Histaminoid reactions in anaesthesia

R. P. McKINNON AND J. A. W. WILDSMITH

The release of small biologically active molecules as a response to anaesthesia is not uncommon. Histamine is the best known of these mediators, but others are almost certainly involved. In most patients such release has no significant effect, but in a minority severe cardiovascular and respiratory complications occur. Complex processes are involved and this review is intended to indicate their relevance to anaesthetic practice.

The incidence of severe “allergic” reactions in anaesthesia is uncertain. Watkins [103] suggested that approximately 5000–10000 severe reactions (with 100 deaths) occur annually in the United Kingdom. This would represent an incidence of between 1 per 350 and 1 per 700 anaesthetics, but other authors have suggested more conservative estimates. The Boston Collaborative Drug Surveillance Program estimated the incidence as 3 per 10000 hospital patients with a mortality between 3 and 9% [9], while in Australia the estimated incidence is 1 per 20000 anaesthetics [26]. The Confidential Enquiry into Perioperative Deaths concluded that only 39 deaths could be attributable directly to drug administration and that only one was possibly attributed to histamine release [11, 12].

In 1839, the French physiologist Magendie published the first record of what would now be termed an anaphylactic reaction, and in 1893 Von Behring coined the term hypersensitivity when describing exaggerated reactions to diphtheria toxin. In 1902, Portier and Richet used the term anaphylaxis to describe the response of dogs to repeated injections of sea anemone venom. Eight years later, Friebemann and Friedberger observed shock after injecting a variety of substances (such as starch, agar and kaolin) into dogs and these reactions were subsequently described as anaphylactoid [89]. At the same time, Sir Henry Dale noted the direct relationship between anaphylactic shock and histamine release [14].

Histamine release has been associated with the administration of anaesthetic agents since 1936, when Alam and colleagues observed it after administration of tubocurarine [1]. One of the first reported anaphylactic reactions to thiopentone was published by Evans and Gould in 1952 [19].

A major difficulty in understanding histamine-related drug reactions is the confusion of terminology. Although terms such as “allergic”, “anaphylactic” “anaphylactoid” or “hypersensitive” have specific meanings, they are commonly used interchangeably. An Association of Anaesthetists’ working party on anaphylactic reactions adopted definitions that are historically accurate and are used here (table 1) [14]. However, there are further difficulties because strictly it is inaccurate to use any of these terms until evidence of the immunological basis of a reaction has been obtained.

A further difficulty is that some reactions may not be caused by histamine, but by other mediators such as prostaglandins, leukotrienes or kinins. Where either the mediator or the mechanism involved is uncertain, such reactions are described best as histaminoid. The main sources of histamine and the other mediators are the mast cell and basophil. An understanding of their physiology is central to understanding drug reactions.

The mast cell and basophil

The mast cell and basophil share many properties, but there are important differences. Both cells are derived from bone marrow, but unlike the basophil, the mast cell matures only after migration to

Table 1 Definitions of terms (definitions reproduced with permission [4])

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergy</td>
<td>An hypersensitive state acquired through exposure to a specific antigen, re-exposure bringing to light an altered capacity to react.</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>A state of altered reactivity in which the body exhibits an exaggerated immune response to a foreign agent.</td>
</tr>
<tr>
<td>Anaphylactic</td>
<td>An exaggerated response of an organism to a foreign protein (or other substance to which it has previously been sensitized) associated with the liberation of histamine, serotonin and other vasoactive substances.</td>
</tr>
<tr>
<td>Anaphylactoid</td>
<td>A term that encompasses all reactions which are clinically indistinguishable from anaphylaxis but for which other mechanisms are responsible.</td>
</tr>
</tbody>
</table>

R. P. McKINNON*, FFARCSI, J. A. W. WILDSMITH, MD, FRCA, Department of Anaesthetics, Royal Infirmary of Edinburgh, Lauriston Place, Edinburgh EH3 9YW.

*Present address: Department of Anaesthetics, University of Newcastle upon Tyne, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP.
connective tissue. Basophils are circulating leucocytes which mature in the bone marrow and only migrate to tissues during an inflammatory response.

