Brief Reports

Anaphylactoid reaction to pentastarch

Gerard J. McHugh FANZCA

Purpose: To report a probable anaphylactoid reaction to pentastarch, a low molecular weight hydroxyethyl starch (HES) colloid solution.

Clinical features: Following a closed head injury, an 18-yr-old male was admitted to the Intensive Care Unit. Therapy was directed towards control of intracranial pressure (ICP) and maintenance of cerebral perfusion pressure (CPP). In the first 12 hr after admission, he had received 2500 ml polygeline (Haemaccel®, Hoechst Marion Roussel Ltd.) and a dopamine infusion (up to $10 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) titrated to achieve a mean arterial pressure (MAP) of ≥ 80 mmHg. Subsequent failure to achieve the target MAP resulted in commencement of a noradrenaline infusion ($2.67 \mu\text{g}\cdot\text{min}^{-1}$), and rapid administration of 500ml pentastarch (Pentaspán®, DuPont Pharmaceuticals). During the HES infusion, marked hypotension (MAP < 60 mmHg) developed associated with marked truncal urticaria. The hypotension was resistant to escalation of noradrenaline to $36 \mu\text{g}\cdot\text{min}^{-1}$. Haemodynamic stability was rapidly restored and maintained with adrenaline boluses (total $450 \mu\text{g}$) and infusion ($1.67 \mu\text{g}\cdot\text{min}^{-1}$). The remainder of the patient's ICU and hospital stay was unremarkable. A serum tryptase drawn in the first 40 min of the reaction was not elevated. Other biochemical markers were not assayed. Skin testing has not been carried out.

Conclusion: The temporal relationship and clinical manifestations observed in this case, together with the resistance to inotropes/vasopressors other than adrenaline is highly suggestive of an anaphylactoid reaction to pentastarch. The diagnostic value of serum tryptase may be compromised when blood samples are drawn too early.

Objectif : Rapporter une réaction anaphylactoïde probable au pentastarch, une solution colloïdale d'hydroxyéthyl amidon (HEA) de bas poids moléculaire.

Aspects cliniques : À la suite d'un traumatisme crânien fermé, un homme de 18 ans a été admis aux soins intensifs. Le traitement institué avait pour but le contrôle de la pression intracrânienne (PIC) et le maintien de la pression de perfusion cérébrale (PPC). Durant les premières 12 heures après l'admission, il a reçu 2500 ml de polygeline (Haemaccel®, Hoechst Marion Roussel Ltd.) et une infusion de dopamine (jusqu'à $10 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) titrée de façon à maintenir une pression artérielle moyenne (PAM) ≥ 80 mmHg. L'incapacité à maintenir la PAM visée a entraîné la mise en route d'une infusion de noradrénaline ($2,67 \mu\text{g}\cdot\text{min}^{-1}$) et l'administration rapide de 500 ml de pentastarch (Pentaspán®, Dupont Pharmaceuticals). Durant l'infusion de HEA, une hypotension sévère (PAM < 60 mmHg) est apparue, associée à un urticaire tronculaire important. L'hypotension a résisté à une augmentation de la perfusion de noradrénaline jusqu'à $36 \mu\text{g}\cdot\text{min}^{-1}$. La stabilité hémodynamique a été rapidement rétablie et maintenue avec des bolus d'adrénaline ($450 \mu\text{g}$ au total) ainsi qu'une infusion ($1,67 \mu\text{g}\cdot\text{min}^{-1}$). Le reste du séjour du patient aux soins intensifs et à l'hôpital a été sans particularité. Un échantillon de sang prélevé durant les premières 40 minutes de la réaction a montré des valeurs normales de tryptase sérique. Les autres marqueurs biochimiques n'ont pas été évalués, et des épreuves cutanées n'ont pas été réalisées.

Conclusion : La réaction présentée par ce patient, de par ses manifestations cliniques ainsi que du moment de sa survenue, associée à une résistance aux inotropes/vasopresseurs autres que l'adrénaline, suggère fortement une réaction anaphylactoïde au pentastarch. La valeur diagnostique du dosage sérique de la tryptase peut être compromise par un prélèvement sanguin trop hâtif.

From the Department of Anaesthesia and Intensive Care, Palmerston North Hospital, Private Bag 11036, Palmerston North, New Zealand.

Address correspondence to: Dr. Gerard J. McHugh.

Accepted for publication December 18, 1997.

