WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.045
Volume 3, Issue 10, 1056-1062. Case report ISSN 2277– 7105

CASE REPORT ON PHENYTOIN SHOWS SKIN REACTIONS (PURPURIC ERUPTION) IN A TERTIARY CARE REFERRAL HOSPITAL- KERALA

Mr.Shibil.PK*, Linu Mohan.P, Shinu.C, Mohammed Fazil R.M, Mammen Paul.

Al-Shifa College of pharmacy, Department of Pharmacy Practice, Kizhattur, Poonthavanam P.O., Perinthalmanna, Kerala-679325.

Article Received on
07 October 2014,

Revised on 29 Oct 2014,
Accepted on 21 Nov 2014

***Correspondence for Author**
Mr.Shibil.PK
Al-Shifa College of pharmacy, Department of Pharmacy Practice, Kizhattur, Poonthavanam P.O., Perinthalmanna, Kerala-679325

ABSTRACT

Phenytoin is an antiepileptic drug. It is useful to treat partial seizures and generalized tonic-clonic seizures but not primary generalized seizures such as absence seizures or myoclonic seizures. We report a case on phenytoin that shows skin reactions (purpuric eruption). A 27 years old male patient admitted in neuro surgery department of the hospital for the treatment of head injury, with multiple wound over forehead, upper lip, lower lip, and left side chest. The causality of the event assessed as per WHO-UMC for standardized case causality assessment criteria can be considered as probable. Analyzed by Naranjo's ADR probability scale, the score was 5, which also make it a probable event.

KEY WORDS: Phenytoin, tonic-clonic seizures, ADR probability scale.

INTRODUCTION

Phenytoin, is an antiepileptic drug. It is useful to treat partial seizures and generalized tonic clonic seizures but not primary generalized seizures such as absence seizures or myoclonic seizures. Phenytoin is believed to protect against seizures by causing voltage-dependent block of voltage-gated sodium channels Phenytoin has low affinity for resting sodium channels at hyperpolarized membrane potentials.

When neurons are depolarized and the channels transition into the open and inactivated states, greater binding and block occur. The inhibitory potency is strongly use dependent, so that block accumulates with prolonged or repetitive activation, such as occurs during a

seizure discharge. The blocking of sodium channels by phenytoin is of slow onset. The time course of fast sodium currents is therefore not altered in the presence of the drug and action potentials evoked by synaptic depolarizations of ordinary duration are not blocked. Thus phenytoin is able to selectively inhibit pathological hyperexcitability in epilepsy without unduly impairing ongoing activity. Phenytoin also blocks persistent sodium current and this may be of particular importance in seizure control. Phenytoin is a class 1b antiarrhythmic.

Phenytoin (diphenylhydantoin) was first synthesized by German chemist Heinrich Biltz in 1908. Biltz sold his discovery to Parke-Davis, which did not find an immediate use for it. In 1938, outside scientists including H. Houston Merritt and Tracy Putnam discovered phenytoin's usefulness for controlling seizures, without the sedative effects associated with phenobarbital. In contrast to the earlier accidental discovery of the antiseizure properties of bromide and phenobarbital, phenytoin was the product of a search among nonsedative structural relatives of phenobarbital for agents capable of suppressing electroshock convulsions in laboratory animals.

There are some indications that phenytoin has other effects, including anxiety control and mood stabilization, although it has never been approved for those purposes by the FDA. Jack Dreyfus, founder of the Dreyfus Fund, became a major proponent of phenytoin as a means to control nervousness and depression when he received a prescription for Dilantin in 1966. He is believed to have supplied large amounts of the drug to Richard Nixon throughout the late 1960s and early 1970s. Dreyfus' experience with phenytoin is outlined in his book, *A* Remarkable Medicine *Has* Been Overlooked Despite more than $70 million in personal financing, his push to see phenytoin evaluated for alternative uses has had little lasting effect on the medical community. This was partially because Parke-Davis was reluctant to invest in a drug nearing the end of its patent life, and partially due to mixed results from various studies. It was approved by the USA Food and Drug Administration in 1953 for use in seizures.

General and vague references to the use of phenytoin for phantosmia can be found by internet browsing, those found have been but tantalizing. One patient with phantosmia {imagined smells) that began in 1995 (including some prarosmia (false or distorted smell), was prescribed phenytoin after other fixes didn't work. This caused close to (and very liveable) complete remission of the phantosmia. In 2012, following both patient and physician concerns (patient: relation to post-phenytoin sleep apnea onset, deteriorating balance),

(physician: long term neuralogical damage) phenytoin use was stopped and another seizure medicine was prescibed (levetiracetam) with no noticeable control over the phantosmia. Following information obtained from internet browsing, venlafaxine was prescribed, but also with no theraputic benefit for the patient. Phenytoin remains the only relief found for this patient.

Dilantin made an appearance in the 1962 novel One Flew over the Cuckoo's Nest by Ken Kesey, both as an anticonvulsant and as a mechanism to control inmate behavior.
In 2008, the drug was put on the FDA's Potential Signals of Serious Risks List to be further evaluated for approval. The list means that the FDA has identified a potential safety issue, but does not mean that FDA has identified a causal relationship between the drug and the listed risk.

