Unexpected outcome (positive or negative) including adverse drug reactions

An atypical case of Purple Glove syndrome: an avoidable adverse event

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Summary

A 73-year-old man presented in status epilepticus. He had a long history of epilepsy for which he was treated with regular phenytoin and phenobarbitone. On admission, his phenytoin level was found to be subtherapeutic and was treated with rectal diazepam and intravenous lorazepam. He was later started on an infusion of phenytoin in preparation to restart his oral medication. The medication was delivered via a peripheral cannula in his forearm. Five days later, he developed redness and swelling of this arm followed by the appearance of a large ulcer. After ruling out infective causes and a compartment syndrome it was felt that the patient had developed a delayed purple glove syndrome secondary to intravenous phenytoin. Following 7 days of regular saline irrigation and dressing changes, the erythema improved and the ulcer showed signs of healing, and eventually resolved.

BACKGROUND

Purple Glove syndrome (PGS) is an adverse reaction to intravenous phenytoin. This phenomenon is characterised by discolouration of a limb with severe oedema and pain within 24 h of intravenous infusion of phenytoin.¹ The aetiology of PGS is still uncertain but suggested explanations include extravasation injury or thrombotic event.^{2 3}

CASE PRESENTATION

A 73-year-old man presented to accident and emergency in status epilepticus. He was a known epileptic, treated with phenytoin 300 mg at night and phenobarbitone 30 mg three times daily. His phenytoin level on admission was subtherapeutic at 8 mg/l (therapeutic range: 10 to 20 mg/l). He received two 10 mg doses of diazepam overnight and 2 mg of intravenous lorazepam after which there were no witnessed seizures. However, the following day he did not receive two doses of his regular antiepileptic medications as he was drowsy and was not tolerating a nasogastric tube.

He was reviewed by the Consultant Neurologist who advised starting an intravenous infusion of phenytoin, 500 mg over 30 min (16.6 mg/min) to cover for the day's deficit. Then he was to continue intravenous phenytoin at 100 mg in the morning, 100 mg at lunchtime and 200 mg in the evening. He also advised intravenous phenobarbital sodium 90 mg stat dose which was the total daily dose equivalent and then to continue at 30 mg three times daily intravenously until oral intake was safe. He received intravenous phenytoin and phenobarbital sodium through a 20 Gauge cannula on his left forearm for a total of 2 days. The intravenous phenytoin was administered undiluted at a rate of 50 mg/min as per local guidelines. The medication is not diluted as there is a risk of drug precipitation in most intravenous fluids. After 2 days, he was switched back to his regular oral medications.

Five days later, he developed pain in his left arm with skin discolouration and swelling. On examination, a 3 cm by 2 cm ulcer was noted on his left forearm, with signs of ascending lymphangitis (figure 1). The oedema and erythema extended up his left arm and left axillary lymphadenopathy was noted. His radial pulse was palpable on that arm and sensation was intact. A plain radiograph of the left arm was normal. An orthopaedic opinion was sought for prophylactic fasciotomy to prevent compartment syndrome but as the forearm was not tense, this was not indicated. The tissue viability nurse was consulted regarding appropriate dressings to promote healing.

OUTCOME AND FOLLOW-UP

Following 7 days of regular saline irrigation of the ulcer and dressing changes, the erythema improved and the ulcer showed signs of healing (figure 2).

DISCUSSION

This case illustrates an unusually delayed presentation of PGS following a phenytoin infusion for management of status epilepticus. The reaction is usually seen within 2–12 h postinfusion, with a prevalence ranging from 1.7% to 5.9%.⁴ There are three stages for the course of PGS (box 1).⁴

The reaction is thought to be caused by the high alkalinity of phenytoin and the propylene glycol content needed to increase its solubility. The alkaline solution may stimulate vasoconstriction and thrombosis in vessels and may allow leakage into interstitial space by break down of endothelial cell junctions.⁵ This in turn leads to the discolouration and oedema noted in PGS. The literature has highlighted possible risk factors for PGS (box 2).

This delay in presentation of this particular case may be explained by the accumulation of free phenytoin in

Figure 1 Five days following intravenous phenytoin infusion, the patient's left hand and arm are swollen and erythematous. The large ulcer is well demarcated and has an erythematous border.

Figure 2 Twelve days following phenytoin infusion, there is a dramatic reduction in swelling and the ulcer is showing signs of healing.

small veins and capillaries and not directly to the infusion at all.⁴

To prevent the occurrence of PGS, it is recommended that slow infusion rates are used, via a large cannula (20G or larger), sited in a large calibre vein (ie, not in distal

extremities). Following which a normal saline flush has been advised.² In cases of PGS, the phenytoin infusion should be immediately stopped and the limb elevated.⁶ Nitroglycerin application to the area and brachial plexus block may reduce vasospasm and oedema and promote

Box 1 The 3 stages of Purple Glove Syndrome⁴

- ▶ **Appearance:** blue or purple discolouration around IV site 2–12 hours post infusion.
- ▶ **Progression:** 12–16 hours post infusion, spreading discolouration, oedema, skin blistering, sloughing and possible ulceration. Further extension distally and proximally may occur.
- ▶ **Resolution:** may take weeks to months, discolouration recedes back toward original IV site.

Box 2 Risk factors for Purple Glove syndrome¹

- ▶ Fast infusion rates (>25 mg/min)
- ▶ Small gauge cannula
- ▶ Large doses
- ▶ Multiple infusions
- ▶ Older

intravascular absorption of phenytoin.⁷ Severe PGS may need fasciotomy or amputation.⁶

It has been suggested that the use of fosphenytoin, the pro-drug of phenytoin, may be preferred to avoid PGS. It is thought to be less toxic than phenytoin and less painful upon extravasation. However, data supporting this are limited and recent studies of cost-effectiveness do not support its use due to its substantial cost.⁸

PGS is an adverse reaction to intravenous phenytoin infusion. Its occurrence is increased when small peripheral lines are used for drug administration. As phenytoin infusion is

most often used in emergency settings, primarily in cases of refractory status epilepticus, it should be borne in mind that safe use is through larger lines in more proximal veins.

Learning points

- ▶ PGS is a rare adverse reaction to intravenous phenytoin administration.
- ▶ PGS is more likely to occur when small peripheral lines are used and when given quickly.

Competing interests None.

Patient consent Obtained.

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