HYDROXYETHYL starch (HES) solutions are frequently used for plasma volume expansion. Pentastarch (Pentastan®, DuPont Pharmaceuticals) and hetastarch (Hespan®, DuPont Pharmaceuticals) have both been available in New Zealand. Amongst other differences, the former has a lower weight-average molecular weight than the latter (250,000 *versus* 480,000). All HES solutions share the characteristic of a low incidence of allergic reactions compared with gelatin and dextran solutions.¹ Whilst previous reactions to hetastarch have been infrequently reported,¹⁻⁴ even fewer reports of reactions to any of the lower molecular weight (MW) starches have been published to date.^{1,5} A case report of a severe reaction to the lower MW HES pentastarch is presented here.

Case report

An 18-yr-old male was involved in a road traffic crash. He sustained a closed head injury, facial/scalp lacerations and a compound fracture of the distal right tibia. Upon arrival at hospital, he was haemodynamically stable, with a Glasgow Coma Scale of 9 (E2, V3, M4). There was no clinical or radiographic evidence of any other injury. His trachea was intubated and mechanical ventilation was commenced. A CT scan of his head confirmed traumatic brain injury with moderate cerebral oedema, widespread petechial haemorrhages and a shallow right frontoparietal subdural haematoma (maximum depth 5 mm) with minimal (<3 mm) mid-line shift. A CT scan of his chest and abdomen revealed no abnormality. He received 1000 ml polygeline (Haemaccel®, Hoechst Marion Roussel Ltd.) to maintain circulatory stability.

He was transferred to the intensive care unit (ICU). His treatment included sedation (morphine and midazolam infusion, titrated up to 10 mg·hr⁻¹ of each), mechanical ventilation with controlled hyperventilation (target PaCO₂ of 30–35 mmHg) and circulatory support directed at maintaining cerebral perfusion (target mean arterial pressure ≥80 mmHg). He was taken to the operating theatre for orthopaedic treatment of his tibial fracture, and then returned to ICU. In response to circulatory instability during the first 12 hr of his admission, he received a further 1500 ml polygeline and a dopamine infusion titrated to 666.7 µg·min⁻¹ (approximately 10 µg·kg⁻¹·min⁻¹). Subsequent failure to achieve the target mean arterial pressure (MAP) resulted in the commencement of a noradrenaline infusion at an initial rate of 2.67 µg·min⁻¹, and administration of 500ml pentastarch (Pentastan®, DuPont Pharmaceuticals) over 15 min. During the HES infusion, the MAP decreased into the mid-fifties, despite rapid escalation of the nora-

drenaline infusion to 36 µg·min⁻¹. Immediate exposure of the patient revealed marked urticaria in both axillae and over the lower abdomen and groins. There was no bronchospasm or erythema. An anaphylactic reaction was suspected, and the MAP was restored with three 150 µg boluses of adrenaline. Low-dose adrenaline infusion (1.67 µg·min⁻¹) was added to the continuing dopamine and reduced-rate noradrenaline. There was no further hypotension and the urticaria subsided completely over the next three hours. The adrenaline was ceased after 12 hr. He was not given any further pentastarch, and there were no further allergic manifestations. All other medications that had been administered before the reaction were subsequently readministered without any untoward events.

A blood sample was drawn for serum tryptase within 40 min of the reaction. The exact time of the sample was not recorded. The result returned at 0.3 µg·l⁻¹ (normal < 5 µg·l⁻¹). Assays for other serum markers of allergic reaction were not requested at the time of the reaction.

The patient's subsequent course in ICU and hospital was uneventful. Two further brain CT scans showed progressive resolution of the oedema. Inotropic and ventilatory supports were successfully weaned. His trachea was extubated after 12 days. He was transferred to the Rehabilitation Unit for treatment of his residual minor cognitive and memory impairments.

Skin testing was not carried out as the regional service does not routinely test against colloids. The patient has been advised of his allergy, and has been furnished with a Medic Alert bracelet.

Discussion

The diagnosis of an anaphylactic reaction depends upon appropriate clinical manifestations, including hypotension, bronchospasm, urticaria, erythema and GI symptoms. A reaction to any colloid should be treated according to standard protocols as for other causes of anaphylaxis. The diagnosis can be supported by a range of acute biochemical markers including blood levels of tryptase, histamine and complement, and urinary methylhistamine levels.⁷ The timing of these tests is important, and modifies their relative merits. Blood for histamine should be drawn within 10 min of the reaction.⁷ Tryptase is more useful as it has a later peak, and allows blood sampling to be delayed until acute management of the anaphylaxis is completed.⁷ The "best" time for this test is one-two hours after the reaction.⁸ In the reported case, the value of this test has been compromised by having drawn the blood too soon, even though anaphylactoid reactions can occur without elevation of tryptase.⁸ The lack of a suitable blood sample

thwarted a delayed request for complement levels. Skin testing was not carried out as such testing for colloids has been advised to be of little value.^{7,9} All other contemporaneous medications were subsequently readministered without any untoward event. Accordingly skin testing to these agents to exclude them as a cause was unnecessary.

