

CASE REPORT

Angiotensinamide in the treatment of probable anaphylaxis to succinylated gelatin (Gelofusine)

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Summary

A patient undergoing anaesthesia for coronary artery bypass surgery developed a probable anaphylactic reaction to succinylated gelatin (Gelofusine). The principal feature of the reaction was one of cardiovascular depression. An infusion of the angiotensin analogue, angiotensinamide was successful in the treatment of the reaction and allowed completion of the surgery.

Key words

Allergy; succinylated gelatin.

Pharmacology; angiotensinamide.

The principal drug in the treatment of anaphylactic reactions is adrenaline, since it is effective against cardiovascular depression, bronchospasm and angio-oedema. Occasionally reactions are severe and refractory to treatment and in such circumstances other drugs such as dopamine, H_2 antagonists and glucagon have been advocated. In addition, ventricular arrhythmias are associated with the use of adrenaline in the presence of halogenated hydrocarbons and some authors believe that the use of adrenaline is contraindicated when volatile anaesthetic agents are used.

The angiotensin analogue angiotensinamide (Hypertensin CIBA, Ciba-Geigy) is indicated for the treatment of severe hypotension unresponsive to traditional pressor agents. We report a case of severe anaphylaxis that responded dramatically to an infusion of angiotensinamide.

Case history

A 48-year-old, 89 kg man presented with a 2-month history of angina. He had no previous medical problems and was initially treated with atenolol, diltiazem, aspirin and glyceryl trinitrate (GTN) spray. Chest X ray was normal and his resting ECG revealed a sinus bradycardia, but was otherwise unremarkable. Coronary angiography demonstrated occlusion of the circumflex and right coronary arteries at their origins and a 70% proximal stenosis of the left anterior descending artery. Intracardiac pressures and left ventricular function were normal. He was scheduled for coronary artery bypass grafting.

Premedication was with lorazepam 4 mg orally, papaveretum 20 mg and atropine 0.3 mg intramuscularly and a GTN-5-patch topically 1 h before anaesthesia. In the anaesthetic room, following infiltration with lignocaine, a 14-G peripheral intravenous cannula and a 20-G right radial artery cannula were inserted. His heart rate was 60 $\text{beat}\cdot\text{min}^{-1}$ and his systemic arterial pressure 120/74 mmHg. An infusion of 500 ml of dextrose 5% was started and cefuroxime 750 mg was given prior to induction of anaesthesia. Following pre-oxygenation, anaesthesia was induced with alfentanil 2.5 mg, midazolam 20 mg and followed by pancuronium 8 mg. Systemic blood pressure decreased to 100/50 mmHg and the heart rate remained at 60 $\text{beat}\cdot\text{min}^{-1}$. Prior to transfer into the operating theatre a right internal jugular central venous line was inserted. Anaesthesia was maintained with infusions of alfentanil and midazolam at 0.8 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (4.3 $\text{mg}\cdot\text{h}^{-1}$). Ventilation was with 50% nitrous oxide in oxygen. On completion of the dextrose 5%, 500 ml of Gelofusine (Vifor Ltd, Chester, UK) was started and following this, 20 min after induction of anaesthesia and still prior to surgery, the systemic arterial pressure suddenly decreased from 100/50 mmHg to 40/10 mmHg. The heart rate and central venous pressures remained unchanged. Peak inspiratory airway pressure increased transiently from 22 cmH_2O to 30 cmH_2O but there was no obvious bronchospasm.

The patient was placed in a head down tilt and his lungs were ventilated with 100% oxygen. Calcium gluconate 2 g, and adrenaline 40 μg were given intravenously with no

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effect on arterial pressure but his heart rate increased to 75 beat.min⁻¹. A diagnosis of anaphylaxis was made, the Gelofusine discontinued and replaced with a 5% albumin infusion. In view of the increase in heart rate, methoxamine and noradrenaline were used to treat the hypotension. Chlorpheniramine 20 mg and hydrocortisone 200 mg were also given.

