CASE REPORT

Localised bullous eruptions and epidermal detachment from the extravasation of hydroxyethyl starch (Voluven)

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SUMMARY

Extravasation occurs frequently with intravenous infusions. In this case report we describe the occurrence of epidermal detachment and multiple cutaneous bullous eruptions in a patient's forearm following the extravasation of hydroxyethyl starch (Voluven, Fresenius Kabi)—a colloid solution derived from corn starch, which is used to replace lost blood volume. The patient's affected body surface area was managed under the direction of our plastic surgical team. Despite a prolonged admission in hospital from other perioperative complications, he made a full recovery and was successfully discharged home. The probable pathogenesis relevant to extravasation of Voluven is discussed; as well as its management principles.

BACKGROUND

Intravenous fluid extravasation is a common complication in the perioperative setting and may have significant adverse effects.^{1–4} Factors that have been associated with the severity of injury, specifically tissue necrosis, are the cytotoxicity of the solution, concentrated electrolyte solutions, osmolality and vasoconstrictive properties.¹

Specific to this case, the extravasation of hydroxyethyl starch (Voluven, Fresenius Kabi) resulted in bullous eruption. This has been previously reported in another case, which also involved an acute compartment syndrome.⁵ Voluven is not considered cytotoxic or hyperosmolar, and does not contain concentrated electrolytes and does not have vasoconstrictive properties. We therefore discuss its probable pathogenesis in this case report as well as outline the management principles.

CASE PRESENTATION

A 67-year-old Caucasian man with metastatic bowel cancer presented for major hepatobiliary surgery. He had no known allergies. The anaesthetic plan included establishing large bore peripheral intravenous access in the dorsum of his left hand, central venous access in his right internal jugular vein and intra-arterial cannulation in his left brachial artery. Subarachnoid block was established with 4 mL of 0.5% anhydrous bupivacaine chloride and 300 µg of morphine. The patient was then induced with 100 µg of fentanyl, 120 mg of propofol and 50 mg of atracurium, and general anaesthesia was maintained with sevoflurane. Prophylactic antibiotics—1 g of cefazolin and 500 mg of metronidazole—were given on induction. Both arms

were tucked in for surgery, so visualisation of intravenous access was obscured.

Approximately 4 h into the surgery, 500 mL of hydroxyethyl starch (Voluven) was administered under pressure through the peripheral intravenous access. After its completion, no further infusions or drugs were given into this line. Over the next hour, the arterial trace in the left brachial artery became increasingly damped. At this stage the arm was exposed and was found to be pale and pulseless with extensive epidermal detachment and bullous eruptions (figures 1 and 2).

INVESTIGATIONS

Urgent vascular and plastic surgical review was subsequently organised. No thrombosis was found in either radial or ulna arteries. Compartment syndrome was also excluded, as measured compartment pressures were less than 30 mm Hg. Therefore a fasciotomy was not performed. Approximately 9% of total body surface area was affected. The left forearm and upper extremity was scrubbed to remove any necrotic tissue, dressed with Acticoat and secured with Hyperfix. Following completion of his surgery, the patient was transferred to the intensive care unit.

TREATMENT

Postoperatively, the patient developed pulmonary infiltrates, acute pulmonary oedema and subsequently suffered a myocardial infarction. In the following days, he returned to theatre under the care of the plastic surgical team for change of dressings

Figure 1 Dorsal left forearm showing epidermal detachment and bullae following extravasation of hydroxyethyl starch.

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Figure 2 Ventral left forearm showing epidermal detachment and bullae.

and further debridement of necrotic skin, with an eventual split-thickness skin graft.

OUTCOME AND FOLLOW-UP

With his admission further complicated by sepsis, the patient remained in hospital for a total of 2 months. He was transferred to a rehabilitation hospital where he made a successful recovery and was discharged home 2 weeks later. His left forearm and upper extremity had healed appropriately and full function was regained.

DISCUSSION

The mechanisms of tissue ischaemia and subsequent injury from extravasation of fluids in the perioperative period are commonly due to vasoconstrictive substances (epinephrine or norepinephrine); concentrated electrolyte solutions (10% Calcium Gluconate, 8.4% sodium bicarbonate) causing prolonged depolarisation and contraction of capillary sphincters leading to tissue ischaemia; or hyperosmolar solutions (20% mannitol)¹ exerting osmotic pressure on surrounding tissues. The recommendation therefore is for these substances to be infused through the most distal port of a central line; and, if possible, to avoid giving them through peripheral intravenous lines.¹ When examining the types of intravenous fluids or drugs involved in cases of extravasation and tissue injury in the perioperative setting,^{2–4} they generally fall into one or more of the above described mechanisms except for Voluven (Fresenius Kabi).⁵ Voluven contains 6 g/L of hydroxyethyl starch (mean molecular weight of 130 000 Da, with 0.42 molar substitution of hydroethyl groups on glucose units of the starch) in 0.9% sodium chloride. It is not considered hyperosmolar with an osmolarity of only 308 mOsm/L and a pH between 4 and 5.5. Also, it is not presented in a concentrated electrolyte solution or considered to be cytotoxic. Therefore its mechanism of tissue injury must be different.

