PHENYTOIN INDUCED ERYTHEMATOUS RASH IN A DIABETIC SEIZURE PATIENT

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ABSTRACT

This is a case report of 1 year old male patient, who has experienced rashes after the use of phenytoin for the treatment of seizures. The blood glucose level of the patient was high, which may have triggered seizure in the patient. This type of seizure is known as diabetic seizure. Phenytoin is a hydantoin compound related to the barbiturates that are used for the treatment of seizures. It is one of the most commonly used anticonvulsant drugs. These drugs frequently cause cutaneous eruptions, especially during inception of new therapy. In addition to causing common and usually limited morbilliform and urticarial eruptions, which have often mild morbidity. In this case, the patient has developed erythematosus rash all over the body on the fifth day after administration of phenytoin. This ADR (Adverse drug reaction) has scored 6 points on naranjo scale of causality assessment. The possible reason for the adverse drug reaction was found to be the drug over-dose.

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INTRODUCTION

A seizure is a paroxysmal clinical event of the central nervous system, characterized by an abnormal electrical discharge and associated with a change in the usual functioning. A seizure occurs when there is a sudden imbalance between the excitatory and inhibitory inputs to a network of neurons in the cerebral cortex, so that there is overall excessive excitability [1]. Seizure disorders are among the most frequent neurologic problems that occur in childhood. Childhood epilepsies are a heterogeneous group of conditions that differ in their diagnostic criteria and management and have dramatically different outcomes [2]. The classification of the seizure is critical for diagnosis and management. Seizures are classified on the basis of clinical event and electroencephalographic abnormalities [1].

1. Partial (focal, local) Seizures
2. Generalized Seizures (convulsive and nonconvulsive)
3. Unclassified Epileptic Seizures

Diabetic Seizures:

Metabolic abnormalities of diabetes mellitus such as hyperglycemia and hypoglycemia could have a damaging effect on the CNS, which may cause seizure [3].

Partial seizures triggered by hyperglycaemia were first identified in 1965. The characteristics of seizures in association with nonketotic hyperglycaemia have been described in a number of case series. Partial seizures may be the first presentation of newly diagnosed diabetes. The typical features are often of a focal motor nature, usually involving upper limb and face and without loss of consciousness, and are equally common with both type 1 and type 2 diabetes [4].

Seizures And Glycemic Variations:

Glucose plays a critical role in brain functions because it serve as the main source of metabolic energy generation [5]. Focal motor epileptic episodes may be associated with hypoglycemia and non-ketotic hyperglycemia (NKH); however, these do not occur with ketotic hyperglycemia, apparently because of the anticonvulsant action of ketosis [6]. Most published reports on diabetic hyperglycemia are concerned with non-ketotic hyperosmolar diabetic coma accompanied by severe hyperglycemia, hyperosmolality and dehydration, with minimal or no ketoacidosis [7,8], a severe condition which represents one extreme of a biochemical continuum. In practice, actually, diabetics show a spectrum of hyperglycemia and they are often detected before development of severe hyperosmolarity [9]. Although occipital focal seizures have also been described [10,11], the clinical features of focal seizures in NKH are usually those of frontal lobe epilepsy [12]. The explanation of this condition by hyperglycemia alone is unsatisfactory, because seizures are rare in diabetic ketoacidosis. It was hypothesized that hyperglycemia leads to a decrease in epileptic seizure threshold by increasing metabolism of gamma-aminobutyric acid accordingly decreasing the level of GABA, so resulting in a reduction of seizures threshold [9,13]. Another hypothesis involves decrease of seizure threshold due to metabolic disturbance. Hyperosmolality and dehydration associated with hyperglycemia can be considered to be triggers for EPC or other focal seizures, and may lead to neurological deficit in some patients [14]; in fact, some experimental studies adduced to show that hypertonic solutions will activate existing seizures foci, in particular a potential mechanism is the hyperosmolar irritation of neurons rendered ischemic by an enhanced tendency to vascular disease and by an acute reduction in cerebral blood flow secondary to hyperglycemia and dehydration [15,16]. Focal seizures can be symptomatic of structural lesions within the brain; for this reason other authors [9] suggested that a previously existing cortical lesion of ischemic nature might lead to these seizures after acquiring an epileptogenic characteristic under altered metabolic conditions.

The physical manifestations of diabetic seizures in children include abnormal movements of the body, with shaking, eyes rolled back and clenching of teeth. Before a seizure, a diabetic child may appear listless, off-balance, sleepy and unfocused. Afterward, the child will appear groggy or lethargic, a condition called the postictal stage. The postictal stage usually lasts a few minutes. If it lasts for more than an hour, the child could still be experiencing a seizure. Prompt medical attention is required whenever a child has a seizure [17].

