**Szeliga Adrianna, Spyt Dominika, Kasinowicz Mateusz. Purple glove syndrome. Journal of Education, Health and Sport. 2019;9(8):298-305. eISNN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.3374299**
**http://ojs.ukw.edu.pl/index.php/johs/article/view/7306**

**The journal has had 5 points in Ministry of Science and Higher Education parametric evaluation. § 8. 2) and § 12. 1. 2) 22.02.2019.**


**The authors declare that there is no conflict of interests regarding the publication of this paper.**

**Received: 10.08.2019. Revised: 20.08.2019. Accepted: 22.08.2019.**

# Purple glove syndrome

**Adrianna Szeliga, e-mail: adria.szeliga@gmail.com**
**ORCID: 0000-0002-3567-051X**

**Dominika Spyt, e-mail: dominikaspyt3@gmail.com**
**ORCID: 0000-0002-1993-2639**

**Mateusz Kasinowicz, e-mail: matkasinowicz@gmail.com**
**ORCID: 0000-0001-6036-3450**

**Wydział Lekarski, Collegium Medicum im. Ludwika Rydygiera w Bydgoszczy, UMK w Toruniu**

## Abstract

**Introduction:** Purple glove syndrome is an atypical and adverse reaction to intravenous phenytoin, which is characterized by oedema, pain and a dark purple-bluish discolouration, typically located on an upper extremity. The clinical manifestation of this syndrome occurs in three stages: appearance, progression and resolution of symptoms. PGS develops up to 12 hours after administration of intravenous phenytoin and it disappears in a few weeks or months.

**Objective:** The aim of this article is to summarize the current state of knowledge about purple glove syndrome: the pathophysiology, risk factors, the diagnosis and the current treatment.

**Brief descriptions of the state of knowledge:** Despite many years PGS is still

unexplained phenomenon. It is claimed that vascular tearing, micro-extravasation, alkaline pH of the solution or unidentified procoagulant mechanism can cause tissue impairment. The treatment depends on a limb elevation, physiotherapy, intravenous heparin administration, pain control, nitroglycerine application and a nerve blocks. To prevent PGS it is recommended to use oral phenytoin whenever possible, slow infusion rate of phenytoin less than 25mg/min, large cannula (20G or larger) in a large calibre vein and suitable, small doses. What is important fosphenytoin, a pro-drug of phenytoin, can also cause PGS, even though it was thought to be a safe drug, and a purple glove syndrome induced by fosphenytoin has never been described before.

**Summary:** Despite the existence of many clinical trials, long term observations and scientific speculations, PGS can still be challenging for clinicians. There is a need for further scientific research to explain this phenomenon and to increase the awareness of this problem in general medical practice.

**Key words:** PGS, purple glove syndrome, phenytoin

## Introduction

Phenytoin, as a well-known, nonsedative anticonvulsant, has been associated with a number of serious adverse drug reactions, including hypotension and arrhythmias after rapid intravenous administration, as well as dermatologic reactions ranging from rashes to Stevens-Johnson syndrome, toxic epidermal necrolysis and severe hepatotoxicity [1]. Purple glove syndrome (PGS) is an atypical, adverse and a rare reaction to intravenous phenytoin. This complication is mainly characterized by pain, edema and a dark purple-bluish discoloration, typically located on the upper limb, distal to the intravenous access [2,3]. Moreover, pain can be present in all stages. What is really important is that PGS can develop to necrosis, ischemia, vascular compression and compartment syndrome, resulting in the need of surgical treatment [2]. The etiology is still unexplained but it is suspected that extravasation injury and thrombotic incident can cause PGS [4]. Despite many theories, the pathophysiology of this phenomenon still remains notional. Intravenous administration of phenytoin is recommended for patients with status epilepticus, refractory to benzodiazepines, for patients with traumatic intracranial injury or intracranial neoplasm [5,6].

