulty in maintaining phonation.There were bilaterally abrupt involuntary rapid and forceful swinging movements of upper limbs at irregular intervals.These used to disappear during sleep.Rest of systemaic examination was normal.Routine haematological and biochemical profile was normal except of raised liver enzymes.MRI of brain normal.The plasma phenytoin level was in toxic range of 32micrograms per millilitres(normal 10-20 microgram per ml).phenytoin was immediately stopped.The involuntary movements disappeared in three days.Fever and rashes subsided in 4 days. Plasma phenytoin level and liver function tests were repeated after 1 week, which was found to be normal and the patient was discharged from hospital.

DISCUSSION

Phenytoin is widely used for seizure disorders in adults as well as children,however it is associated with many side effects including cardiovascular,neurologic, hematologic, dermatologic,gingival hyperplasia. Chorea and hyperkinetic movements ,phenytoin hypersensitivity syndrome are the rare side effects of phenytoin. Phenytoin toxicity depends on the route of administration, duration, exposure, drug interaction, and dosage. Oral exposures are associated predominantly with CNS symptoms. Individuals with impaired metabolic or excretory pathways may exhibit early signs of toxicity. Phenytoin produces its anticonvulsant activity through blocking sustained high frequency repetitive firing of action potentials. This is accomplished by reducing the amplitude of sodium-dependent action potentials through enhancing steady state inactivation. Sodium channels exist in three main conformations 1.Resting state 2.Open state 3.Inactive state Phenytoin binds preferentially to the inactive form of the sodium channel. Because it takes time for the bound drug to dissociate from the inactive channel, there is a time dependent block of the channel. Since the fraction of inactive channels is increased by membrane depolarization as well as by repetitive firing, the binding to the inactive state of phenytoin sodium can produce voltage-dependent, use- dependent and time-dependent block of sodium-dependent action potentials.The primary site of action appears to be the motor cortex where spread of seizure activity is inhibited. Phenytoin tends to stabilize the threshold against hyperexcitability possibly by promoting sodium efflux from neurons caused by excessive stimulation or environmental changes capable of reducing membrane sodium gradient. This includes the reduction of post-tetanic potentiation at synapses, which prevents cortical seizure foci from detonating adjacent cortical areas. Phenytoin reduces the maximal activity of brain stem centers responsible for the tonic phase of generalized tonic-clonic seizures. Phenytoin elimination kinetics show mixed-order behaviour at therapeutic concentrations. A

small increase in dose may lead to a large increase in drug concentration as elimination becomes saturated. The time to reach steady state is often longer than 2 weeks Phenytoin is predominantly metabolized by CYP2C9 and to a lesser extent by CYP2C19 [1]. Mechanism of chorea due to phenytoin is still not clear. Prolonged phenytoin therapy or its high plasma concentration is related to increased dopaminergic and serotonergic activity in basal ganglia that may be considered as a cause of chorea [2]. Anticonvulsant-induced choreoathetosis was first reported in 1962 with phenytoin. The use of phenytoin with other medications was reported to an increase the risk of developing abnormal movements. Pharmacokinetic interaction leading to increased free phenytoin level was suggested as a plausible explanation. Both generalized and focal movements have been described. Duration of dyskinesia has been variable, but has often responded to discontinuation of the anticonvulsants. Dyskinesias most commonly involved the limbs, but orofacial involvement has been noted in some cases. Early identification and withdrawal of phenytoin may prevent the permanent damage to the basal ganglia. Drugs that alter the functions of these enzymes can place the patient at risk of toxicity [3]. PHS is a rare syndrome, potentially fatal non-dose related idiosyncratic complication of phenytoin use. In most cases the reaction occurs between two weeks to two months after administering the drugs.A broader terminology of the Anticonvulsant hypersensitivity syndrome (AHS) has been used as this syndrome can result from usage of any aromatic anti epileptic drug (AED) such as phenytoin, carbamazapine (CBZ), phenobarbitol and occasionally lamotrigine the commonest being carbamazepine and phenytoin [4.] Anticonvulsant Hypersensitivity Syndrome (AHS) is a drug-induced, multiorgan syndrome which is potentially fatal. The syndrome has been reported with anticonvulsants such as carbamazepine, phenytoin, phenobarbitone and lamotrigine. Other medicines, such as sulphonamides, sulphones, allopurinol and NSAIAs (e.g. piroxicam), have also caused a multiorgan hypersensitivity syndrome. It is a clinical diagnosis. The interval between first drug exposure and symptoms is usually 2-4 weeks but has been reported in individuals receiving anticonvulsants for 3 months. The syndrome is more severe in previously sensitised individuals. The incidence of AHS is not known because of the variability in presentation, lack of strict diagnostic criteria and underreporting of cases. However, it is considered rare. While up to 1 in 5 patients on phenytoin may develop cutaneous eruptions, only a small proportion will progress to AHS. Fever, rash and hepatitis are common features. Fever is the most common feature, seen in 90-100% of cases[5]. High and spiking fevers are characteristic although an intermittently elevated temperature may persist for weeks after the offending drug is discontinued. The fever may precede or be concurrent with the cutaneous eruption. A rash is present in 90% of cases. This is usually a macular erythema that becomes confluent and may generalise into erythroderma. The face, trunk and upper limbs are the first to be involved followed by the lower limbs. The rash may spare the face. Desquamation occurs with resolution. Periorbital and facial oedema may be severe and occurs in 25% of cases. Blistering may be seen over oedematous areas. Hepatitis, seen in 50% of cases of AHS, is usually mild but can be severe. The mortality rate is between 18 and 40% if hepatitis is present. Liver function tests, may be grossly elevated and continue to rise after the drug has been discontinued. Return of liver function tests to normal may take up to a year. Tender lymphadenopathy occurs in 70% of cases and may be either local or generalised. Splenomegaly may be seen. Fifty per cent of patients with AHS have haematological abnormalities.The clinical course is variable. Initially, patients appear toxic. If,AHS is recognized early and the culprit drug(s) is discontinued, the course is often less eventful, with the syndrome resolving over the next few weeks. The rash may disappear with mild desquamation. There is a resolution of fever and hematologic abnormalities become normal. Patients often experience a brief flare of signs and symptoms 2-3 weeks after improvement. Sometimes, however, even after discontinuation of the culprit AED the hypersensitivity reaction process may progress, and the patient become worse, before any improvement is seen. The syndrome is sometimes fatal. Particularly if hepatitis is present, the mortality is about 20%. Patients who are rechallenged with the culprit

