ORIGINAL RESEARCH PAPER

Neurology

KEY WORDS: Phenytoin, toxicity, ataxia.

STUDY OF TOXICITY PROFILE OF PHENYTOIN

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ABSTRACT

Phenytoin is one of the most commonly used Anti-Epileptic drugs(AEDs). We studied the clinical profile of patients admitted with Phenytoin toxicity. This is a retrospective study of 10 patients diagnosed with Phenytoin toxicity who presented between July 2014 and December 2015. Data on age, sex, duration and dose of phenytoin, concomitant AED use, presenting symptoms, duration of complaints, MRI changes and treatment were recorded. The mean age of patients was 39 years. Nine of the ten patients manifested symptoms at or below 300 mg. The average Phenytoin level was 41.54 mcg/ml. Eight of the ten patients were switched to Levetiracetam and nine of the ten patients recovered. Phenytoin toxicity can develop even at doses of 300 mg daily which is widely used when initiating therapy. This highlights the need to follow up patients, measure plasma levels if required and take steps to reduce risk of toxicity.

INTRODUCTION

Phenytoin (Diphenylhydantoin) is one of the most commonly used AEDs. It was synthesised as a barbiturate analogue but has only mild sedative properties at usual doses. Ironically, at toxic doses Phenytoin tends to produce excitement and muscular rigidity. At therapeutic doses, Phenytoin acts by prolonging the inactive state of the voltage sensitive Sodium channels in neurons; thus, it inhibits high frequency neuronal discharges. At higher doses Phenytoin acts by reducing Calcium influx, Glutamate inhibition and GABA facilitatory action. It is particularly effective in abolishing the tonic phase of Generalised Tonic Clonic Seizures (GTCS). Its effectiveness in a wide variety of partial and tonic-clonic seizures, coupled with its low cost and availability makes it one of the drugs on the WHO Essential list of Medicines. [1][2][3]

Due to its specific chemical structure and behaviour, it has a tendency for drug interactions and in itself has a very narrow therapeutic range necessitating Therapeutic Drug monitoring (TDM).[1]This study aims to shed light on the clinical profile of patients admitted at our centre with symptoms of toxicity and their course under our care.

MATERIALS AND METHODS:

We did a retrospective analysis of 10 patients diagnosed with Phenytoin toxicity at our centre betweenJuly 2014 and December 2015.

Patients who were at least 18 years old and who had received oral Phenytoin for a minimum of two weeks were included in the study. Patients who received Phenytoin for a period less than 2 weeks and patients with documented cerebellar abnormalities prior to Phenytoin use were excluded from the study.

The data collected was as follows: age, sex, duration of Phenytoin use, dose of Phenytoin, concomitant AED use, presenting symptoms, duration of complaints, MRI changes and details of treatment. To prove causality, the Naranjo algorithm and the WHO-Uppsala Monitoring Centre scales were retrospectively applied on the available data to assess the likelihood of the symptoms being a result of Phenytoin use. The severity of the adverse reactions was judged by the Hartwig severity assessment scale.

The data were analysed using Microsoft Excel 2010.

RESULTS

Ten patients diagnosed withPhenytoin toxicity who had visited our centre were included in the study. The mean age of patients was 39years with 5 males and 5 females. All of the patients presented with incoordination, four of them were diagnosed with Phenytoin induced encephalopathy. The duration of such symptoms varied widely with the median being 10.5 days (Range: 1-180 days). The duration of phenytoin intake among the documented cases was usually in years. Two of the patients were on concomitant AEDs with one of these patients on Valproate and Phenobarbitone while another was on additional Phenobarbitone. Eight of the ten patients were on 300 mg of Phenytoin, the other two being on 200mg and 600 mg daily. MRI brain had been done in seven of the ten patientswiththree studies revealing cerebellar atrophy. The average drug level in plasma was 41.54 mcg/ml (Range: 25- 48.7 mcg/ml). With withdrawal of Phenytoin and switch to alternative drugs such as Levetiracetam (8/10), Valproate (1/10) and Clobazam (1/10)- most patients (9/10) recovered with no long-term deficits. The one other patient was discharged against medical advice.

