

Quantification of volume loss and haemodynamic changes of Gelofusine®-induced anaphylaxis during cardiopulmonary bypass

R. CLARKE*, P. SADLEIR*, A. W. VAN NIEKERK†, P. PLATT*

Departments of Anaesthesia, Sir Charles Gairdner Hospital, Nedlands and Fremantle Hospital, Perth, Western Australia

SUMMARY

A patient undergoing anaesthesia for coronary artery bypass surgery developed what was subsequently confirmed to be an anaphylactic reaction to succinylated gelatin (Gelofusine®). By virtue of being on cardiopulmonary bypass, rapid detection, quantification and treatment of volume loss (by vasodilatation and extravasation) was possible. The patient required 51 ml/kg of resuscitative fluids in the 15 minutes after onset of anaphylaxis, or 73% of her calculated preoperative blood volume. Alpha-adrenoceptor agonists and vasopressin were required to manage ongoing vasoplegia. This case emphasises the importance of volume resuscitation and vasopressors in the treatment of anaphylaxis.

Key Words: anaphylaxis, Gelofusine®, cardiopulmonary bypass

One of the mainstays in the treatment of cardiovascular collapse in anaphylaxis is aggressive fluid administration. Mediators released during anaphylaxis produce peripheral vasodilatation and increase capillary permeability resulting in a mixed distributive-hypovolaemic shock pattern¹.

This report outlines a case of confirmed Gelofusine®-induced (succinylated gelatin, B. Braun, Bella Vista, New South Wales, Australia) anaphylaxis during cardiopulmonary bypass (CPB) and offers an insight into the resulting changes in volume status and haemodynamics during the ensuing cardiovascular collapse.

Hypotension results from either a fall in cardiac output or systemic vascular resistance (SVR). This case is unique as the cardiac output was relatively fixed because the patient was on CPB. The assessment of haemodynamic changes seen in this case was further assisted by the monitoring of the CPB reservoir volume. This allowed rapid quantification of the volume loss associated with vasodilatation and extravasation.

CASE HISTORY

A 76-year-old female was admitted with an ischaemic left leg and subsequently underwent above-knee amputation. Her other medical conditions included paroxysmal atrial fibrillation, hypertension, hypercholesterolaemia, peripheral vascular disease, type 2 diabetes mellitus and chronic renal impairment. Her only allergic history was the development of a pruritic rash after penicillin administration for a chest infection 10 years previously.

Her postoperative course was complicated by acute pulmonary oedema and a silent non-ST-segment-elevation myocardial infarction. Subsequent investigations demonstrated triple-vessel coronary artery stenosis with mild hypokinesis of the apical septum but otherwise preserved left ventricular systolic and diastolic function with normal heart valves.

Two months after admission she was scheduled for coronary artery bypass grafting with CPB using saphenous vein and internal mammary artery grafts. Her weight was 72 kg and preoperative haemoglobin concentration (Hb) measured 103 g/l.

Induction of anaesthesia was uneventful and coronary artery grafting, while on CPB, was without incident. Her initial Hb after commencement of CPB was 57 g/l, and three units of packed cells were transfused. After an aortic cross-clamp time of 45 minutes she was rewarmed and prepared for separation from bypass. Reservoir volume was low at this point and following 1000 ml of Plasma-Lyte

* M.B., B.S., F.A.N.Z.C.A., Consultant Anaesthetist, Sir Charles Gairdner Hospital.

† M.B., Ch.B., F.A.N.Z.C.A., P.G.Dip.Echo, Consultant Anaesthetist, Fremantle Hospital.

Address for correspondence: Dr R. Clarke, email: rclarke@meddent.uwa.edu.au

Accepted for publication on December 10, 2010.

with intravenous fluids, receiving four units of packed red cells, two units of fresh frozen plasma and two litres of crystalloid. Despite these measures to correct venodilatation and extravasation of fluid, minimum volumes in the CPB reservoir were barely maintained even at low flows (1.5 l/minute/m²).