Both cell types contain similar specialized intracellular organelles such as cytoplasmic granules and lipid bodies. Cytoplasmic granules are the source of the pre-formed mediators of anaphylaxis such as histamine, tryptase, chymotryptase and glycosaminoglycans such as heparin. Lipid bodies are the source of arachidonic acid metabolites and non-specific esterases and peroxidases. There are two main subtypes of human mast cells depending on the type of serine protease they contain. Tryptase is common to all, but chymase is restricted to skin and intestinal mucosal mast cells.

The bronchoalveolar mast cell, possibly an additional subtype [8], is 1000-fold more sensitive to anti-IgE (IgE antibody) than lung, gut or skin mast cells and produces three times as much prostaglandin D₂ than lung parenchymal mast cells [45]. The bronchial secretions of asthmatic patients contain large numbers of these cells and they may have a role in the pathogenesis of exercise- and cold-induced asthma. Little is known about the exact physiological function of mast cells, but they are believed to play a role in the prevention of infection, especially parasitic infection. The physiological function of the basophil is not known. Within 3 min of mast cell stimulation, degranulation occurs. Initially the cytoplasmic granules swell and coalesce to form cytoplasmic channels that fuse with the plasma membrane, thereby expelling their contents. When degranulation has occurred, the mast cell recovers both structurally and functionally.

The intracellular events controlling histamine release are poorly understood. Intracellular cyclic AMP (cAMP) concentration increases and then decreases sharply, with the concentration of cyclic GMP following in a reciprocal manner [95]. The increase in cAMP is preceded by an increase in intracellular calcium and an influx of extracellular calcium through non-voltage-dependent calcium channels. These intracellular events are mediated through the hydrolysis of inositol phospholipids [7]. Similarly, the mechanisms that control the secretion of prostaglandins and leukotrienes are poorly understood, but involve activation of the enzyme phospholipase A₂.

Cell stimulation
Antibody, complement, peptides and changes in osmolality are capable of stimulating the mast cell, but the most important stimulus is cross-linking of cell surface IgE by antigen [52].

ANTIBODY
Antibodies or immunoglobulins are glycoproteins that are secreted from transformed and activated B lymphocytes, the plasma cell. The number of IgE receptors on the mast cell is variable, being proportional to serum IgE concentrations. When the receptor is cross-linked and aggregated, degranulation occurs. Helm and colleagues have produced various peptides that when bound to the receptor prevent cross-linking and therefore mediator release [43]. Such peptides have obvious clinical significance in the prevention of allergic disease.

COMPLEMENT
Complement is a cascade system comprising approximately 20 serum proteins which are involved in host defence. Activation is either by the classical or the alternative pathway, both culminating in a final common or lytic pathway (fig. 1).

Classical pathway
The Cl component is activated by the binding of a subcomponent of C1 (Clq) to an antigen–antibody complex of either the IgG or IgM class. In addition to antibody, many polyanionic substances such as heparin and dextran, in addition to bacteria, viruses and C-reactive protein are capable of direct Cl activation. The complement system is influenced by many control proteins such as Cl esterase inhibitor. Hereditary angioneurotic oedema is a syndrome caused by low or absent Cl esterase inhibitor. Relatively low concentrations of Cl esterase have been measured in patients who react to x-ray contrast media [55]. The significance of similarly low Cl esterase concentrations in reactions associated with anaesthesia is unknown.

Alternative pathway
The alternative pathway is a non-specific natural defence system that serves as an amplification process.

Cell stimulation
Antibody, complement, peptides and changes in osmolality are capable of stimulating the mast cell, but the most important stimulus is cross-linking of cell surface IgE by antigen [52].

ANTIBODY
Antibodies or immunoglobulins are glycoproteins that are secreted from transformed and activated B lymphocytes, the plasma cell. The number of IgE receptors on the mast cell is variable, being proportional to serum IgE concentrations. When the receptor is cross-linked and aggregated, degranulation occurs. Helm and colleagues have produced various peptides that when bound to the receptor prevent cross-linking and therefore mediator release [43]. Such peptides have obvious clinical significance in the prevention of allergic disease.

COMPLEMENT
Complement is a cascade system comprising approximately 20 serum proteins which are involved in host defence. Activation is either by the classical or the alternative pathway, both culminating in a final common or lytic pathway (fig. 1).

