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ORIGINAL ARTICLE

Clinical Allergy

Anaphylaxis Refractory to intramuscular adrenaline during in-hospital food challenges: A case series and proposed management

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Abstract

Background: Anaphylaxis is a severe, systemic hypersensitivity reaction that can be potentially life-threatening. Anaphylaxis during oral food challenge is not uncommon and can usually be effectively managed with intramuscular adrenaline as first line treatment. Although very rare, fatal anaphylaxis during in-hospital food challenge has been reported.

Objective: We describe our experience of cases of refractory anaphylaxis at in-hospital challenge and propose a framework for escalation of treatment in such cases using intravenous infusion of adrenaline which has been adopted for widespread use elsewhere.

Methods: We present four patients who all experienced severe life-threatening anaphylaxis, refractory to intramuscular adrenaline treatment, during supervised oral food challenges. Patient data were collected from contemporaneous notes, and patient consent was obtained.

Results: In all four cases, the anaphylaxis reactions were amenable to treatment with low-dose intravenous adrenaline, with no reported adverse effects.

Conclusion and clinical relevance: These cases demonstrate the need for clinicians undertaking higher risk allergen challenges to be able to manage cases of severe anaphylaxis refractory to intramuscular adrenaline, and to consider a framework for managing these reactions. While peripheral intravenous adrenaline infusions should always be initiated only in conjunction with expert input, the protocol suggested is simple enough to be undertaken within the hospital environment while more experienced support is obtained.

KEYWORDS

adrenaline, allergy, anaphylaxis, food allergy, oral food challenge

1 | INTRODUCTION

Anaphylaxis is a "serious systemic hypersensitivity reaction that is usually rapid in onset and may cause death. Severe anaphylaxis is characterized by potentially life-threatening compromise in breathing and/or the circulation and may occur without typical skin features or circulatory shock being present".[1] Based on 10 European studies, the incidence of anaphylaxis is around 1.5-7.9 per 10 000 person years, with a prevalence of 0.3%.[2] Hospitalizations due to anaphylaxis have increased over the past two decades, but fatal anaphylaxis is very uncommon and the rate of fatal food anaphylaxis has not increased over the same time period.[3]

Oral food challenges (OFC) are a key tool to confirm the diagnosis or resolution of food allergy.[4] Anaphylaxis during OFC is not uncommon, and rates vary by patient age, food tested and geographical region. Anaphylaxis is not predictable.[5] A retrospective, multicentre survey of 1635 children and adolescents undergoing a hospital-based peanut food OFC demonstrated an 11% anaphylaxis rate in this group,[6] which is in line with previously reported rates of adrenaline use in 9%-11% of OFC.[7,8] Fatal anaphylaxis due to food is rare,[9] and until recently, no cases of fatal anaphylaxis had been reported during hospital-based OFC. However, two recent deaths have been reported in the context of OFC conducted in specialist centres: a 3-year-old boy following a baked milk OFC in the USA,[10] and an 11-year-old boy who died after a peanut OFC.[11] The risk of severe anaphylaxis during OFC conducted under medical supervision must therefore be recognized. In this paper, we present four cases of severe anaphylaxis during hospital-based OFC that were refractory to initial treatment and discuss the management approach to these cases.

2 | METHODS

This paper is based on four paediatric cases of severe anaphylaxis during hospital-based food challenge that were refractory to initial treatment, between 2018 and 2019 in the South-East of England. Informed consent was obtained from the families for this report. Data on the indications for challenge, challenge procedure, nature of the reaction, treatment given and response to therapy were collected from the chart of each patient.

3 | RESULTS

3.1 | Case 1

A 17-year-old Caucasian male with isolated peanut allergy and index reaction at age 1 year (hives and facial angioedema after eating peanut butter). He had since avoided peanut, with no further reactions. He had been prescribed fluticasone/salmeterol inhaler for asthma but was non-compliant although this did not cause him significant symptoms and baseline spirometry was within normal range. Allergy testing at most recent follow-up was consistent with PR10 sensitization and declining levels of IgE against seed storage proteins, suggesting that true peanut allergy may have resolved and been replaced by pollen food allergy syndrome (see Table 1). An OFC was therefore undertaken to clarify his diagnosis prior to transitioning to adult services, given his decision not to carry adrenaline auto-injector on the basis that he could not remember experiencing a reaction.