DISCUSSION:

Phenytoin has a very narrow therapeutic range as it is between 10-20 mcg/ml.[2]Ataxia is known to occur at concentrations above 30mcg/ml.Phenytoin has a peculiar pharmacokinetic profile. It is not very soluble and thus oral absorption is slow. Once absorbed 90% of the drug is protein bound, with the unbound fraction of the drug being the active moiety. The unbound fraction is higher in neonates, elderly, patients with hypoalbuminemia, hyperbilirubinemia or those using drugs such as Salicylates or Tolbutamide that are known to displace the bound drug.[4]Metabolism shows saturation kinetics – changing from first order to zero order kinetics over the therapeutic range.[1] As a clinical corollary, small up-titrations of Phenytoin can cause significant increases in Phenytoin plasma levels.Further, Phenytoin is known to interact with a variety of drugs with many Cytochrome enzyme inhibitors such as Valproate, Chloramphenicol, Isoniazid and Cimetidine capable of precipitating toxic symptoms by interfering with the metabolism of Phenytoin.[4]Phenytoin toxicity usually presents with cerebellar and vestibular manifestations. With further increasein concentration, patients can present with mental confusion, rigidity, hallucinations and disorientation. Treatment is primarily by drug withdrawal and supportive care with a switch to alternate AED.[5]

Four patients in our study were diagnosed to have Phenytoin induced encephalopathy and it has been documented to present with such features.[6][7] A careful drug history is a must to exclude this cause. Eight of the ten patients in our study had nystagmus on examination and had cerebellar signs. The symptom duration varied widely highlighting the need to educate patients on the signs of toxicity. Two of the patients in our study were on concomitant AEDs that have known interactions with Phenytoin. While Valproate is known to increase plasma levels by displacing bound Phenytoin and by interfering with its metabolism,

Phenobarbitone has a more erratic interaction pattern.[1] The concomitant use of such drugs should be avoided to reduce the risk of Phenytoin toxicity. Nine of the ten cases developed signs of toxicity at(or below) doses of 300 mg which is the usual starting dose regardless of body weight. This highlights the need to watch for signs of toxicity at these doses as well. Further, it is important to note that dosage should be increased gradually at 25-30 mg/day with ample time for a new steady state to be achieved.[2]Individual variation in toxicity is a function of the fraction of the free drug, responsiveness to the drug and the baseline neurological condition of the individual.[4]Also, it has been suggested that patients with structural abnormalities of the brain are more prone to develop signs of toxicity. Six of the seven patients in whom an MRI had been performed demonstrated radiological abnormalities. Post marketing surveillance had demonstrated that cerebellar atrophy was a side effect of Phenytoin use.[8][9]Three of the seven patients in whom an MRI was performed had some degree of cerebellar atrophy. The mean concentration of Phenytoin was 41.54 mcg/ml. Although concentration of Phenytoin in plasma does not always correspond to the clinical response or toxicity profile, it is a useful guide to tailoring therapy. Levetiracetam is a safe and effective alternative which has fewer drug interactions than most other AEDs.[10] All patients in our study responded well to the drug when it was used as an alternative to Phenytoin therapy.

To determine the probability that the adverse effects that the patients presented with were the result of Phenytoin ingestion, the Naranjo and World Health Organization-Uppsala Monitoring Centrescales were applied.[11][12]As per the Naranjo algorithm, the cases were determined to have score of 6 i.e. 'Probable adverse drug reaction'. As per the World Health Organization-Uppsala Monitoring Centrescale the likelihood of the symptoms being a result of the Phenytoin use was probable/likely association. All the patients in our study were determined to have experienced a level 4 event as per the Hartwig Severity assessment scale. The following are steps that can be taken to reduce the risk of phenytoin toxicity:

- Start Phenytoin at doses of 300 mg in divided doses after ensuring that the patient is not on any other medication that has known interactions with Phenytoin. Up-titrate by 25 mg/day with a minimum of two weeks between dose increments. Avoid changes in formulation as they may differ in bioavailability.
- Educate the patient about the symptoms of toxicity and request them to report to a healthcare centre at the earliest if such features develop. Further, request them to inform future healthcare providers about their drug history and ask them to avoid certain drugs (such as salicylates and enzyme inhibitors).
- Avoid the use of multiple AEDs in patients with seizures especially in those with structural abnormalities of the brain. Consult a clinical pharmacist if necessary.
- Monitor drug levels as necessary.

CONCLUSION:

Phenytoin toxicity can develop even at doses of 300 mg daily which is widely used when initiating therapy. This highlights the need to follow up patients, measure plasma levels if required and take steps to reduce risk of toxicity. With watchful care and switch of AED, almost all patients can be expected to make a smooth recovery and remain symptom and seizure free. Phenytoin toxicity is often an avoidable consequence of therapy. By keeping the principles of up-titration, careful blood monitoring, drug interactions and side effect profile in mind a vast majority of toxic manifestations can be avoided.

Conflicts of interest : Nil

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