According to the FDA's New Safety Information Identified by the Adverse Event Reporting System (AERS) Phenytoin Injection (Dilantin) has been associated with the risk of Purple Glove Syndrome.

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. The mechanism of action of phenytoin sodium. Sodium channels are: 1. Closed channels 2. Open channels 3. Inactive channel (phenytoin effect) 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 by phenytoin sodium can produce voltage-dependent, use-dependent and time-dependent block of sodium-dependent action potentials.

Major side effects includes at therapeutic doses, phenytoin may produce horizontal gaze nystagmus. At toxic doses, patients experience sedation, cerebellar ataxia, and ophthalmoparesis, as well as seizures. Idiosyncratic side-effects of phenytoin, as with other anticonvulsants, include rash and severe allergic reactions.

Phenytoin may accumulate in the cerebral cortex over long periods of time, as well as causing atrophy of the cerebellum when administered at chronically high levels. Despite this, the drug has a long history of safe use, making it one of the more popular anti-convulsants prescribed by doctors, and a common "first line of defense" in seizure cases. It has been suggested that phenytoin causes a reduction in folic acid levels, predisposing patients to megaloblastic anemia. Folic acid is presented in foods as polyglutamate, which is then converted into monoglutamates by intestinal conjugase. Phenytoin acts by inhibiting this enzyme, thereby causing folate deficiency. Other side effects may include: agranulocytosis, aplastic anemia, leukopenia, and thrombocytopenia. Phenytoin is a known teratogen. The syndrome consists of craniofacial anomalies (broad nasal bridge, cleft lip and palate, microcephaly) and a mild form of mental retardation (average IQ=71). This syndrome resembles the well-described Fetal Alcohol Syndrome and has also been called the "fetal hydantoin syndrome". Some recommend avoiding polytherapy and maintaining the minimal dose possible during pregnancy, but acknowledge that current data do not provide clear answers. Data now being collected by the Epilepsy and Antiepileptic Drug Pregnancy Registry may one day answer this question definitively.

Phenytoin has been associated with drug-induced gingival enlargement (overgrowth of the gums), probably due to above-mentioned folate deficiency; indeed, evidence from a randomized controlled trial suggests that folic acid supplementation can prevent gingival enlargement in children who take phenytoin. Plasma concentrations needed to induce gingival lesions have not been clearly defined. Effects consist of the following: bleeding upon probing, increased gingival exudate, pronounced gingival inflammatory response to plaque levels, associated in some instances with bone loss but without tooth detachment. Following almost 200 studies of 11 anti-seizure drugs the FDA has also warned of an increased suicide risk for any patients treated with certain anti-seizure drugs. The study of 44,000 patients found that patients whose epilepsy is treated with drugs face about twice the risk of suicidal thoughts compared to placebo-takers. Although phenytoin was not named in the study, the FDA announced that it expected the risk applied to every epilepsy drug.

Hypertrichosis, rash, exfoliative dermatitis, pruritis, hirsutism, and coarsening of facial features Phenytoin has been known to cause drug-induced lupus.

Phenytoin therapy has been linked to the life-threatening skin reactions Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). These conditions are significantly

more common in patients with a particular HLA-B allele, HLA-B*1502. This allele occurs almost exclusively in patients with ancestry across broad areas of Asia, including South Asian Indians. Phenytoin is also associated with induction of reversible IgA deficiency
If these problems do not diminish within several days, a reduction in the dose of phenytoin often will solve the problem. Problems with sedation also may be helped by splitting the dose or giving the largest dose at bedtime.

The most common side effects of long-term use affect appearance. About 20% to 40% of these patients notice a problem with gingival hyperplasia. This effect appears to be dose-related and is more common in children than in adults. Its occurrence and its associated problems can be minimized by good dental care, including vigorous brushing, daily flossing, and regular dental care. It usually resolves within a few months if phenytoin is discontinued.
Hirsutism is more of a problem for people with light complexions. It can be controlled with hair removal creams. Most acne can be treated effectively with facial hygiene, antibiotics, ointments, or lotions.

Dyskinesias, including chorea, dystonia, tremor, and asterixis, may be caused by phenytoin. Also, a small number of patients report sensory peripheral polyneuropathy.