## History

Since 1956, phenytoin sodium has been used in the prevention and treatment of seizures as an anticonvulsant. Phenytoin has found indication for treatment of status epilepticus as the second-line agent after IV benzodiazepines. Moreover, this medicine is recommended by the European Federation of Neurological Societies (EFNS) and also Epilepsy Foundation of America (EFA). Since 1950, there have been many reports of soft tissue injuries or

extravasation following administration of IV phenytoin. An important report, that was first published by Comer et al. in 1984 brought closer the adverse effect of phenytoin, some specific symptoms were reported, such as pain, rapid onset of discoloration, tissue necrosis and also progressive tissue necrosis to the distal extremity through which the phenytoin was intravenously administered. The name "purple glove syndrome" (PGS) appeared in the publication published by Hanna in 1992. PGS was characterized by following IV administration of phenytoin delayed, soft tissue mutilation of the hand and forearm [1]. PGS gets its term from the characteristic bluish colouration of the skin [7]. In 1996 FDA approved the pro-drug of phenytoin, named fosphenytoin which found out to be less probable to cause PGS than phenytoin [1]. Fosphenytoin in comparison with phenytoin does not require ethanol or propylene glycol and it is soluble in aqueous solutions [8]. In addition, it has been shown that fosphenytoin is less toxic compared with phenytoin. Moreover, it can be given through either intramuscular or intravenous injection and it is also less painful after extravasation [9].

## Epidemiology

Observations show that not all patients who receive intravenous phenytoin develop PGS. It is speculated that the most significant and preventable factor to lead the development of PGS can be to downplay adherence to the guidelines for intravenous recommendations of phenytoin usage [10]. There are many risk factors that can have a significant impact on PGS, like age - patients who are 60 years old and above are more likely to develop PGS. However, Dilek Ulubaş et al. reported complication after intravenous phenytoin infusion in newborn and the appearance of PGS [11]. Moreover, patients who receive large or multiple doses of IV phenytoin are more predisposed to develop PGS . Another less supported risk factor may be the conditions that weaken vascular and skin integrity. Additionally, important risk factor is high phenytoin infusion rates (estimated value >25 mg/min). It is considered that the diameter of the catheter smaller than 20 gauge can also be a risk factor. Unfortunately, there is no consensus regarding the observation in the research of many researchers. As the reports of O'Brien et al. present – the 89% patients developed PGS after usage of catheter of size greater than 20 gauge [12]. On the other hand Spengler et al. reported that catheter sizes smaller than 20 gauge caused higher risk of PGS. [13]. The observation also shows that the female gender is more likely to develop PGS [7]. The table summarizes risk factors that may contribute to the development of PGS.

**Table 1**

| **Risk factors for Purple Glove Syndrome** [1,2,3,4,5] |
| --- |
| ▪ the concentration of phenytoin<br>▪ the rate of infusion<br>▪ extravasation<br>▪ chemical irritation by solvents (propylene glycol, sodium hydroxide and ethanol)<br>▪ drug-induced vasculitis<br>▪ drug-induced vasoconstriction<br>▪ genetic predisposition<br>▪ use of an appropriate catheter (20-gauge or more)<br>▪ elderly age group<br>▪ female gender<br>▪ conditions that weaken vascular and skin integrity<br>▪ number of IV phenytoin doses received<br>▪ high alkalinity of phenytoin |

## Etiology and Pathophysiology

Purple glove syndrome has been described many times in both nursing and medical literature. Unfortunately, despite the existence of many clinical reports about PGS, scientists are still not able to clearly determine pathophysiological mechanism of this adverse effect. Many theories have been made to explain the etiology and pathophysiology of PGS. Some of them implicate the chemical properties of phenytoin [14-17], other site the physical damage induced by the insertion of the intravenous catheter [18]. Other authors, though, proposed a drug-induced vasculitis [19,20]. In order to understand each point of view, it is good to know that the physiochemical properties of many drugs can indicate whether it will or not produce cellular toxicity. Phenytoin is a chemically weak, poorly water soluble acid, which includes an alkaline compound soluble only at a high pH. Therefore, the solution is manufactured with sodium hydroxide. What is more, a combination of propylene glycol and ethyl alcohol is also used to increase solubility. These substances are known tissue irritants itself [18]. Because of high pH of 12, it may induce local vasoconstriction and finally result in vascular compromise, disruption of the endothelial interstitial junctions and subsequent leakage of the drug into soft

tissue. After then, the protein-bound phenytoin leads to increase of interstitial oncotic pressure, resulting in edema [14,16,21]. Phenytoin extravasation has also been explained as a result of vascular tears from intravenous insertion [18]. Scientists has also taken into consideration an incidence of drug precipitation upon mixing with blood [17]. Another interesting theory was about drug-induced vasculitis or mechanical vessel damage with micro thrombi formation as a causative mechanism [20].