Five minutes after the second dose (0.16 g peanut protein), he developed urticaria and rhinitis, followed by wheezing and chest tightness. Despite prompt treatment with a 500 mcg IM adrenaline auto-injector (Emerade, Bausch and Lomb) administered by a specialist nurse, his symptoms progressed with worsening bronchoconstriction, hypoxia (oxygen saturations 91% in room air), tachycardia and a widened pulse pressure. He was kept in a semi-recumbent position and received a further three doses of 500 mcg IM adrenaline by auto-injector over the following 20 minutes (alternating limbs for administration), IV hydrocortisone and chlorphenamine, 500 mL of intravenous saline and nebulized salbutamol. Despite this, the bronchospasm persisted with ongoing tachycardia. At 40 minutes after onset, a peripheral adrenaline infusion of 0.1 mcg/kg/min was commenced via a large-bore peripheral cannula. He responded rapidly and was then transferred to the paediatric intensive care unit (PICU) where he was weaned off the infusion over the following 6 hours. He was discharged the following day.

3.2 | Case 2

A 15-year-old teenage male of Afro Caribbean origin, with multiple allergies to cow's milk, egg, peanut, cashew, pistachio and shrimp. He was prescribed a regular budesonide/formoterol inhaler, and his asthma was well-controlled with minimal breakthrough symptoms. He had experienced previous anaphylaxis at age 10 years to an unknown trigger (possibly nut/egg contamination) which was treated with IM adrenaline. During his most recent clinic review, he reported he was eating significant quantities of rice cakes containing milk. Based on this history and clinical testing (Table 1), was booked to undergo a baked milk OFC to assess tolerance to baked milk.

He completed the full challenge protocol (1.37 g milk protein baked into a muffin). Thirty minutes later, he experienced chest tightness and self-administered his salbutamol inhaler prior to informing the supervising nurse. He immediately received 500 mcg IM adrenaline via needle and syringe, oral cetirizine and prednisolone, nebulized salbutamol and high flow oxygen. Despite this, he continued to experience significant dyspnoea and was treated with a further two 500 mcg doses of IM adrenaline (also via needle and syringe) with no improvement. He was given an intravenous adrenaline bolus of 10 micrograms of adrenaline (equivalent to 0.17 mcg/kg) over five minutes with immediate benefit. No further adrenaline was required, and he was discharged the following day.

TABLE 1 Patient characteristics

Case	Age (years)	Food allergies	Co-morbidities	Food challenged, eliciting and cumulative allergen dose	SPT	sIgE (kUA/L)	Key events post-triggering dose (minutes)	Initial treatment	Final treatment
1	17	Peanut	Asthma (ICS + LABA)	Peanut Eliciting: 0.16 g Cumulative: 0.32 g	Peanut 7 mm Birch pollen 6 mm	Peanut 2.33 Ara h 2 0.47 Ara h 8 6.7	Any symptoms: 5 Anaphylaxis: 8 IM adrenaline: 10 IV adrenaline: 40 Improving: 50	IM adrenaline 0.5 mg x4, hydrocortisone, chlorphenamine, nebulized salbutamol, fluid bolus, oxygen	0.1 mcg/kg/min peripheral adrenaline infusion
2	15	Cow's milk, egg, peanut, cashew, pistachio, shrimp	Asthma (ICS + LSBA), eczema	Baked milk Eliciting: 0.68 g Cumulative: 1.37 g	Milk 18 mm Boiled milk 7 mm	Cow's milk > 100	Any symptoms: 30 Anaphylaxis: 30 IM adrenaline: 35 IV adrenaline: 60 Improving: 65	IM adrenaline 0.5 mg x3, cetirizine, prednisolone, nebulized salbutamol, oxygen	10 mcg adrenaline as an IV bolus (equivalent to 0.17 mcg/kg)
3	11	Peanut	Asthma (ICS + LABA)	Peanut Eliciting: 0.10 g Cumulative: 0.14 g	Peanut 5 mm	Peanut> 100 Ara h 1 41.5 Ara h 2> 100 Ara h 3 6.78	Any symptoms: 10 Anaphylaxis: 160 IM adrenaline: 162 IV adrenaline: 220 Improving: 235	IM adrenaline (0.3 mg x 3), chlorphenamine, nebulized adrenaline and salbutamol, iv fluids, hydrocortisone	0.17 mcg/kg/min peripheral adrenaline infusion
4	15	Peanut, tree nuts	Asthma (ICS)	Peanut Eliciting: 0.10 g Cumulative: 0.14 g	Peanut 15 mm	Peanut> 100 Ara h 1 86.5 Ara h 2 > 100 Ara h 3 > 100	Any symptoms: 2 Anaphylaxis: 19 IM adrenaline: 20 IV adrenaline: 40 Improving: 43	IM adrenaline (0.5 mg x 3), nebulized salbutamol, iv fluid bolus	0.17 mcg/kg/min peripheral adrenaline infusion