Classical pathway
The Cl component is activated by the binding of a subcomponent of C1 (Clq) to an antigen–antibody complex of either the IgG or IgM class. In addition to antibody, many polyanionic substances such as heparin and dextran, in addition to bacteria, viruses and C-reactive protein are capable of direct Cl activation. The complement system is influenced by many control proteins such as Cl esterase inhibitor. Hereditary angioneurotic oedema is a syndrome caused by low or absent Cl esterase inhibitor. Relatively low concentrations of Cl esterase have been measured in patients who react to x-ray contrast media [55]. The significance of similarly low Cl esterase concentrations in reactions associated with anaesthesia is unknown.

Alternative pathway
The alternative pathway is a non-specific natural defence system that serves as an amplification process.
Histaminoid reactions in anaesthesia

for the antibody-dependent classical pathway. It is often viewed as a system with a background tonic activity under the influence of the control proteins H and I. An imbalance in these proteins can activate the pathway, but for this to proceed an activating surface is necessary. Such surfaces are found on many gram-negative bacteria, immunoglobulins, polysaccharides and on various polyanionic substances.

Final common pathway

The C3 and C5 fragments produced by each pathway are activated with the formation of the two anaphylatoxins, C3a and C5a and the larger C3b and C5b fragments. The larger C3b fragment provides a link between the target cell and the macrophage, a process termed oponsonization, which is essential for phagocytosis. When fixed to the target cell membrane, the C5b fragment is joined by the sequential addition of C6, C7, C8 and C9. The resulting complex is the membrane attack complex which penetrates the target cell membrane, allowing free exchange of ions and water. Colloid osmotic pressure increases, followed by cell lysis and death.

PEPTIDES AND POLYBASIC COMPOUNDS

Substance P, vasoactive intestinal peptide and bradykinin release histamine in addition to their direct cardiovascular effects. Pearce, Kassessinoff and Liu have suggested that these peptides act via the "polyamine receptor" [76], which produces rapid histamine release and is independent of added Ca^{2+} or phosphates. Basophils, skin, intestinal mucosa and lung parenchymal mast cells are not affected by these compounds. As high concentrations of these activating substances are necessary for histamine release, it is thought unlikely that they are clinically significant [75].

HYPEROSMOLALITY

Basophils, lung parenchymal and bronchoalveolar mast cells release histamine when exposed to a hyperosmolar environment [18]. Bronchoalveolar mast cells are more responsive than lung parenchymal mast cells. At an osmolality of 360 mosmol kg⁻¹, histamine is released from the mast cell and is maximal at 770 mosmol kg⁻¹. Changes in osmolality may be important in the pathogenesis of exercise-induced asthma.

Mediators of anaphylaxis

HISTAMINE

The cardiorespiratory effects of histamine are listed in table 2. There is generally a good correlation between plasma histamine concentration and its clinical manifestations, except for bronchospasm (table 3). Occasionally, very high concentrations may be found without the expected severity of symptoms. For example, in experimental cold-induced urticaria, plasma histamine concentrations of 36 ng ml⁻¹ were not uncommon [88]. In addition, Lorenz and colleagues have suggested that histamine concentrations of less than 1 ng ml⁻¹ are associated with significant clinical effects including bradycardia and hypertension, effects not often attributable to histamine release [66].

In healthy volunteers, histamine decreases systolic and diastolic pressures and increases heart rate in a dose-dependent manner. The concurrent administration of H₁ and H₂ antagonists attenuates these effects. H₁ antagonism is effective initially, while the H₂ antagonists are only effective in attenuating the late decrease in diastolic pressure [10]. Vigorito and colleagues observed the effects of histamine in patients for cardiac catheterization [101]. Decreases in systolic, diastolic and mean arterial pressures were accompanied by increases in heart rate, LV dP/dmax and cardiac index, effects which were associated with plasma histamine concentrations of approximately 5 ng ml⁻¹. The increases in heart rate, LV dP/dmax and cardiac index were thought to be a reflection of increased baroreceptor activity and increased sympathetic stimulation as adrenaline and noradrenaline concentrations were also increased.

