19 Colloids and infrequent trigger agents

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Key findings

- Three cases of perioperative anaphylaxis were caused by gelatin or gelatin-containing intravenous fluids, giving an estimated incidence of 6.2 per 100,000 administrations, a risk rate similar to that of rocuronium.
- Ondansetron was the trigger agent in two cases.
- There were single cases in which one of the following triggers were identified:
  - Propofol
  - Aprotinin
  - Protamine
  - Heparin.
- A single case of non-immunologically-mediated anaphylaxis to ibuprofen was reported.
- Two cases of anaphylaxis related to blood products (neither red cells) were reported.

Table 1. Trigger agents identified in NAP6 with low prevalence

	Definite	Probable	Total
Succinylated gelatin-containing IV fluids	3	-	3
Ondansetron	1	1	2
Propofol	1	-	1
Ibuprofen	1	-	1
Protamine	1	-	1
Aprotinin	-	1	1
Heparin	-	1	1
Blood product	2	-	2

What we already know

A number of drugs are rare causes of perioperative anaphylaxis either because they have a very low incidence of per-use anaphylaxis or because they are used only in a fraction of anaesthetics. These drugs are discussed individually in this chapter.

Methods of analysis are the same as in other sections of the report (Chapter 5, Methods).

Intravenous gelatin solutions

There were three cases of anaphylaxis caused by succinylated gelatin solutions – one each due to Gelofusine, Geloplasma and Isoplex. The patients were scheduled for general surgery or urological surgery, which was abandoned in one case after the surgical procedure had started. The first feature of anaphylaxis was hypotension in two patients and bronchospasm in the third. Onset occurred within five minutes in two patients, and between 5-10 minutes in the third. Two patients received general anaesthesia with propofol, fentanyl and rocuronium. One patient received epidural anaesthesia, and initial hypotension was treated with vasopressors and an intravenous (IV) gelatin infusion, following which the patient's condition rapidly deteriorated. Cardiac arrest (pulseless electrical activity – PEA) occurred in one patient.

All cases received IV adrenaline boluses and one required a continuous infusion. One patient received vasopressin. Two patients required continuing vasopressor therapy in the ICU. One patient died.

In each of the cases the anaesthetist correctly suspected that the IV gelatin solution was responsible for anaphylaxis, although recognition of anaphylaxis was not prompt in all the cases due to confounding differential diagnoses.

Comment

The Allergen Survey (Chapter 9) estimated that each year 48,203 UK patients are exposed to gelatin or gelatin-containing IV fluids during anaesthesia. The calculated incidence was 6.2 per 100,000 administrations, a rate similar to that of rocuronium (Chapter 16, NMBAs).

In a single specialist UK allergy clinic, Low *et al* described three cases (≈1.7% of all cases) over a seven-year period (Low 2016). In an eight-year multi-clinic report, Mertes *et al* recorded 56 cases of IgE-mediated anaphylaxis due to IV gelatin solutions, but Grade 1 and 2 reactions were included and the total number of patient exposures during that period was not stated (Mertes 2011).

Ondansetron

The review panel identified two cases of ondansetron-induced anaphylaxis. In the first case the patient developed cough and felt unwell and anxious after the administration of ondansetron prior to induction of anaesthesia. Following induction, there was rapid-onset urticaria and hypotension, progressing to PEA cardiac arrest. Adrenaline and noradrenaline were required during resuscitation. Skin prick and intradermal tests were positive to ondansetron. The second patient underwent spinal anaesthesia and became unwell, with respiratory distress, itching and flushing almost immediately

after receiving ondansetron. There was severe hypotension which was unresponsive to phenylephrine but resolved after administering intramuscular (IM) adrenaline. The review panel considered that ondansetron was the probable cause as skin testing was not conclusive.

Comment

Ondansetron is administered very commonly during anaesthesia as a prophylactic anti-emetic. The Allergen Survey estimated that this drug was administered in 78% of general anaesthetics and 66% of all cases (Chapter 9). The occurrence of only a single definite case of ondansetron-induced anaphylaxis during NAP6 indicates the extreme rarity of this reaction. However, these reactions may be severe: two fatal reactions and one case of PEA cardiac arrest attributed to ondansetron-anaphylaxis have been reported (Ouni 2017, Goyal 2016). In relation to drugs that are only rarely allergenic, there may be uncertainty about the optimum concentration to use for skin testing in order to avoid false positives due to non-specific irritation and false negatives due to over-dilution. It has been suggested that ondansetron 0.02 mg/ml is optimum for intradermal testing (Fernando 2009).

