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# Unstable angina following anaphylaxis

R Ameratunga,[1] M Webster,[2] H Patel[3]

[1] Department of Clinical Immunology, Auckland City Hospital, Grafton, Auckland, New Zealand; [2] Department of Cardiology, Auckland City Hospital, Grafton, Auckland, New Zealand; [3] Department of Cardiology, North Shore Hospital, Takapuna, North Shore City, New Zealand

Correspondence to: Associate Professor R Ameratunga, Department of Clinical Immunology, Auckland City Hospital, Park Road, Grafton, Auckland 1001, New Zealand; rohana@adhb.govt.nz

All authors have contributed to this manuscript.

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## ABSTRACT

A 55-year-old woman developed unstable angina following an episode of severe anaphylaxis which was treated with 0.5 mg intramuscular epinephrine (adrenaline). The exact cause of her ongoing unstable angina was uncertain but may have reflected either vasospasm superimposed upon an area of atherosclerotic coronary disease, or vasospasm induced plaque rupture. Four weeks later, she had a second episode of anaphylaxis, and suffered a cardiac arrest after receiving a bolus of intravenous epinephrine. This case illustrates the importance of careful assessment of patients after anaphylaxis, both to prevent recurrence and to treat complications from the episode. It highlights the dangers of intravenous epinephrine in treating anaphylaxis outside anaesthetic and intensively monitored settings.

Anaphylaxis is a life threatening disorder with many possible triggers, carrying significant mortality.[1] In almost all situations the appropriate treatment is the prompt use of epinephrine (adrenaline) and other resuscitation measures, depending upon the clinical situation. The appropriate use of epinephrine reverses the pathophysiology of anaphylaxis and may be lifesaving. Published guidelines emphasise the intramuscular route for epinephrine at a dose of 0.01 mg/kg up to 0.5 mg, because anecdotally this appears to be effective and can be administered without delay and because it avoids the potentially lethal effects of a large intravenous (iv) bolus of epinephrine.[2]

We describe a patient suffering from sulfite induced anaphylaxis who developed a syndrome consistent with unstable angina after an appropriately administered intramuscular injection of epinephrine. She was subsequently given a bolus dose of intravenous epinephrine during a second episode of anaphylaxis, with consequent cardiac arrest. This case illustrates the importance of early referral to an allergy specialist for identification of trigger factors and any complications arising from the anaphylaxis.

## CASE HISTORY

A previously well 55-year-old woman suffered an anaphylactic reaction after eating a meal of lasagne with a heavy tomato sauce and a glass of white wine. Over 45 min she developed angioedema of the eyelids, urticaria and throat tightness associated with a sensation of dyspnoea. Her initial heart rate was 112/min and blood pressure 142/90 mm Hg. Her oxygen saturation was 98% breathing room air, she did not have stridor or wheeze, and her tongue and throat were normal at examination. She was treated with 0.5 mg of intramuscular epinephrine, 25 mg of intravenous promethazine hydrochloride, and 200 mg of intravenous hydrocortisone at a local emergency clinic. The urticarial rash and eyelid swelling resolved almost completely after 15 min.

She was referred to a metropolitan hospital, where the history was confirmed. In addition she also described tightness in the chest that had resolved. The resting electrocardiogram (ECG) showed a sinus tachycardia of 120/min, but was otherwise normal. Cardiac troponin values were not measured. After discharge, she had further bouts of a central chest tightness with radiation to the throat and arms. The bouts were of 20–30 min duration, occurred with mild exertion and at rest, were associated with dyspnoea and dizziness, and were unresponsive to a trial of omeprazole.

One month later she suffered a second anaphylactic reaction with urticaria, shortness of breath and throat tightness after consuming a meal of brown rice and broccoli with cheese sauce, in addition to a glass of white wine, containing sulfites.[3] At the hospital emergency department the initial heart rate was 129 beats/min, blood pressure 142/80 mm Hg, and oxygen saturation of 100% (on 6 litres/min of oxygen via a Hudson mask). She was given 100 μg of epinephrine as an intravenous bolus. Fifteen minutes later she developed ventricular fibrillation after a "R on T" phenomenon (ventricular ectopic occurring on the T wave of the preceding sinus beat).