The bronchodilator effect of histamine may be mediated through a subtype of the H₂ receptor [32], the so-called H₃ receptor [3]. This modulates cholinergic neurotransmission at parasympathetic ganglia and post-ganglionic neurones in human bronchi [48,49]. The H₃ receptor antagonist, thio-

<table>
<thead>
<tr>
<th>Condition</th>
<th>Conc (ng ml⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline concn</td>
<td>0.6 ± 0.2</td>
</tr>
<tr>
<td>30% increase in heart rate</td>
<td>1.6 ± 0.3</td>
</tr>
<tr>
<td>Significant flush, headache</td>
<td>2.39 ± 0.5</td>
</tr>
<tr>
<td>30% increase in pulse pressure</td>
<td>2.45 ± 0.3</td>
</tr>
<tr>
<td>Increase LV dP/dt</td>
<td>4.6 ± 2</td>
</tr>
<tr>
<td>Severe hypotension</td>
<td>&gt; 12</td>
</tr>
</tbody>
</table>

Table 2: Cardiorespiratory effects of histamine

<table>
<thead>
<tr>
<th>Effect</th>
<th>Receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>H₁</td>
</tr>
<tr>
<td><strong>Circulatory system</strong></td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td>Positive chronotropism</td>
</tr>
<tr>
<td></td>
<td>Positive inotropism</td>
</tr>
<tr>
<td></td>
<td>Coronary vasodilatation</td>
</tr>
<tr>
<td></td>
<td>Arrhythmogenesis</td>
</tr>
<tr>
<td></td>
<td>Increase in PR interval</td>
</tr>
<tr>
<td></td>
<td>Ventricular irritability</td>
</tr>
<tr>
<td></td>
<td>Decrease in VF threshold</td>
</tr>
<tr>
<td></td>
<td>Shift in pacemaker site</td>
</tr>
<tr>
<td></td>
<td>Peripheral circulation</td>
</tr>
<tr>
<td></td>
<td>Decrease in systemic vascular resistance</td>
</tr>
<tr>
<td></td>
<td>Increase in vascular permeability</td>
</tr>
<tr>
<td><strong>Respiratory system</strong></td>
<td></td>
</tr>
<tr>
<td>Bronchoconstriction</td>
<td>+</td>
</tr>
<tr>
<td>Bronchodilatation</td>
<td>+</td>
</tr>
<tr>
<td>Stimulation of lung irritant receptors</td>
<td>+</td>
</tr>
<tr>
<td>Pulmonary vasoconstriction</td>
<td>+</td>
</tr>
<tr>
<td>Pulmonary vasodilatation</td>
<td>+</td>
</tr>
</tbody>
</table>
Leukotrienes

- Hypertension
- Negative inotrope
- Sensitizes the heart to the effects of histamine
- Decrease in coronary perfusion pressure, peak blood flow and coronary blood flow
- Increase in vascular permeability
- Bronchoconstriction
- Increase in mucus production
- Chemotaxis and adherence of white cells

Prostaglandins

- Bronchoconstriction (PGD₂)
- Bronchodilatation (TXA₂)

Platelet activating factor

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative inotrope</td>
<td>Coronary vasoconstriction</td>
</tr>
<tr>
<td>Increase in pulmonary vascular resistance</td>
<td>Increase in systemic vascular resistance</td>
</tr>
<tr>
<td>Decrease in vascular permeability</td>
<td>Increase in cellular infiltration</td>
</tr>
<tr>
<td>Increase in airway reactivity</td>
<td></td>
</tr>
</tbody>
</table>

LIPID MEDIATORS OF HYPERSENSITIVITY

The lipid mediators of anaphylaxis are the metabolites of arachidonic acid derived from membrane-bound phospholipids by the enzyme phospholipase A₂. In anaphylaxis, only the 5-lipoxygenase and the cyclooxygenase pathways are considered clinically important. The products of the 5-lipoxygenase pathway are the leukotrienes and an intermediary compound, 5-hydroperoxyeicosatetraenoic acid (5-HPETE), which is important because it exerts positive feedback control on histamine release. The metabolites of the cyclooxygenase pathway are the prostaglandins and the thromboxanes. Of the arachidonic acid mobilized for mediator production, more than 50% is metabolized to produce PGD₂, the principal product of the cyclooxygenase pathway, while 20% is metabolized to produce LTC₄ [77].