In the 30 min prior to cardiopulmonary bypass, a noradrenaline infusion at 0.08 µg.kg⁻¹.min⁻¹ (0.4 mg.h⁻¹) and methoxamine 40 mg were required to maintain systemic arterial pressure at 80/45. Central venous pressure and heart rate remained constant at 7 mmHg and 80 beat.min⁻¹ respectively. On visual inspection the heart was contracting vigorously, which supported our view that the cardiovascular depression was not due to primary pump failure. There was no evidence of myocardial ischaemia.

On institution of cardiopulmonary bypass, mean arterial pressure decreased to 30 mmHg despite a pump flow of 5 l.min⁻¹ and an additional 20 mg of methoxamine. An infusion of angiotensinamide, (Hypertensin CIBA, Ciba-Geigy Pharmaceuticals) was started in addition to the noradrenaline. An infusion rate of 0.09 µg.kg⁻¹.min⁻¹ (0.5 mg.h⁻¹) restored mean arterial pressure to 60 mmHg.

The patient was weaned from bypass whilst receiving infusions of noradrenaline 0.04 µg.kg⁻¹.min⁻¹ and angiotensinamide 0.045 µg.kg⁻¹.min⁻¹, with a systemic arterial pressure of 130/70 mmHg, heart rate 65 beat.min⁻¹ and central venous pressure of 9 mmHg. Total bypass time was 75 min. Vasoconstrictor therapy was reduced and discontinued in the intensive care unit 4 h following cardiopulmonary bypass. The tracheal tube was removed 10 h postbypass.

Postoperatively, the patient was noted to have a petechial rash over his upper trunk and haematuria which lasted for 24 h. Nevertheless, he made an uneventful recovery and was discharged from hospital 7 days following surgery. Venous blood sampling was performed immediately and at 2 h and 4 h postreaction for haematology, serum proteins, complement and total IgE.

Results

Total IgE was elevated in all specimens at 411–531 KU.l⁻¹ (normal range less than 144 KU.l⁻¹). In all samples CH₅₀ and C4 assays were within normal limits; however C3 concentrations fell in the immediate and 2 h sample, 0.67 g.l⁻¹ and 0.61 g.l⁻¹ respectively (normal range 0.73–1.4 g.l⁻¹) but not in the 4 h sample. There were small decreases in the serum protein and other immunoglobulin concentrations in the 2 h and 4 h samples.

Discussion

The predominant feature of this reaction was cardiovascular collapse, which is consistent with published reactions to modified fluid gelatin [1,2]. Unusually in this case the central venous pressure did not fall, but this is consistent with anaphylaxis in patients with previous heart disease [3]. In addition, there was a transient increase in airway pressure, although there was no obvious bronchospasm. This increase in airway pressure may be a manifestation of the transient form of bronchospasm described by Fisher [4].

Bleeding disorders are rare in anaphylaxis but are not uncommon following cardiopulmonary bypass.

Haematuria may be due to lysis of red blood cells during the period on bypass or secondary to urethral trauma during catheterisation in the presence of systemic anticoagulation. However, a petechial rash is uncommon following cardiopulmonary bypass but may be associated with an anaphylactic reaction.

The cardiovascular changes that accompany anaphylactic reactions to intravenous drugs usually occur within 3 min of administration and since the features of this reaction did not occur until 20 min after induction it is unlikely that the drugs given at induction were responsible. In addition, reactions are virtually unknown to either midazolam or alfentanil. Cefuroxime was excluded because it was given following the reaction without adverse effect. The temporal relationship of the reaction to the Gelofusine infusion led us to conclude that this was most probably implicated. Skin testing was not performed because it is thought to be of little value in the investigation of reactions to colloids.