Thirty minutes after the administration of Gelofusine, the patient's condition began to improve with a more stable mean arterial blood pressure, a rise in central venous pressure and improved return to the bypass reservoir allowing higher flows to be achieved (2.0 l/minute/m²). At 50 minutes, separation from bypass was achieved. Post-CPB haemodynamic measurements found the patient to be vasodilated, with a SVR of 850 dyn.s.cm⁻⁵ and cardiac index of 3.5 l/minute/m². Transoesophageal echocardiography demonstrated a hyperdynamic, relatively empty left ventricle with preserved systolic and diastolic function. A vasopressin infusion was commenced. Heparinisation was then reversed with protamine. The patient's chest was closed and her condition continued to improve.

Prior to transfer from theatre her SVR had increased marginally to 950 dyn.s.cm⁻⁵ and her cardiac index had remained relatively constant at 3.3 l/minute/m².

The patient was transferred to the intensive care unit and was extubated 24 hours later. She had significant peripheral oedema which resolved over several days and made a complete recovery with no neurological deficit. She was discharged from hospital two weeks after surgery.

Mast cell tryptase levels peaked at 36.4 µg/l (normal <14 µg/l), one hour after the onset of the anaphylaxis. Two months after surgery, allergy testing was undertaken. Skin prick and intradermal skin testing, using Fisher's Protocols², confirmed Gelofusine as the causative agent with marked seriginous weals with surrounding flares developing at both Gelofusine test sites.

Consent was obtained from the patient to publish this report.

DISCUSSION

Gelofusine allergy is well described, usually occurring during anaesthesia or resuscitation^{3,6}. This often makes diagnosis and treatment difficult due to confounding pathophysiological states. The exact mechanism is largely unknown, but both IgE and non-IgE mechanisms have been postulated⁵. It is estimated that the incidence of allergic reactions to gelatin-based solutions is 0.038%⁷.

In this case, adrenaline 3 mg, phenylephrine 3 mg and 3680 ml of fluid (four units packed red cells, two

units FFP and 2 litres Plasmalyte) were given in the first 15 minutes of the reaction to maintain reservoir levels.

We estimated her normal circulating blood volume to be 5.04 litres, assuming that blood volume is 70 ml/kg in the non-obese⁸. The volume of the bypass circuit was 2.4 litres. The volume of resuscitation fluids given in the first 15 minutes therefore represented 49.4% of her circulating CPB volume or 73% of her estimated blood volume by weight. This was despite aggressive co-administration of adrenaline and vasoconstrictors.

In addition to hypovolaemia and maldistribution of blood, the mechanisms of shock in anaphylaxis are postulated to include cardiac dysfunction from poor venous return as well as the direct effects of anaphylactic mediators on the myocardium causing depressed contractility¹⁹. Pulmonary vasospasm has also been implicated in obstruction to filling of the left ventricle¹⁰. The circumstances of this case are novel in that the patient's heart and lungs were largely isolated from the systemic circulation during the period of distributive-hypovolaemic shock. The hypotension was clearly the result of reduced venous return to the CPB circuit and decreased systemic vascular resistance, as the cardiac output was fixed.

The second novel aspect of this case was that it was possible to directly measure the expansion of intravascular volume required to maintain the venous reservoir volume. In the treatment of anaphylaxis, the exact requirement for fluid resuscitation is not known. Maldistribution due to venodilatation and hypovolaemia secondary to increased capillary permeability and plasma extravasation contribute to circulatory shock. The component resulting from plasma losses in the first 10 minutes has been estimated to be as high as 35% of the circulating blood volume, as inferred from changes in the haemoglobin concentrations of 22 patients having acute anaphylactic reactions^{9,11}. The volume of fluid administered in this case was much greater, and may possibly reflect measurement of the additional requirements due to blood pooling from venodilatation.

Current guidelines for fluid resuscitation in acute anaphylaxis indicate that large volumes may be required, recommending multiple boluses of 10 to 20 ml/kg up to a total of 50 ml/kg over the first 30 minutes^{9,12}. This case, in which a total of 51 ml/kg of fluid was administered within 15 minutes of the trigger for anaphylaxis, supports these recommendations.