Cutaneous drug eruptions are one of the most frequent types of adverse reaction to drug therapy, with an overall incidence rate of 2–3% in hospitalized patients. Certain drug classes, such as non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics and antiepileptics, have drug eruption rates approaching 1–5% [18].

Antiepileptic drugs (AEDs) frequently cause cutaneous eruptions, especially during initiation of new therapy. In addition to causing common and usually limited morbilliform and urticarial eruptions, which have often mild morbidity, AEDs are also implicated to
Induce widespread maculopapular rash, hypersensitivity syndrome (HSS), psoriatic dermatitis and occasionally severe reactions such as Steven Johnson’s syndrome (SJS), toxic epidermal necrolysis (TEN) and erythema multiform (EM) [19].

Phenytoin is a hydantoin compound belonging to the barbiturates that are used for the treatment of seizures. It is one of the most commonly used anticonvulsant drugs. The spectrum of activity includes simple and complex partial and generalized tonic-clonic seizures, generalized convulsive and simple or complex partial status epilepticus, and neonatal seizures. Phenytoin is not useful in the treatment of absence epilepsy, West or Lennox±Gastaut syndromes [20]. It was approved in 1938 for the treatment of seizures.

The primary site of action appears to be the motor cortex where spread of seizure activity is inhibited. Possibly by promoting sodium efflux from neurons, phenytoin tends to stabilize the threshold against hyperexcitability caused by excessive stimulation or environmental changes capable of reducing membrane sodium gradient. This includes the reduction of posttetanic potentiation at synapses. Loss of posttetanic potentiation 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.

**Pharmacokinetics and drug metabolism of phenytoin:** The plasma half-life in man after intravenous administration ranges from 10 to 15 hours. Optimum control without clinical signs of toxicity occurs most often with serum levels between 10 and 20 mcg/mL. Phenytoin is metabolized by the cytochrome P450 enzymes CYP2C9 and CYP2C19.

Naranjo et al. has designed a questionnaire for determining the likelihood of whether an (adverse drug reaction) is actually due to the drug rather than the result of other factors, this questionnaire is known as Naranjo Nomogram. Probability is assigned by a score termed definite, probable, possible or doubtful. Values obtained from this algorithm are sometimes used in peer reviews to verify the validity of author's conclusions regarding adverse drug reactions. It is also known as Naranjo Scale or Naranjo Score.

The study was carried out at Princess Esra Hospital, Hyderabad. Prior permission from the Head of the Department was taken to conduct the study.

**CASE REPORT**
A one year old male child was admitted to Princess Esra Hospital (PEH), Hyderabad with chief complaints of convulsions and up-rolling of eyes. Weight of the patient was 8kg.

**Table 1:** Medications on day one

<table>
<thead>
<tr>
<th>Sl. no.</th>
<th>Drug</th>
<th>Generic Name</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Inj Lorazepam</td>
<td>Lorazepam</td>
<td>1 cc</td>
<td>iv</td>
<td>SOS</td>
</tr>
<tr>
<td>2</td>
<td>Inj Eptoin</td>
<td>Phenytoin</td>
<td>200 mg</td>
<td>iv</td>
<td>SOS</td>
</tr>
<tr>
<td>3</td>
<td>O₂ inhalation</td>
<td>Oxygen</td>
<td>-</td>
<td>nasal</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Inj C.Tri</td>
<td>Ceftriaxone</td>
<td>400 mg</td>
<td>iv</td>
<td>SOS</td>
</tr>
<tr>
<td>5</td>
<td>Inj Mikacin</td>
<td>Amikacin</td>
<td>75 mg</td>
<td>iv</td>
<td>BD</td>
</tr>
<tr>
<td>6</td>
<td>IVF DNS+5ml Kcl</td>
<td>Normal saline</td>
<td>500 ml</td>
<td>iv</td>
<td>BD</td>
</tr>
<tr>
<td>7</td>
<td>Syp. P₁₂₅</td>
<td>Paracetamol</td>
<td>3 ml</td>
<td>oral</td>
<td>BD</td>
</tr>
</tbody>
</table>

Day 1:
CVS: S1S2 heard
CNS: Drowsy
P/A: Soft

www.iajpr.com
GRBS: 235 mg/dL
Complete blood picture and Serum electrolytes were advised

On the first day, the medications prescribed are given in table 1

Day 2:
Cough and wheezing were developed on the second day, temperature was normal, CNS was conscious and abdomen was soft.
Serum Electrolytes report is given in table 2