The reported incidence of allergic reactions to HES varies between 0.058% and 0.085%.^{1,2,6} Varying formulations of the lower MW starches have been implicated in only a few of these reported reactions,^{1,5} but this the first report of such events involving pentastarch.

The mechanism of allergic reactions to HES remains unclear. Hydroxyethyl starch *per se* has been shown to have very low immunogenicity.¹⁰ Starch infusions do not cause histamine release.¹¹ Hydroxyethyl-starch-reactive antibodies have been demonstrated by ELISA techniques,¹² and it seems likely that non-IgE HES-specific antibodies⁵ and complement activation² are responsible for the HES-related reactions. These HES-specific antibodies are likely to be only extremely rarely preformed in starch-naïve subjects,¹² which is in keeping with the very low incidence of allergic reactions. The low immunogenicity of HES also suggests that acquisition of the HES-specific antibody through previous exposure is likely to be infrequent.

All artificial colloid solutions can cause severe allergic-type reactions.^{1,6,9} The temporal relationship and clinical manifestations observed in this case, together with the resistance to inotropes/vasopressors other than adrenaline suggest it to be an anaphylactoid reaction to pentastarch. A serum tryptase level taken within 40 min of the reaction was not elevated, and skin testing was not performed. There have been no previous reported reactions to this formulation of HES. Vigilance and prompt treatment of any anaphylactic/anaphylactoid reaction remain essential when using any of the artificial colloids. Appropriate selection and timing of acute blood sampling is required to assist in confirmation of the diagnosis.

References

- 1 Laxenaire MC, Charpentier C, Feldman L, et al. Groupe Français d'Etude de la Tolerance des Substituts Plasmatisques. Réactions anaphylactoïdes aux substituts colloïdaux du plasma: incidence, facteurs de risque, mécanismes. Enquête prospective multicentrique française. *Ann Fr Anesth Réanim* 1994; 13: 301–10.
- 2 Ring J, Seifert J, Messmer K, Brendell W. Anaphylactoid reactions due to hydroxyethyl starch infusion. *Eur Surg Res* 1976; 8: 389–99.
- 3 Porter SS, Goldberg RJ. Intraoperative allergic reactions to hydroxyethyl starch: a report of two cases. *Can Anaesth Soc J* 1986; 33: 394–8.
- 4 Cullen MJ, Singer M. Severe anaphylactoid reaction to hydroxyethyl starch. *Anaesthesia* 1990; 45: 1041–2.
- 5 Kreimeier U, Christ F, Kraft D, et al. Anaphylaxis due to hydroxyethyl-starch-reactive antibodies. *Lancet* 1995; 345: 49–50.
- 6 Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet* 1977; I: 466–9.
- 7 Fisher M, Baldo BA. Anaphylaxis during anaesthesia: current aspects of diagnosis and prevention. *Eur J Anaesth* 1994; 11: 263–84.
- 8 Laroche D, Vergnaud M-C, Sillard B, Soufarapis H, Bricard H. Biochemical markers of anaphylactoid reactions to drugs. Comparison of plasma histamine and tryptase. *Anesthesiology* 1991; 75: 945–9.
- 9 Ring J. Anaphylactoid reactions to plasma substitutes. *Int Anesthesiol Clin* 1985; 23: 67–95.
- 10 Maurer PH, Berardinelli B. Immunologic studies with hydroxyethyl starch (HES). A proposed plasma expander. *Transfusion* 1968; 8: 265–8.
- 11 Lorenz W, Doenicke A, Freund M, et al. Plasma histamine levels in man following infusion of hydroxyethyl starch: a contribution to the question of allergic or anaphylactoid reactions following administration of a new plasma substitute. (German) *Anaesthesist* 1975; 24: 228–30.
- 12 Kraft D, Sirtl C, Laubenthal H, et al. No evidence for the existence of preformed antibodies against hydroxyethyl starch in man. *Eur Surg Res* 1992; 24: 138–42.