AED, whether inadvertently or in a controlled setting, develop the symptoms of fever, sun rash, and lymph- adenopathy almost immediately after reexposure . clinical features may be of variable onset, leading to confusion and delay in diagnosis[6]. The complete pathogenesis of AHS is unknown. There is evidence suggesting that AHS induced by PHT, CBZ, or PB is associated with a relative excess of reactive metabolites. These toxic metabolites can occur as a result of oxidative metabolism of the parent compounds by cytochromes P450 and other oxidative enzyme systems (e.g., myeloperoxidases, thyroid peroxidases). These toxic metabolites are usually further biotransformed and detoxified by epoxide hydroxylase . One hypothesis is that this enzyme may be lacking or mutated in persons who develop AHS. However, various studies found that a genetic defect altering the structure and function of epoxide hydroxylase is unlikely to be respon- sible for predisposing patients to AED adverse reactions. Defective detoxification may lead to cell death or con- tribute to the formation of an antigen that triggers an immune reaction . In relatives (parents, siblings) of patients who have been exposed to AEDs, toxicity was found to be intermediate between controls and patients, suggesting an inherited defect [7]. However, other theories have been proposed, e.g., that the AHS represents a form of graft-vs.-host disease or that the reaction is mediated in part by circulating antibodies . In vivo and in vitro tests (with the lymphocyte toxicity assay) showed that cross reactivity between PHT, CBZ, or PB was as high as 70-80% . If the diagnosis of AHS is in doubt and seizure control with one of these medications is required, patch testing may be helpful.It is recommended that negative patch tests should be repeated several months after an episode of AHS, as delayed results have been reported.In vitro lymphocyte transformation tests have also been used to diagnose AHS. However, they are not generally available in clinical practice. Both tests are reliable only after the signs of AHS have subsided [8]. Treatment of AHS is largely symptomatic. The offending medicine should be immediately discontinued. Topical steroids and antihistamines are helpful in controlling symptoms associated with the rash [9]. Systemic corticosteroids are often used, although there have been no trials to assess the efficacy of this treatment. It appears that they may benefit the cutaneous but not the systemic manifestations of the syndrome. Supportive care and monitoring of haematological and biochemical values is important. Relapse of the condition is often seen. Patients who have experienced AHS should avoid arene oxide anticonvulsants (carbamazepine, phenytoin and phenobarbitone) in the future [10]. In our case both chorea and Phenytoin hypersensitivity syndrome (PHS) have manifested at the same time within 1 month of starting phenytoin which is a very rare presentation. Patient recovered completely on stopping phenytoin Normal CT-scan ,MRI brain reports has ruled out any structural damage to the brain. Involuntary movements caused by phenytoin are mainly related to its high plasma concentration (32 micrograms/ml).

CONCLUSION

Phenytoin induced chorea and hypersensitivity syndrome occuring in the same time in a person is very rare..The early recognition of multi organ involvement is important.. Anticonvulsant Hypersensitivity Syndrome should be considered in any patient treated with phenytoin, carbamazepine or phenobarbitone who presents with fever, rash or lymphadenopathy. The medication should be immediately discontinued pending investigation. Although the syndrome is rare, recognition is essential to avoid considerable morbidity and possible fatal outcome.

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