She was successfully resuscitated with a single 200 J DC shock. An ECG revealed sinus tachycardia, 2 mm horizontal ST depression in the lateral leads, and a normal corrected QT interval. The cardiac troponin I value immediately post-cardiac arrest was normal (<0.04 μg/l, Centaur assay) rising to a peak of 0.91 μg/l 13 h later. Subsequent ECGs revealed resolution of the ST depression but evolution of biphasic anterior T inversion. A transthoracic echocardiogram on the second day did not find any structural abnormality; the left ventricle was of normal size with good systolic function of all segments. Her serum tryptase, a specific marker for mast cell degranulation, was notably raised at 46.4 μg/l (normal <10 μg/l), compared with a subsequent baseline serum mast cell tryptase of 9.5 μg/l.

She had no obvious risk factors for coronary artery disease. She was normotensive, had normal lipids and was a lifelong non-smoker. Coronary angiography revealed a 65% stenosis in the proximal left anterior descending coronary artery, thought likely to be the culprit for her angina (fig 1). The lesion was eccentric but had no other features (such as ulceration, overhanging edges, angiographic thrombus) to suggest plaque rupture, and she had no other significant coronary disease. The angiographic appearances did not change with 200 μg intracoronary glyceryl trinitrate.

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**Figure 1** Coronary angiography before percutaneous coronary intervention, showing a 65% stenosis in the proximal left anterior descending coronary artery (arrow).

Intravascular ultrasound examination was not undertaken. She had successful percutaneous coronary intervention with deployment of a paclitaxel eluting stent (fig 2). There was no inducible ventricular tachycardia on ventricular stimulation at subsequent electrophysiological studies, and biplane right ventriculography showed no evidence of dysplasia.

The patient was referred for allergy evaluation after the second episode of anaphylaxis. Her history was remarkable for late onset asthma. This was well controlled with fluticasone and salbutamol inhalers. Tests for common food and inhalant allergens were negative. Low dose aspirin and clopidogrel were prescribed following insertion of the drug eluting stent. Aspirin provoked facial angioedema. She was desensitised and has subsequently been able to tolerate regular low dose (100 mg) aspirin. Skin testing for sulfite sensitivity was not undertaken, as this was considered an unnecessary risk. She has been placed on a low sulfite and salicylate diet by a dietician familiar with food chemical hypersensitivity, and remains well 3 years later with no further episodes of anaphylaxis. She has had occasional episodes of minor facial angioedema, which have been triggered by inadvertent sulfite exposure.

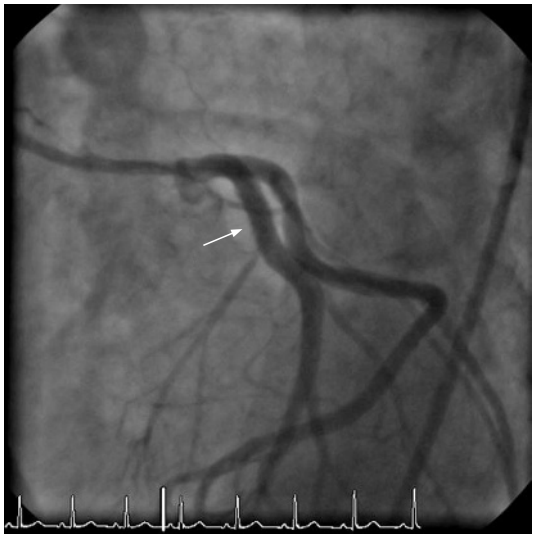


**Figure 2** Coronary angiography following percutaneous coronary intervention, showing deployment of a paclitaxel eluting stent (arrow).

## DISCUSSION

Anaphylaxis is a life threatening medical emergency, and is seen in general practice as well as in hospital based specialties. Controversy about its exact definition[2] may in part be due to varying manifestations in different clinical settings triggered by different allergens and routes of exposure. In community based anaphylaxis, most allergy and immunology physicians would accept the diagnosis if a patient suffered a systemic allergic disorder involving the respiratory tract and/or cardiovascular system, in addition to the skin.