PLATELET ACTIVATING FACTOR

Platelet activating factor (PAF) is an unstable, ether-linked phospholipid that was discovered as a mediator of anaphylaxis in 1972 [79]. It is derived directly from membrane-bound phospholipids and is released from a variety of inflammatory cells. PAF is the single most potent inducer of shock. The effects of PAF on lung tissue can be inhibited partially by atropine and tetrodotoxin, suggesting that acetylcholine may play a role in modulating its physiological effects [94].

A summary of the biological effects of the leukotrienes, prostaglandins and thromboxanes is shown in Table 4.

Mechanisms of drug reaction

What information exists on mechanisms is based largely on the results of the investigation of clinical reactions. For example, Watkins found that 50% of thiopentone reactions were associated with increases in serum IgE and 30% with alterations in complement, but that in 43% there were no alterations in either. Of the complement reactions, 7% were attributed to alternative complement activation [102]. Based on these and similar investigations, four mechanisms for histaminoid reactions have been postulated (Table 5) [13].

Table 5  Mechanisms of adverse drug reactions

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Type I hypersensitivity involving IgE</td>
</tr>
<tr>
<td>2.</td>
<td>Classical complement activation involving IgG or IgM</td>
</tr>
<tr>
<td>3.</td>
<td>Alternative complement activation—no antibody involved</td>
</tr>
<tr>
<td>4.</td>
<td>Direct pharmacological effects</td>
</tr>
</tbody>
</table>

There are inherent difficulties in attributing a mechanism to a drug based on blood tests taken during a reaction. First, complement changes may occur irrespective of the mechanism of mast cell degranulation. For example, the proteolytic enzyme trypsin, released with histamine, directly activates complement [86]. Second, changes in the components of humoral immunity which follow reactions may be the result of the reaction and not the cause. Third, the normal immunological response to anesthesia has not been investigated adequately, although it is known that classical complement activation occurs after induction of anesthesia in 30% of patients [60]. Therefore, it is possible that differences have been drawn from the results of immunological investigations which really represent the physiological response to anesthesia.

NON-CELLULAR-MEDIATED REACTIONS

Some drugs act on various plasma constituents to release vasoactive molecules. For example, plasma protein solutions may contain a prekallikrein activator (PKA) that is a degradation product of Hageman factor (factor XII). PKA activates the kallikrein–kinin system producing bradykinin and hypotension [2]. PKA may also be responsible for reactions to factor VIII concentrates and immunoglobulin preparations.

Sodium acetate, which was once used in plasma protein solution, may cause hypotension by a direct vasodilator effect. Some reactions to x-ray contrast media and protamine may be caused by activation of the kallikrein–kinin system. In addition, protamine is known to inhibit carboxypeptidase, the enzyme that inactivates both bradykinin and the anaphylatoxins C3a and C5a [98].

DIRECT PHARMACOLOGICAL RELEASE

Thiopentone, suxamethonium, tubocurarine, atracurium, morphine and colloids release histamine. Propofol, etomidate, vecuronium, pancuronium, dextran and hydroxyethyl starch are thought not to
release histamine directly. X-ray contrast media, glucose and mannitol may release histamine because of their hyperosmolarity.

Mast cells isolated from different anatomical sites differ in their responses to a variety of different pharmacological stimuli. For example, morphine induces histamine release from skin mast cells, but not from intestinal or lung mast cells [75]. Stellato and colleagues found that atracurium, uniquely, released histamine from lung, skin and heart mast cells which is in contrast with suxamethonium which failed to release histamine from either skin or lung mast cells and tubocurarine which released histamine from skin and lung mast cells but only at high concentrations [93]. Basophils were virtually unresponsive to all neuromuscular blockers tested.

Plasma histamine concentration of 4 ng ml⁻¹ are common after administration of each drug, but such concentrations are unlikely to cause severe clinical effects. However, with the growing tendency for polypharmacy, the cumulative effects of histamine release may be important. Many anaesthetic agents [42], including isoflurane and particularly vecuronium [33], can inhibit the enzyme N-methyltransferase. This enzyme is principally responsible for metabolism of histamine and its inhibition may compound the effects of direct histamine release. Interpretation of histamine results may be further complicated because anaesthetic drugs may interfere with a radioimmunoassay utilizing this enzyme.