## Symptoms

Most commonly PGS is associated with upper extremities, however it has been many times reported also in lower extremities and referred to as purple sock syndrome [8, 22, 23, 24]. The hallmark of this syndrome is purplish discoloration and edema of the distal extremity, seen in most cases. Pain is often present in this area but its existence can be omitted by patients due to alterations in consciousness after a seizure. Skin changes can take a variety of forms ranging from more common blistering, erythema and necrosis to deficits of function, such as sensor changes and even paralysis [1]. PGS can be extremely painful and in severe cases it can be even the cause of arterial insufficiency and compartment syndrome [23]. Generally, three stages of PGS has been described [14]. During the initial stage, blue to purple discoloration around the intravenous insertion site is seen, usually appearing 2–12 h after administration of phenytoin. The second, fully developed stage is characterized by the formation of edema and worsening discoloration. The severity of the signs and symptoms may be dose-related. There may be subsequent blister formation, sloughing and reddish-purple discoloration of the affected area. Third stage lesions show a decrease in size of the discolored area and diminished edema. As for the healing, it takes place usually from peripheral towards the intravenous site.

## Diagnosis and treatment

The diagnosis of PGS is based on characteristic symptoms and it is suspected that these symptoms occur after intravenous administration of phenytoin. It is necessary to exclude other illnesses e.g. cellulitis or necrotizing fasciitis [7].

**Table 2**

| **Differential diagnosis of purple glove syndrome** [9] |
|---|
| ▪ Cellulitis<br>▪ Necrotizing fasciitis<br>▪ Raynaud's phenomenon<br>▪ Polyarteritis nodosa<br>▪ Livedo reticularis<br>▪ Acrocyanosis<br>▪ Buerger's disease |

The treatment of PGS depends on intensification of symptoms and patient's general condition. A non-pharmacological therapies such as limb elevation, physiotherapy and reassurance to the patient should be considered for everyone. What is more, affected arm should not be used to draw blood and blood pressure measurement [4,7]. A pharmacological treatment relies on intravenous heparin administration, pain control, nitroglycerine application to the affected area and brachial plexus block using local anaesthetics like ropivacaine which may reduce vasospasm. Pain relieving by blocking A and B fibres, brachial plexus blockade, sympathetic blockade or stellate ganglion blockade should be perform by advanced anaesthesiologists. In traumatic situation, a surgical intervention may be required like fasciotomy or amputation [3,4,7]. To prevent PGS it is recommended to use oral phenytoin whenever possible, slow infusion rate of phenytoin less than 25mg/min, large cannula (20G or larger) in a large calibre vein and suitable, small doses [3,4]. Medical care of the PGS patient require multidisciplinary care from anaesthesiologist (pain control), surgeon (surgical intervention),neurologist (neurological assessment), dermatologist (dermatological consultation).

**Table 3**

| **The 3 stages of purple glove syndrome** [4] | | | |
|---|---|---|---|
| | **Appearance** | **Progression** | **Resolution** |
| **Time** | 2-12 hours post infusion | 12-16 hours post infusion | Weeks to months |
| **Characteristic** | Bluish or purple discoloration of the skin around the cannula | • Spreading discoloration<br>• Oedema<br>• Skin blistering<br>• May occur ulceration | • Healing<br>• Declining oedema, discoloration |

## Summary

Despite the existence of many clinical trials, long term observations and scientific speculations, PGS can still be challenging for clinicians. In order to provide the highest level of professional medical care it is necessary to make research and to spread knowledge about PGS among medical staff.