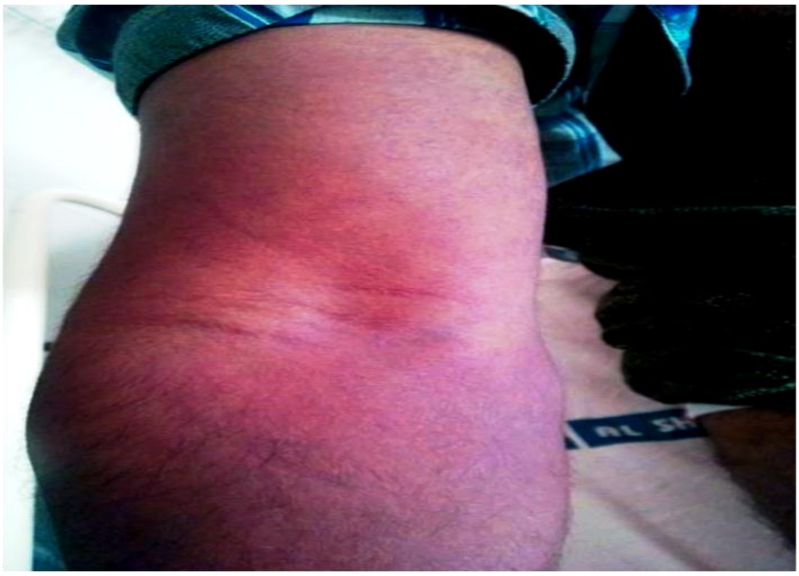
Cerebellar atrophy may be another long-term effect of phenytoin, especially if high doses are used. Damage severe enough to produce significant problems is uncommon, however.

Rash is a common allergic reaction seen in about 5% to 7% of those who use phenytoin. This reaction usually occurs early in the course of therapy, within 5 to 17 days after the initial dose. Most patients will need to stop taking phenytoin and replace it with a different antiepileptic medication. The rash itself may require treatment with an antihistamine or steroid if it is severe.

CASE REPORT

A 27 years old male patient was admitted to neuro surgery department for presenting with head injury, mode of incident: H/O RTA multiple wound over forehead, upper lip, lower lip, left side chest and pain in the facial region. He is smoker, alcoholic and non-vegetarian. The vital parameters was not normal in first few days, elevated temperature and blood pressure. The laboratory test reports of blood showed in normal in range. But ESR was elevated as 80mm/hr. he was prescribed with cefaperazone sulbactum injection 3gm BD and gentamycin

tab 80mg BD was given for first three days. On first day patient had problems with convulsion he was prescribed with phenytoin 100mg injection every 8th hourly. On 3rd day patient was started with phenytoin 100mg tab instead of phenytoin 100mg injection, paracetamol 650mg tab was given every 12th hourly, betadine gargling was done 8th hourly, clonazapam 0.5mg tab was given every 12th hour for last few days. On 6th day patient had a severe allergic reaction, was prescribed With calamine lotion and cetrizine10mg OD, the reaction was continued. Cross consultation was done on 7th day and dermatologist confirmed as phenytoin adverse reaction, then stopped giving phenytoin tablet, after 6 hrs patient had relief from skin eruption slowly. The causality of the event assessed as per WHO-UMC system for standard case causality assessment criteria can be considered as probable. Analyzed by the naranjos ADR probability scale the score was 5. Which also make it a probable adverse drug reaction.



Appearance of purpuric eruption on the Forearm.

DISCUSSION

There have been many adverse drug reaction reported with phenytoin skin reactions. Reported adverse drug reactions include, Phenytoin hypersensitivity syndrome, Multi-system organ failure, Phenytoin-induced drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, Drug reaction with eosinophilia and systemic symptoms syndrome in a patient taking phenytoin and levetiracetam, pruritic, maculopapular rash with associated periorbital swelling, fever, and transaminitis. Phenytoin is associated with both dose-related side effects andhypersensitivity reactions. Hypersensitivity reactions occur in up to 19% of patients receiving this medication, and range from a mild morbilliform eruption to more

severe reactions, including erythroderma, erythema multiforme, and toxic epidermal necrolysis. A small percentage of patients will experience a distinctive reaction referred to as the phenytoin hypersensitivity syndrome. This syndrome can have a variable spectrum of clinical and laboratory findings. So safe use and monitoring drug therapy is essential.

CONCLUSION

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. Clinicians should be aware of the potential for this severe hypersensitivity reaction particularly in starting any new anti-epileptic medication.

REFERENCE

1. P Marik. *Phenytoin Hypersensitivity Syndrome Presenting as Multi-System Organ Failure*. The Internet Journal of Emergency and Intensive Care Medicine. 1996 Volume 1 Number 2.
2. Rapp RP, Norton JA, Young B, TIbbs PA. Cutaneous reaction in head injured patients receiving phenytoin for seizure prophylaxis. Neurosurg 1983;13: 372-375
3. Schmidt D, Kluge W. Fatal toxic epidermal necrolysis following re-exposure to phenytoin: a case report. Epilepsia 1983; 24:440-443.
4. David Jeffrey Hall[1] and Jason Steven From Corresponding author: Jason Steven Fromm jason.fromm@medicine.ufl.edu
   College of Medicine, University of Florida College of Medicine, 1600 SW Archer Road, PO Box 100277, Gainesville, FL, 32610-0277, USA
   Department of Medicine, University of Florida College of Medicine, 1600 SW Archer Road, PO Box 100277, Gainesville, FL, 32610-0277, USA .
5. Bocquet H, Bagot M, Roujeau JC: Drug-induced pseudolymphoma and drug hypersensitivity syndrome (Drug Rash with Eosinophilia and Systemic Symptoms: DRESS).