Abbreviations: ICS, inhaled corticosteroids; LABA, long acting beta-agonist.

3.3 | Case 3

An 11-year-old Caucasian female underwent double-blind, placebo-controlled, food challenge (DBPCFC) to peanut, as part of a research study. She had a history of prior anaphylaxis at age 3 years (generalized urticaria and wheeze, approximately 15 minutes after ingestion of breakfast cereal containing peanut), which responded to IM adrenaline and salbutamol nebulizer. Her asthma was well-controlled on a daily fluticasone/salmeterol inhaler.

During OFC, she developed mild lip oedema, odynophagia and abdominal pain to cumulative 143 mg peanut protein. The challenge was stopped, and she was treated with cetirizine, 500 mL intravenous saline and buscopan. She vomited 60 minutes later, which caused throat tightness and was associated with generalized urticaria. She was given 5 mg iv chlorphenamine. Her symptoms settled, and she fell asleep for 40 minutes. When she awoke, she went to the bathroom and was noted to develop facial flushing. She became sleepy again and was noted to have a soft inspiratory stridor. On auscultation, she has markedly reduced air entry, bilateral biphasic wheeze which worsened despite IM adrenaline administered using an auto-injector 300 mcg (Epipen, Meda Pharmeceuticals), nebulized adrenaline (4ml of 1:1000) and high flow oxygen. Over the next 50 minutes, she was given 2 further doses of IM adrenaline (10mcg/kg by needle/syringe), iv hydrocortisone, back-to-back nebulized salbutamol while senior PICU input was awaited. She had ongoing severe dyspnoea, with use of accessory muscles but maintained her saturations in high flow oxygen. Given her ongoing respiratory distress, a decision was made by the team to commence a peripheral adrenaline infusion (0.17 mcg/kg/min). Her blood pressure remained normal throughout. Within 30 minutes, her respiratory distress had resolved, and she was able to talk in complete sentences. The infusion was weaned over the following 6 hours, and she was discharged from PICU the next day.

3.4 | Case 4

A 15-year-old white Caucasian female with multiple nut allergies (peanut, hazelnut, macadamia) and prior anaphylaxis to peanut requiring 2 doses of IM adrenaline at age 13 years. She had well-controlled asthma (beclomethasone twice daily). She attended hospital for a DBPCFC to peanut, as part of a research study.

Two minutes after her fifth dose (100 mg peanut protein, cumulative dose 144 mg), she developed abdominal pain and throat tightness. She was noted to have some throat clearing, but her peak flow remained normal and she had no wheeze. Twenty minutes later, she developed bilateral, biphasic wheezing and was given 500 mcg IM adrenaline (Emerade, Bausch and Lomb) and salbutamol (10 puffs via spacer). 500 ml of normal saline was commenced over 30 minutes. However, she had minimal response to treatment, with worsening dyspnoea and progressive truncal urticaria. A further 2 doses of IM adrenaline (500 mcg) were given, while an intravenous adrenaline infusion was set-up. This was commenced 20 minutes following the initial IM adrenaline dose, at (0.17 mcg/kg/min). Within 2 minutes, her inspiratory effort had normalized although she still had some expiratory wheeze which settled within 10 minutes. Blood pressure was normal throughout. The infusion was weaned over the following 3 hours, and she was transferred to the ward for overnight observation.