## References

1. Garbovsky L.A., Drumheller B.C., Perrone J. Purple Glove Syndrome after Phenytoin or Fosphenytoin Administration: Review of Reported Cases and Recommendations for Prevention. J. Med. Toxicol. ,2015; 11:445–459
2. Joseph W. Newman, Joseph R. Blunck, Ronald K. Fields, John E. Croom, ,Fosphenytoin-induced purple glove syndrome: A case report, 2017, Clinical Neurology and Neurosurgery 160 (2017) 50–53
3. *John I. Okogbaa, PharmD*,, Phenytoin-Induced Purple Glove Syndrome: A Case Report and Review of the Literature, 2015, Hosp Pharm 2013;50(5):391–395
4. Rajabally H, Nageshwaran S, Russell S. An atypical case of Purple Glove syndrome: an avoidable adverse event. *BMJ Case Reports* 2012;10.1136/bcr.01.2012.5653,
5. Meierkord H, Boon P, Engelsen B, Gocke K, Shorvon S, Tinuper P, et al. EFNS guideline on the management of status epilepticus in adults. Eur J Neurol. 2010;17(3):348–55.
6. Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons, Joint Section on Neurotrauma and Critical Care, AANS/CNS, Bratton SL, Chestnut RM, et al. Guidelines for the management of severe traumatic brain injury. XIII. Antiseizure prophylaxis. J Neurotrauma. 2007; 24 Suppl 1:S83–6.
7. Uma B., Kochhar A. An anaesthesiologist's encounter with purple glove syndrome. Indian J Anaesth. 2016;60(3):199–201.
8. Chabra P., Gupta N., Kaushik A. Compartment syndrome as a spectrum of purple glove syndrome following intravenous phenytoin administration in a young male: A case report and review of literature. Neurol India. 2013;61(4):419-20
9. Chokshi, R., Openshaw, J., Mehta, N. N., Mohler, E. (2007). Purple glove syndrome following intravenous phenytoin administration. Vascular Medicine, 12(1), 29–31
10. Lalla R., Malhotra H.S., Garg R.K., Sahu R. Purple glove syndrome: a dreadful complication of intravenous phenytoin administration. BMJ Case Rep. 2012;2012:bcr2012006653. Published 2012 Aug 24

11.Ulubaş Işık D., Demirel N., Erol S., Ünal S., Baş A.Y. A Rare Complication of Phenytoin Infusion in Newborn: Purple Glove Syndrome. Balkan Med J. 2017;34(6):584–585
12. O'Brien TJ, Cascino GD, So EL, Hanna DR. Incidence and clinical consequences of the purple glove syndrome in patients receiving intravenous phenytoin. Neurology 1998; 51: 1034
13. Okogbaa J.I., Onor I.O., Arije O.A., Harris M.B., Lillis R.A. Phenytoin-Induced Purple Glove Syndrome: A Case Report and Review of the Literature. Hosp Pharm. 2015; 50(5):391–395.
14.Hanna DR. Purple glove syndrome: a complication of intravenous phenytoin. J Neurosci Nurs 1992; 24: 340
15.Comer JB. Extravasation from intravenous phenytoin. Am J Intrav Ther Clin Nutr 1984; 11: 23
16.Kilarski DJ, Buchanan C, Von Behren L. Letter: soft-tissue damage associated with IV phenytoin. N Engl J Med 1984; 311: 1186
17.Spengler RF, Arrowsmith JB, Kilarski DJ, Buchanan C, Von Behren L, Graham DR. Severe soft tissue injury following intravenous infusion of phenytoin. Arch Intern Med 1988; 148: 1329
18.MacCara ME. Extravasation: a hazard of intravenous therapy. Drug Intell Clin Pharm 1983; 17: 713
19.Garcia-Porrua C, Gonzalez-Gay MA, Lopez-Lazaro L. Drug associated cutaneous vasculitis in adults in northwestern Spain. J Rheumatol 1999; 26: 1942
20.Holder, S. M. ten, Joy, M. S., & Falk, R. J.. *Cutaneous and Systemic Manifestations of Drug-Induced Vasculitis. Annals of Pharmacotherapy, 2002; 36(1), 130–147*
21.Hayes AG, Chesney TM. Necrosis of the hand after extravasation of intravenously administered phenytoin. J Am Acad Dermatol 1993; 28: 360
22.Jain RS, Nagpal K, Kumar S, Prakash S, Handa R. Purple glove syndrome occurring after oral administration of phenytoin in therapeutic doses: mechanism still a dilemma. Am J Emerg Med. 2015;33(1):123.e5–6
23.Helfaer M, Ware C. Purple glove syndrome. J Neurosurg Anesthesiol. 1994;6(1):48–9
24.Sharief N, Goonasekera C. Soft tissue injury associated with intravenous phenytoin in a neonate. Acta Paediatr. 1994;83(11):1218–9