<table>
<thead>
<tr>
<th>Sl.no.</th>
<th>Parameter</th>
<th>Lab value</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sodium</td>
<td>137 meq/L</td>
<td>135-145</td>
</tr>
<tr>
<td>2</td>
<td>Potassium</td>
<td>4 meq/L</td>
<td>3.5-5.5</td>
</tr>
<tr>
<td>3</td>
<td>Calcium</td>
<td>8.9 meq/L</td>
<td>8.4-10.2</td>
</tr>
<tr>
<td>4</td>
<td>Magnesium</td>
<td>1.8 meq/L</td>
<td>1.6-2.7</td>
</tr>
<tr>
<td>5</td>
<td>Phosphorous</td>
<td>6.7 meq/L</td>
<td>4.3-5.4</td>
</tr>
</tbody>
</table>

The following drugs were added to the regimen:
1. Syp Zincovit (Multivitamin) 5ml OD
2. Syp Ambrodil (Ambroxol) 3 ml TID
3. Syp Atarax (Hydroxyzine HCL) 3 ml TID

Day 3:
No fresh complaints were observed, general condition was fare and temperature was normal. Same therapy was continued on the third day.

Day 4:
No fresh complaints were observed, cough was decreased, temperature was normal and general condition was fare. Same therapy was continued on the fourth day.

Day 5:
Maculopapular rashes were observed all over the body associated with pruritis on the fifth day.
Inj Eptoin (Phenytoin) was stopped immediately and the following drugs were added:
1. Syp. Valparin (Sodium valproate) 2.5 ml OD
2. Ezinapi Ointment (Zinc oxide, Cetylated fatty acid, Panthenol)
3. Limisil Soultion (Terbinafine HCL)

Day 6:
No fresh complaints were observed, rashes were improving, temperature was normal, general condition was fare and vitals were stable. Patient was discharged.

DISCUSSION
In this case report, the patient was suffering from diabetic seizures, for which he was prescribed phenytoin. Five days after administration of phenytoin, erythematosus rashes were developed all over the body.
This may have happened because Phenytoin carries a special risk of dose-related toxicity, due to its saturation (zero-order) pharmacokinetics: serum levels often rise much more than would ordinarily be expected after initiating or increasing a maintenance dose.

This predicts a vulnerability to toxicity, but does not predict exactly when this will occur in the individual. The risk of toxicity can be minimized, however, by applying practical dosing and monitoring strategies based on the understanding of phenytoin pharmacokinetics, and by educating patients appropriately [22].

Phenytoin overdose may have played a role in ADR. Based on the weight of the patient, the dose of phenytoin should have been less compared to the dose administered.

This ADR has scored 6 on naranjo scale of causality assessment, which proves that the ADR is probable.
Prevention of Diabetic seizure:
The best way to prevent diabetic seizures is close monitoring of blood sugar levels. This is important once a child starts therapy with insulin or other glucose-controlling agents. It is also important to maintain appropriate nutrition and follow a diabetic diet. Skipping meals is a common cause of abnormal blood sugars, especially in very active children and adolescents, and this can lead to low glucose levels and a seizure. Dietary supplements should be identified which may prevent or decrease the risk of diabetic seizures, as Chocolates appear to reduce risk factors for cardiovascular diseases[21].

CONCLUSION
Information on Phenytoin induced rash is present in considerable studies data. But phenytoin induced rashes in diabetic seizure patient is a new observation. Careful dose calculations should be done before prescribing phenytoin to a pediatric patient to avoid any untoward reaction.

CONFLICT OF INTEREST
Authors state that there is no conflict of interest.

ACKNOWLEDGEMENT
Most importantly we are thankful to the Almighty who is the creator & director of all that initial and final modes to destiny. We take this opportunity to express our deep sense of gratitude, respect to Dr. S.A. Azeez Basha, Principal, Deccan School of Pharmacy, Hyderabad for encouraging us during the work.

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LIST OF ABBREVIATIONS:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADR</td>
<td>Adverse Drug Reaction</td>
<td>iv</td>
<td>Intravenous</td>
</tr>
<tr>
<td>AED</td>
<td>Anti Epileptic Drug</td>
<td>meq/L</td>
<td>Milli equivalents per litre</td>
</tr>
<tr>
<td>BD</td>
<td>Twice a day</td>
<td>ml</td>
<td>Milli litre</td>
</tr>
<tr>
<td>CVS</td>
<td>Cardio Vascular System</td>
<td>NKH</td>
<td>Non-ketotic Hyperglycemia</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous System</td>
<td>OD</td>
<td>Once a day</td>
</tr>
<tr>
<td>EM</td>
<td>Erythema Multiforme</td>
<td>SJS</td>
<td>Stevens-Johnson Syndrome</td>
</tr>
<tr>
<td>GABA</td>
<td>Gamma Amino Butyric Acid</td>
<td>TEN</td>
<td>Toxic Epidermal Necrolysis</td>
</tr>
<tr>
<td>HSS</td>
<td>Hyper Sensitivity Syndrome</td>
<td>TID</td>
<td>Thrice a day</td>
</tr>
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</table>