Bullous eruptions from drug reactions are the result of an immunologically mediated inflammatory response from cytotoxic T-cell mediated diseases, which along with natural killer cells induces keratinocyte apoptosis.^{6–7} The current two main hypotheses of the T-cell mediated activation are the: (1) pharmacological interaction of the drug with the immune system and (2) pro-hapten concept.⁸ We believe the second hypothesis represents the most likely pathogenesis, as it is unlikely that hydroxyethyl starch could stimulate the immune system by binding directly to the major histocompatibility

complex I and the T-cell receptor, as the molecule itself is too large. Instead, with the extravasation of hydroxyethyl starch, tissue macrophages would digest these carbohydrates into smaller metabolites that could bind cellular proteins creating haptens. This would promote an immune response and result in tissue injury.

Interestingly, intravascular administration of hydroxyethyl starch has been implicated in renal impairment through an immune-mediated response via macrophages in the renal tubules.⁹ This has been associated with an increased risk of kidney injury requiring dialysis and mortality in critically ill patients.^{10–12} Currently, the use of hydroxyethyl starch (Voluven) is allowed only under specific conditions in the UK, Australia and New Zealand.

The general management of extravasation injuries with obvious tissue injury requires immediate attention. This includes cessation of the substance to reduce further damage and flushing, and drainage of the affected area with normal saline. We also recommend early referral to the burns or plastic unit. Wound treatment should include debridement of any necrotic tissue and avoidance of frequent dressing changes to avoid affecting re-epithelisation. Prevention can be achieved by ensuring Voluven is not given through an intravenous catheter that is outside the view of the anaesthetist.

Learning points

- ▶ Extravasation of hydroxyethyl starch can cause significant tissue injury.
- ▶ The mechanism of injury is likely immune-related as Voluven is not considered to be cytotoxic, vasoconstrictive or hyperosmolar and is not presented in a concentrated electrolyte solution.
- ▶ Following diagnosis of tissue injury from extravasation, it is important to cease any possible causes and seek early referral to the burns or plastic unit for best patient outcome.
- ▶ Voluven should be given through an intravenous catheter that is within the view of the anaesthetist at all times.

Competing interests None.

Patient consent Obtained.

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REFERENCES

- 1 Schummer W, Schummer C, Bayer O, *et al.* Extravasation injury in the perioperative setting. *Anesth Analg* 2005;100:722–7.
- 2 Edwards JJ, Samuels D, Fu ES. Forearm compartment syndrome from intravenous mannitol extravasation during general anesthesia. *Anesth Analg* 2003;96:245–6.
- 3 Chang KA, Jawan B, Luk HN, *et al.* Bullous eruptions caused by extravasation of mannitol—a case report. *Acta Anaesthesiol Sin* 2001;39:195–8.
- 4 Robijns BJ, de Wit WM, Bosma NJ, *et al.* Localized bullous eruptions caused by extravasation of commonly used intravenous infusion fluids. *Dermatologica* 1991;182:39–42.
- 5 Scholtes JL, Loriau E, Tombal B. Severe intraoperative acute compartment syndrome with bullous eruption complicating IV fluid administration. *Anesth Analg* 2006;103:783–4.
- 6 Nassif A, Bensussan A, Boumsell L, *et al.* Toxic epidermal necrolysis: effector cells are drug-specific cytotoxic T cells. *J Allergy Clin Immunol* 2004;114:1209–15.
- 7 Nassif A, Bensussan A, Dorothée G, *et al.* Drug Specific cytotoxic T-cells in the skin lesions of a patient with toxic epidermal necrolysis. *J Invest Dermatol* 2002;118:728–33.

- 8 Schwartz RA, McDonough PH, Lee BW. Toxic epidermal necrolysis: Part I. Introduction, history, classification, clinical features, systemic manifestations, etiology, and immunopathogenesis. *J Am Acad Dermatol* 2013;69:173.e1–13.
- 9 Hüter L, Simon TP, Weinmann L, *et al.* Hydroxyethylstarch impairs renal function and induces interstitial proliferation, macrophage infiltration and tubular damage in an isolated renal perfusion model. *Crit Care* 2009;13:R23.
- 10 Perner A, Haase N, Guttormsen AB, *et al.* Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med* 2012;367:124–34.
- 11 Brunkhorst FM, Engel C, Bloos F, *et al.* Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008;358:125–39.
- 12 Myburgh JA, Finfer S, Bellomo R, *et al.* Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med*. 2012;367:1901–11.

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