Although a large number of preformed and generated mediators have been implicated in

anaphylaxis, resulting in the concept of the mast cell-leucocyte cytokine cascade⁹, it is the histamine level that is most closely correlated with the severity of the hypotension. Moss et al¹³ measured a 20-fold increase in plasma histamine from normal after an anaphylactic reaction to suxamethonium, associated with a profound fall in the SVR. Although they measured a massive increase in endogenous catecholamine levels, it was not sufficient to attenuate the effect of the histamine. The case was unusual since resuscitation was with fluid alone with a return to normal haemodynamic parameters concomitant with a fall to normal in the plasma histamine level at around 20 minutes.

Loss of circulating volume in anaphylaxis is due to a combination of increased capillary permeability with fluid extravasation into the interstitial space and sequestration in grossly dilated vascular beds leading to a profound reduction in venous return. This mechanism was well demonstrated in this case by the transoesophageal echocardiogram showing an empty heart even after massive fluid replacement.

Adrenaline has mast cell stabilising and bronchodilating effects, clearly of benefit in the treatment of anaphylaxis. More recently there have been calls for guidelines in the treatment of anaphylaxis unresponsive to adrenaline to include the use of pure alpha agonists¹⁴. It is thought that this would more effectively treat the vasoplegia and reduce the risk of tachyarrhythmias and the beta₂-induced vasodilatory effects of adrenaline. We would support this proposed change. A similar argument would support the earlier use of vasopressin, for which there are a number of case reports in the literature, one paper describing its role as 'pivotal'¹⁵.

This case highlights and reinforces the importance of volume replacement in anaphylaxis. It also serves as a reminder that gelatin-based colloids, which are most commonly resorted to in critical situations, may have undesirable effects. Our understanding of the physiological effects of histamine and the

responses seen in this case would support the earlier use of alpha agonists and vasopressin.

REFERENCES

1. Brown SGA. Cardiovascular aspects of anaphylaxis: implications for treatment and diagnosis. *Curr Opin Allergy Clin Immunol* 2005; 5:359-364.
2. Fisher M. Intradermal testing after anaphylactoid reaction to anaesthetic drugs; practical aspects of performance and interpretation. *Anaesth Intensive Care* 1984; 12:115-120.
3. Isbister J, Fisher M. Adverse effects of plasma volume expanders. *Anaesth Intensive Care* 1980; 8:145-151.
4. Jenkins S, Clifton M. Gelofusine allergy – the need for identification. *Ann R Coll Surg Engl* 2002; 84:206-207.
5. Pepys J, Pepys E, Baldo B, Whitwam J. Anaphylactic/anaphylactoid reaction to anaesthetic and associated agents: skin prick tests in aetiological diagnosis. *Anaesthesia* 1994; 49:470-475.
6. Russell W, Fenwick D. Anaphylaxis to Haemaccel and cross reactivity to Gelofusine. *Anaesth Intensive Care* 2002; 30:481-483.
7. Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet* 1977; 1:466-469.
8. Singbartl K, Innerhofer P, Radvan J, Westphalen B, Fries D, Stögbauer R et al. Hemostasis and hemodilution: a quantitative mathematical guide for clinical practice. *Anesth Analg* 2003; 96:929-935.
9. Brown SGA. Anaphylaxis: clinical concepts and research priorities. *Emerg Med Australas* 2006; 18:155-169.
10. Brown SG. The Pathophysiology of Shock in Anaphylaxis. *Immunol Allergy Clin North Am* 2007; 27:165-175.
11. Fisher M. Clinical observations on the pathophysiology and treatment of anaphylactic cardiovascular collapse. *Anaesth Intensive Care* 1986; 14:17-21.
12. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A et al. Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006; 117:391-397.
13. Moss J, Fahmy NR, Sunder N, Beaven MA. Hormonal and hemodynamic profile of an anaphylactic reaction in man. *Circulation* 1981; 63:210-213.
14. McBrien ME, Breslin DS, Atkinson S, Johnston JR. Use of methoxamine in the resuscitation of epinephrine-resistant electromagnetic dissociation. *Anaesthesia* 2001; 56:1082-1089.
15. Schummer C, Wirsing M, Schummer W. The Pivotal Role of Vasopressin in Refractory Anaphylactic Shock. *Anesth Analg* 2008; 107:620-624.

Copyright of Anaesthesia & Intensive Care is the property of Australian Society of Anaesthetists and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.