4 | DISCUSSION

National and international guidelines recommend the administration of intramuscular adrenaline for initial management of anaphylaxis.[12-14] Despite this, adrenaline remains significantly underused, both in the community,[15] but also in hospital[16] and even in simulated scenarios errors frequently occur.[17] There are, unsurprisingly,

ADRENALINE INFUSION GUIDELINE FOR ANAPHYLAXIS

1 PREPARATION

- Requires continuous physiological monitoring **(ECG, SpO2, BP 3-5 minutely)**
- Give via an **infusion pump** through a **dedicated line**, or piggybacked with **anti-reflux valves on all other lines** to prevent the adrenaline going back up into another fluid bag instead of into the patient
- BEWARE infusions on the same side as a BP cuff; frequent BP measurements may interfere with the infusion
- FIRST BAG: **1mg adrenaline in 100 mL saline = 0.01mg/mL (1:100,000)**
  i.e. 1 ml/kg/Hr gives the equivalent of a 0.01 mg/kg dose over 1 hour (0.17 ug/kg/min)

2 INITIATION & ADJUSTMENT

- **Start at 0.5-1 mL/kg/Hr** (30-100 mL/Hr in adults) depending on reaction severity:
  Moderate severity: 0.5 mL/kg/Hr Severe (hypotensive or hypoxic): 1 mL/kg/Hr
- **Titrate** up or down according to response, aiming for the lowest effective infusion rate
  Allow for a short elimination half-life; steady state is reached 5-10 minutes after a change in the infusion rate
- **Tachycardia, tremor, and pallor with a normal or raised blood pressure are signs of adrenaline toxicity:**
  Reduce the infusion rate (if toxicity is severe, stop the infusion briefly before recommencing at a lower rate)
- **The safe maximum rate of adrenaline infusion** is unknown, but is probably <1 ug/kg/min (6mL/kg/Hr of the above solution of 1mg in 100 mL).

3 DE-ESCALATION AND CESSATION

- **As the reaction resolves, an infusion that was previously therapeutic can start to have toxic effects:** Therefore, when features resolve begin reducing the infusion, aiming for around half the starting rate if possible
- 60 minutes after the resolution of all symptoms and signs, wean the infusion over another 30 minutes and stop; watch closely for reaction recurrence

FIGURE 1 Proposed adrenaline infusion guideline[29]

no randomized controlled on the use of adrenaline for anaphylaxis, and recommendations are based on observational data, consensus opinion and pharmacological effect.[14,18,19] Adrenaline should be administered intramuscularly to the anterolateral thigh, using 1:1000 adrenaline at a dose of 0.01 mL/kg (maximum dose 500 mcg or 0.5 mL of 1:1000). Alternatively, fixed doses based on age and weight can be used for greater ease.[12,13]. Intramuscular adrenaline works best if used promptly, before anaphylaxis has had time to progress[20] and it has an excellent safety profile.[12,13,21] Transient effects after IM adrenaline administration include pallor, tremor, dizziness, palpitations and headache; these indicate that a therapeutic dose has been given.[14]

Around 10% of patients who use IM adrenaline for food-induced anaphylaxis continue to experience anaphylaxis requiring at least one further dose to alleviate symptoms.[15,22] All of our patients experienced life-threatening anaphylaxis, with prominent lower respiratory tract involvement (bronchoconstriction). All four were teenagers, an age group known to be at higher risk of fatal reactions.[23,24] They also had asthma, a common feature in fatal food-induced anaphylaxis, affecting up to 75% of cases.[23,24] Of note, they demonstrated worsening of symptoms despite multiple doses of IM adrenaline, thus it is possible that these patients might have suffered a fatal outcome had their reactions occurred out of hospital.[25]

Intramuscular adrenaline administration alone is not a guarantee of anaphylaxis reversal: in fact, one third of fatalities due to food-anaphylaxis in the UK receive timely adrenaline and yet still die.[26-28] Given the available data from venom-induced anaphylaxis,[29] it is likely that this reflects a need for more intensive adrenaline administration—beyond that achievable with adrenaline auto-injectors—together with intravenous fluids. A further concern is the limited impact of intramuscular adrenaline on cardiovascular function during anaphylaxis, in contrast to the significant beneficial effects on respiratory symptoms.[30] Therefore, patients requiring more than two doses of IM adrenaline are likely to require an adrenaline infusion.[12,13]