Propofol

A single case of propofol-induced anaphylaxis was confirmed by the review panel. The event occurred within five minutes of induction of anaesthesia with propofol, rocuronium and fentanyl, and the anaesthetist suspected that rocuronium was the culprit drug. The first clinical feature of anaphylaxis was flushing, which proceeded to hypotension, wheeze, and oxygen desaturation. This was a severe reaction and the patient required several doses of IV adrenaline. The mast cell tryptase measurements demonstrated a dynamic increase, and skin prick and intradermal tests were positive to propofol with other potential trigger agents excluded by negative testing.

Comment

Propofol is an extremely uncommon cause of anaphylaxis. The NAP6 Allergen Survey estimated that more than two million patients in the UK are exposed to this induction agent each year (Chapter 9). Twenty-four IgE-mediated cases were reported in an eight-year French study (Mertes 2011), and two cases were recorded in a seven-year single-clinic UK study (Low 2016). Asserhøj and colleagues in Denmark recently suggested that propofol-induced anaphylaxis may occur in some patients through a non-IgE-mediated mechanism (Asserhøj 2016). Skin testing would be negative in this situation, and controlled provocation testing with IV propofol is necessary to confirm the diagnosis. This procedure is probably restricted to the Danish clinic, although other clinics may offer this test in the future. In the same publication, the authors dispelled the notion that propofol is contraindicated in adults who are allergic to egg, soya or peanut, but some uncertainty still exists in the case of children who have experienced anaphylaxis to egg (Harper 2016). A diagnosis of hypersensitivity to propofol has serious implications for the patient, given the ubiquity of this induction agent and thelikelihood of re-exposure unless a hazard warning is carried at all times.

Protamine

The review panel attributed anaphylaxis to protamine in one case, with high probability. The patient received protamine after cardiac surgery, and immediately developed severe hypotension and bronchospasm necessitating cardiopulmonary bypass and IV adrenaline. Skin testing was positive and the mast cell tryptase level was greatly elevated.

Comment

Several case reports of anaphylaxis due to protamine have been published, mainly relating to cardiac interventions. Mertes reported four cases in an 8-year multicentre study in France, but the severity of the individual cases was not described (Mertes 2011). It has been suggested that patients who have been exposed to Neutral Protamine Hagedorn insulin, which contains protamine, are more likely to experience protamine-induced anaphylaxis (Stewart 1984). Fish allergy has been implicated as a risk factor for protamine-anaphylaxis, as protamine is traditionally extracted from the sperm of fish. It is possible that the drug will be increasingly synthesised by recombinant biotechnology, and sensitisation to the fish-derived product may be unlikely to result in anaphylaxis when a patient is exposed to the recombinant formulation.

Ibuprofen

A single case of anaphylaxis to ibuprofen was reported, in which the review panel considered that there was high diagnostic certainty. This was a delayed reaction to oral premedication in a child (further described in Chapter 21, Paediatric anaesthesia). An oral provocation test was positive, but skin testing was negative, indicating a non-IgE-mediated (non-allergic) mechanism.

Comment

Anaphylaxis due to non-steroidal anti-inflammatory drugs (NSAIDs) has been comprehensively reviewed by Kowalski and colleagues (Kowalski 2013). There is a wide spectrum of severity and pathogenesis. Reactions may be immunologically-mediated or, more commonly, non-immunologically-mediated. Many of the latter may be characterised by cross-reactivity to drugs sharing COX-1 enzyme inhibition. An eight-year national study in France identified only three immunologically-mediated perioperative hypersensitivity reactions to NSAIDs (Mertes 2011).

Aprotinin

A single case of aprotinin-induced anaphylaxis occurred within 5 minutes of administration. The clinical presentation was bronchospasm, followed by hypotension and cutaneous features. The review panel designated this case 'probable'.

Comment

Hypersensitivity to aprotinin is well-recognised. A series of over 12,000 exposures to aprotinin during cardiac surgery identified 23 cases of anaphylaxis, with a greater incidence in patients who had been previously exposed (Dietrich 2007).

Heparin

A single case of anaphylaxis to unfractionated heparin was reported, given IV during surgery. The reaction was delayed and presented with hypotension, flushing and urticaria. Mast cell tryptase results were not available. Skin prick tests were positive to unfractionated heparin and enoxaparin and all others were negative. The review panel judged the likelihood was 'probable'.

Blood products

There were only two incidents related to blood products: one to cryoprecipitate and one to fresh frozen plasma. The very small number of cases of reactions to blood products (with none to red blood cells) is notable. The Activity Survey estimated approximately 84,000 perioperative administrations of blood products. The relative infrequency of these reactions is perhaps attributable to the success of the Serious Hazards of Transfusion (SHOT) haemovigilance scheme https://www.shotuk.org/.

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