Reactions to Gelofusine are rare (0.066%) [5]. The mechanism of reaction with gelatin solutions is uncertain, although direct release of histamine has been reported with urea-linked gelatin. IgE antibodies to gelatin have been discovered in patients with a gelatin food allergy [6]. However, no such antibodies have yet been detected in patients who react to intravenous gelatin solutions. Previous exposure to modified fluid gelatin had not occurred in this patient although sensitisation may have resulted through oral ingestion of a gelatin food product. However, this patient reported no food intolerances.

The concentration of the C3 component of complement fell in the immediate and 2 h sample which, in association with unchanged CH₅₀ and C4 assays, is consistent with alternative complement activation. Alternative complement activation occurs with cardiopulmonary bypass [7] but in this case the activation occurred before the start of bypass. Complement activation occurring before bypass would be consistent with an anaphylactoid reaction. From published case reports, alternative complement activation does not appear to be an important mechanism of adverse reactions to modified fluid gelatin. The neutral protease tryptase, released from the mast cell during degranulation, activates the C3 component of complement [8]. In this case it is possible that mast cell degranulation occurred by either antibody, or by a direct mechanism, and the released tryptase activated the C3. However, it is unclear whether the decrease in C3 concentration, as occurred in this case, was due to alternative pathway activation or was a consequence of the released tryptase.

Adrenaline was discontinued because the increased heart rate without an increase in arterial pressure was felt to be detrimental to myocardial oxygen balance in this patient. Vasoconstrictor therapy was started with a noradrenaline infusion and intermittent methoxamine but this again failed to increase arterial blood pressure and only with the institution of angiotensinamide did mean arterial pressure increase to an acceptable level.

Angiotensinamide is indicated when hypotension is secondary to a decrease in systemic vascular resistance and if traditional pressor drugs have been ineffective. In therapeutic doses tachyphylaxis does not occur and there is no arrhythmogenic potential.

Angiotensin is a powerful vasoconstrictor that is some eight to ten times more potent than noradrenaline [9]; the

skin, splanchnic and renal vasculature are predominantly affected. These vasoconstrictor effects are mediated through the sympathetic nervous system by several mechanisms. First of all, angiotensin increases the biosynthesis and the output, and decreases the re-uptake, of noradrenaline at sympathetic nerve terminals [10]. Secondly, transmission in sympathetic nerves is facilitated and vagal activity is inhibited [11]. Thirdly, central sympathetic outflow is increased [12]. In addition, angiotensin increases cardiac output through the release of myocardial catecholamines, an increase in calcium influx and by direct myocardial stimulation, independent of the β receptor [13].

In the presence of a sympathetic block, anaphylactic reactions are usually severe and refractory to treatment [14]. In patients receiving β_2 selective antagonists such as metoprolol or atenolol, unopposed vasodilation may occur with adrenaline, and this may explain why the reactions are difficult to treat in these patients. The fact that the patient was receiving atenolol, pre-operatively may explain why adrenaline, albeit in a small dose, did not have the desired effect.

Although intravenous administration of adrenaline is recognised as the drug of first choice in anaphylaxis, concern has been expressed about its use in the presence of halogenated hydrocarbons, hypoxia or hypercarbia, due to the cumulative arrhythmogenic effects. Fisher, in his review of 205 patients, found ventricular fibrillation in four, all of whom had been treated with intravenous adrenaline in the presence of halothane [15]. Jacobs found that ventricular fibrillation occurred in those patients previously treated with β receptor antagonists [14]. In such cases, if the reaction is primarily one of cardiovascular collapse then angiotensinamide may be the agent of choice because of its low arrhythmogenic potential.

Angiotensinamide has no effect on bronchospasm or angioedema, therefore if these are significant features then adrenaline must remain the drug of first choice. In addition, angiotensinamide, unlike adrenaline, does not inhibit mast cell mediator release.

In summary, angiotensinamide is a useful drug in the

treatment of anaphylactic reactions during anaesthesia, particularly when cardiovascular depression is the principal feature.

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