TABLE 2 Recommendations for management of anaphylaxis refractory to initial IM adrenaline

Table 2: Author's recommendations where anaphylaxis occurs refractory to initial dose of IM adrenaline
1. Call for help 2. Apply high flow oxygen. Do not move the patient but leave in semi-recumbent position. 3. Administer 2nd dose of IM adrenaline at 10 mcg/kg maximum 500 mcg using needle and syringe, into anterolateral thigh (use opposite side to initial IM adrenaline) 4. Apply ECG/HR/BP monitoring
IV adrenaline infusion (see Figure 1): • Secure 2 x wide-bore intravenous cannula, for example antecubital fossa. • Prepare IV adrenaline infusion and initiate as per Figure 1 • Give IV fluids vis second cannula (adrenaline may be ineffective in the absence of adequate fluid resuscitation) • Seek urgent intensive care or anaesthetic support

Intravenous adrenaline is not without risks, and guidelines suggest its use be limited to "those experienced in the use and titration of vasopressors in their normal clinical practice (e.g. anaesthetists, emergency physicians, intensive care doctors)."[12] However, the protocol suggested by Brown et al[29] and reproduced in Figure 1 forms part of established anaphylaxis management in Australia and Spain and was used in Cases 3 and 4. In a series of 19 patients treated successfully with this protocol, no adverse reactions were noted related to the intervention.[29] The protocol suggested by Brown et al is simple enough to be undertaken within the hospital environment while more experienced support is obtained. After failure to respond to the second dose of adrenaline, an IV infusion should be prepared; in our experience, this can be achieved in under 5 minutes where an emergency box has been prepared in advance. At the same time, large-bore peripheral IV access should be obtained, continuous ECG monitoring established and support from the local anaesthetic or intensive care team sought. We consider an intravenous infusion to be the safest option, given that intravenous adrenaline boluses are associated with greater dosing errors and can contribute to adverse outcomes, including tachyarrhythmias, pulmonary oedema and hypertensive crisis.[14,21,25,31]

An additional key element in the management of severe anaphylaxis is avoiding an upright posture, which has been associated with fatal events (thought to be due to postural hypotension in the context of an anaphylaxis-induced decrease in venous return, causing sudden circulatory collapse[14,32]). A recumbent or semi-recumbent posture with legs elevated is preferable.[14,26] It is crucial that in severe reactions, healthcare staff avoid the temptation to move patients to a stabilization/ high dependency area prior to stabilization. This may entail the setting up of an adrenaline infusion in a clinical area where staff are unfamiliar with its use: this must be addressed in any local protocol, and risk mitigated through staff training and support from critical care areas.

In summary, we report four cases of refractory anaphylaxis successfully treated with low-dose intravenous adrenaline through a peripheral canula. While IM adrenaline remains the mainstay of first aid management of anaphylaxis, we encourage physicians who routinely perform procedures such as OFC to consider a framework for managing refractory reactions; this should include consideration of a peripheral intravenous adrenaline infusion (according to Figure 1 & Table 2) as a rescue option while specialist critical care support is obtained.

CONFLICT OF INTEREST

PJT reports grants from UK Medical Research Council, NIHR/ Imperial BRC and JM Charitable Foundation during the conduct of the study; personal fees from UK Food Standards Agency, personal fees from DBV Technologies, personal fees and non-financial support from Aimmune Therapeutics, other support from Allergenis, personal fees from ILSI Europe, outside the submitted work. PJT is also the current chairperson of the World Allergy Organisation Anaphylaxis Committee, and co-chair of the Working Group for the Resuscitation Council UK Anaphylaxis Guideline. GR is current

chairperson of the EAACI Anaphylaxis Guideline Committee. The remaining authors have no COI to declare.

AUTHOR CONTRIBUTION

CA wrote the manuscript, with review and contributions from PT, GR and MEL. SB, AM and SE provided case information.

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