Purple glove syndrome: A potentially serious complication of phenytoin

Bela Verma*, Riddhi Thaker, Vishal Baldua

Department of Pediatrics, Grant Government Medical College and Sir J.J. Group of Hospitals, Mumbai- 400 008, India.

Received: 18-03-2016 / Revised: 28-04-2016 / Accepted: 30-04-2016 / Published: 30-04-2016

ABSTRACT

Purple Glove Syndrome is a grave complication of intravenous phenytoin administration that is unfamiliar to many in the medical profession. It presents with edema, pain and bluish-purple discolouration of the limb and can lead to gangrenous changes in severe cases. Mild cases can be managed conservatively, with a positive outcome, whereas severe cases may require surgical treatment. Ignorant medical practitioners may have to face medicolegal complaints of this complication; wrongly attributed to mismanagement, overdosing and improper intravenous cannulation or extravasation. In the past Purple Glove Syndrome has been reported majorly in adult and elderly patients. However, we report a case of a three year old male child with Purple Glove Syndrome who had to undergo left upper limb-below elbow amputation due to the setting in of gangrene.

Key Words: Phenytoin, adverse events, Purple Glove Syndrome, amputation.

INTRODUCTION

Phenytoin induced Purple Glove Syndrome (PGS) is a potentially serious local complication characterised by the triad of progressive limb edema, discoloration and pain. In severe cases, the condition can lead to limb amputation and even death. Physicians often do not report adverse events caused by the therapy [1]. Many epileptologists have been aware of this side effect since mid-1980s [2]. Nevertheless, Purple Glove Syndrome is not mentioned in the chapters of phenytoin in comprehensive textbooks on epilepsy and anti-epileptic drugs. The complications of PGS have required surgical treatment such as fasciotomies, skin grafting, limb amputations [4,5,6,7,8] and have also occasionally contributed significantly to patient's death [3,4].

Objectives: To present a case report of a pediatric patient with PGS and to discuss the clinical features, probable pathophysiology, preventive and curative measures and consequences of severe complications of this syndrome.

CASE REPORT

Three year old male child was hospitalized with history of first episode of right upper limb tonic-clonic seizures involving the head and neck, lasting half an hour. The child had post-ictal drowsiness. There were no neurological deficits. Apart from mild malnutrition and fever of 39 degree C, general and systemic examinations were normal. A provisional diagnosis of atypical febrile seizures was made and the child was further investigated.

Complete blood counts were - Hb: 10g/dL, total leucocyte count: 9x10^3/mL with a differential of Polymorphs-50% Lymphocytes-48% Eosinophils-1% Monocytes-1% and adequate platelet count. Chest X Ray was normal.

Mantoux test (TT) – Negative

Lumbar Puncture was not done as parents did not give consent

CT brain- normal

Child was administered oral azithromycin and paracetamol.

Two days later, the child had a second episode of right upper limb tonic-clonic seizures with deviation of head and neck to right side. Child was afebrile this time. IV access was attained at left wrist and loading dose of phenytoin 20 mg/kg was administered. Since the seizure recurred within 15 minutes, second dose of phenytoin by 10 mg/kg was administered. Seizures persisted; hence a loading dose of 20 mg/kg phenobarbitone was given intravenously. Fifteen minutes later, seizures had not subsided; therefore a second dose of phenobarbitone 10mg/kg had to be given.
The seizures were refractory (Status Epilepticus), finally IV calcium gluconate 2mL/kg diluted and IM magnesium sulphate 0.2mL/kg were given which resulted in the seizures being controlled.

Six hours later, bluish discoulouration of the left hand nails and fingers was noticed which progressively increased to involve the forearm in the next twenty four hours. The left hand was cold, swollen and tender. There was no evidence of extravasation at the IV site.

There was patchy bluish skin discoulouration with poor demarcation. The left radial and ulnar arteries were poorly felt, while the brachial was well felt. Doppler study of left upper limb revealed normal flow with no evidence of thrombus/block.

In view of compartment syndrome with probable thrombophlebitis, the child was immediately transferred to surgical side. Fasciotomy was done and conservative management was continued for 2 weeks. But gangrene had set in, the left hand was not salvageable and a below-elbow amputation had to be done. Thus, it was a case of Purple Glove Syndrome due to phenytoin toxicity.