Severe anaphylaxis carries a significant mortality.[1] To a large extent the route of exposure to the allergen determines the time course of anaphylaxis and its appropriate treatment. Recent data from Pumphrey[4] indicates that insect stings and intravenous drugs—for example, anaesthetic agents and antibiotics—are most likely to cause rapid, severe anaphylaxis with profound hypotension and death; in this situation, an intravenous epinephrine infusion may be lifesaving.[5]

Anaphylaxis caused by insect stings, drugs and foods is more likely to be seen in the community. In this situation the best treatment is intramuscular epinephrine, which has been shown to produce reliable blood concentrations in volunteers.[6] Subcutaneous epinephrine should not be used because of unreliable absorption compared with intramuscular administration,[6 7] particularly as shock redistributes blood flow away from the skin.

Our patient appropriately received 0.5 mg intramuscular epinephrine for her first episode of anaphylaxis, and then developed symptoms of unstable angina. Acute myocardial infarction caused by anaphylaxis and its treatment in patients with normal coronary arteries is well recognised, and thought to be secondary to coronary artery spasm.[8–10] In patients with pre-existing coronary artery disease, anaphylaxis and/or administered epinephrine can lead to increased demand, resulting in tissue ischaemia with arrhythmias. Coronary arteries have an increased density of mast cells, which might predispose to hypoxaemia after mediator release.[11] Patients with mastocytosis appear to be at high risk of adverse cardiac events following anaphylaxis and treatment.[12]

Review of the literature has not revealed similar cases of ongoing unstable angina precipitated by anaphylaxis and/or epinephrine. Our patient's left anterior descending lesion was not critically narrowed, but perhaps was unmasked by superimposed coronary artery spasm. The other possibility is that vasospasm induced by anaphylaxis or epinephrine triggered plaque rupture, leading to a significant lesion and an acute coronary syndrome.

The intravenous bolus of epinephrine on the second occasion induced life threatening complications[10] due to R on T phenomenon. There was no inducible ventricular tachycardia on ventricular stimulation. Outside the anaesthetic or intensively monitored settings intravenous epinephrine should only be used during a cardiac arrest. An intramuscular dose of epinephrine on the second occasion would less likely have caused ventricular fibrillation.

Epinephrine contains metabisulfite and some sulfite sensitive patients may deteriorate after being given epinephrine.[13] Although it was more likely that the intravenous epinephrine rather than the metabisulfite triggered the life threatening cardiac events in this patient, an adverse reaction to sulfite is

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## Key learning points

- Ischaemic coronary syndromes have been linked to anaphylaxis. These may be coincidental, secondary to the pathophysiological impact of anaphylaxis and its treatment or due to plaque rupture at the time of the first episode of anaphylaxis and/or ongoing inflammatory process within the coronary arteries. In many cases the precise pathophysiological mechanisms are unclear.
- Intramuscular epinephrine (adrenaline) is the treatment of choice in most cases of anaphylaxis. An intravenous bolus of epinephrine can trigger serious cardiovascular adverse events including severe hypertension, intracerebral haemorrhage, myocardial ischaemia, acute pulmonary oedema, cardiac arrhythmias and cardiac arrest.
- Patients suffering anaphylaxis should be referred to an allergy specialist to identify triggers. This may reduce the risk of recurrence.
- In complex situations such as the patient described here, a multidisciplinary approach with input from cardiology, allergy and nutrition specialists may be needed.

also a possible contributor. Preservative-free epinephrine (American Regent Inc, New York, USA) is available for sulfite sensitive individuals. A possible adjunct is the use of glucagon, which has been advocated in the treatment of anaphylaxis in patients taking β-blockers.[14]

Once anaphylaxis has been appropriately treated, early referral to an allergy specialist is indicated.[15] It is now 3 years since the patient suffered her two episodes of anaphylaxis. With careful attention to her diet and aspirin desensitisation, she has had only minor episodes of facial angioedema. It is likely that this patient would have been at risk for further episodes of anaphylaxis if the triggers had not been identified and addressed.

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**Patient consent:** Obtained

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