**DISCUSSION**

Parenteral phenytoin is being used to treat status epilepticus in children since 1950’s [9]. However, a true pediatric dosage range was established only in 1984 by Koren and colleagues. Children in status epilepticus are among those at the highest risk for phenytoin infusion-site reactions [9]. Most cases of Purple Glove Syndrome have been described in adult patients. Moreover, female and elderly patients are found to have an increased risk of the syndrome [5]. On the contrary, our patient was a three year old male child.

PGS is a poorly understood, potentially serious local complication of intravenous phenytoin administration resulting in dark purple discoulouration, progressive limb edema and pain, in the absence of fever [1,2,3]. It was first reported in 1984 and first described in 1992 [6,7,10].

Three stages have been described:

Stage I (2-12 hours post-dose) – purple-blue colour around intravenous site.

Stage II (next 12-16 hours) – edema, discoulouration spreading distally and proximally. Local skin blistering, sloughing and ulceration may occur, resulting in skin necrosis, compartment syndrome and extensive limb gangrene necessitating limb amputation.

Stage III- gradual resolution of edema and then of discoulouration over a few weeks [9].

The reported risk of PGS with IV phenytoin is 3% to 7% [2,5]. The side effects associated with parenteral administration of phenytoin result primarily from the very high pH value 12 of the formulation and the propylene glycol required to increase its solubility [2,9]. It is hypothesized that highly alkaline solution induces vasoconstriction of the vein resulting in disruption of the endothelial-intercellular junctions and seepage of the drug into the interstitial space [11]. Extravasation of the highly albumin-bound (70–90%) phenytoin increases the interstitial oncotic pressure leading to edema. Propylene glycol with its high osmolality causes necrosis of the tissue [12]. It is puzzling however, that in most of the reported cases, including our case, no obvious extravasation had been noted. A number of authors have even noted that PGS also occurs under the most ideal conditions of intravenous infusion. Hence, the exact pathophysiology remains uncertain. In the present case, the affected limb showed no evidence of a thrombus or blockage on Doppler study. Histologically too, thrombotic occlusion is often absent [2,9]. Various histopathologic features of PGS described include edema, perivascular lymphocytic inflammation and epidermal, dermal and subcutaneous necrosis [13].

It is found that with early detection and intervention (such as limb elevation, application of dry, gentle heat, physiotherapy, pain control and patient reassurance) mild cases may resolve spontaneously, whereas in severe cases the condition has led to extensive skin necrosis and limb ischemia [1,2,3,4,5,6,10,12]. Compression of vascular structures by severe edema may result in compartment syndrome. The complications of PGS have required surgical treatment such as fasciotomies, skin grafting and limb amputation [4,5,6,7,8]. This scenario was seen in our patient who unfortunately developed compartment syndrome and eventually gangrene in his left hand and forearm, which had to be treated with a left upper limb-below elbow amputation. On rare occasions, PGS has been reported to have contributed significantly to patient’s death [3,4].

To prevent this distressing adverse event of IV phenytoin, investigators recommend measures like use of intravenous catheters smaller than 20-gauge, flushing the line with normal saline following intravenous administration, use of large-bore veins, greater dilution of the drug, lower infusion rates (not exceeding 50 mg/min), immediate discontinuation of the intravenous catheter upon symptom presentation and substitution of IV phenytoin with fosphenytoin [2,10,11,12]. Fosphenytoin, the prodrug of phenytoin has a pH value of 8 and is far more water soluble than
phenytoin. Randomised double blind studies have shown IV fosphenytoin causes significantly less pain, discomfort and has a lower incidence of venous phlebitis [2,9]. The disadvantages of fosphenytoin are serious arrhythmias and hypotension following infusion. Also, fosphenytoin costs five times more than phenytoin and recent studies of cost-effectiveness do not support regular use [13,14]. Finally, oral drug should be used whenever possible. However, there have been two reports of PGS with oral phenytoin administration as well [15,16].

**CONCLUSION**

Purple Glove Syndrome is a rare complication of intravenous administration of phenytoin that is not yet well known and understood. It often results in dissatisfied patients, deaths and lawsuits against the medical practitioners, regardless of the standard of care administered. This adverse event needs to be borne in mind when administering phenytoin, to avoid serious consequences of the syndrome.

**REFERENCES**