COMPLEMENT-MEDIATED REACTIONS

The evidence for complement initiating a drug reaction is limited. Complement activation is often found after a reaction, but it is uncertain if this is the actual mechanism or the end result of the reaction. The induction agents alphaxalone-alphadolone and propanidid, solubilized in Cremophor EL, were cited as classic examples of complement-mediated reactions. Activation of the classical pathway was associated with previous exposure involving antibodies of either the IgG or IgM class, while alternative activation occurred without previous exposure.

Alternatively, complement may be activated independently of the two pathways, as in the case of some x-ray contrast media reactions [74]. In addition, with x-ray contrast material, complement activation is not associated with histamine release [90]. Similarly, in a patient who reacted to hydroxyethylstarch, complement was activated, but there was no increase in plasma histamine [81].

The classical complement pathway can be activated by a variety of substances such as C-reactive protein and various polyanionic substances. The latter may explain some drug reactions involving complement but not antibody.

ANTIBODY-MEDIATED REACTIONS

Specific IgE antibodies to thiopentone, suxamethonium, non-depolarizing neuromuscular blocking drugs, pethidine and protamine, have been identified. Recently, antibodies to other potential antigens that the surgical patient may encounter have been identified, including latex, chlorhexidine and ethylene oxide.

Specific subgroups within a molecule determine antigenicity and are referred to as antigenic determinants. For thiopentone, the antigenic determinants are the pentyl group at position 5 and the thiogroup at position 2 [41]. Antibodies to neuromuscular blocking drugs can cross react with thiopentone, the ring N atoms attached to the pyrimidine nucleus of the thiopentone ring cross reacting with antibodies to neuromuscular blocking drugs [5]. Some reports of simultaneous anaphylaxis to thiopentone and neuromuscular blocking drugs may be explained by this cross reactivity [71]. However, a recent report of a fatal reaction described separate antibodies to thiopentone and suxamethonium [29].

Neuromuscular blocking drugs account for 70% of the reactions in anaesthesia [56], but only 30–40% of patients have a history of previous exposure. With these drugs, the antigenic determinant is the quaternary ammonium group. Cross linking of IgE by neuromuscular blockers occurs only when the molecules are at least bivalent and the inter-quaternary distance is at least 4.5 Å. Such molecules include suxamethonium, vecuronium, pancuronium and atracurium. Vecuronium, which is monovalent, would appear to be inherently safe, but in France it accounts for 37% of all reactions to neuromuscular blockers [56]. Its antigenicity is caused by formation of multivalent multimolecular complexes that occur in solution [69].

Cross reactivity, caused by the quaternary ammonium group, is common with neuromuscular blockers (52%). Some individuals, clinically allergic to a neuromuscular blocker, do not have antibodies detectable by radioimmunoassay. In such cases the quaternary group of the drug may not bind to the solid support of the assay [40]. The detection rate for antibodies to neuromuscular blocking agents can be improved using inhibition studies with trimethylamine, triethylamine and morphine. Detection rates for suxamethonium and gallamine antibodies increase from 83 to 100%. For alcuronium and tubocurarine, they increase from 67 to 88% and 92 to 100%, respectively [40]. Cross reactivity between the substituted ammonium ion in cosmetics and household chemicals and the quaternary ammonium groups on the blocker molecule has been postulated for the preponderance of reactions to neuromuscular blockers among females. However, in Australia there are three times as many operations on females as males and this may at least partly explain this preponderance [28].

In vitro reactions to suxamethonium can be reduced by preventing antibody binding to the drug with choline [99]. Choline, a small univalent metabolite of suxamethonium, inhibits suxamethonium–antibody binding, a process known as hapten inhibition. Unfortunately choline is painful on injection and cannot be used clinically but reactions to dextran can be prevented by pretreatment with hapten dextran [65].
The degradation products of the β-lactam ring (benzoylpenicilloyl) are believed to be the antigenic determinants for penicillin. Traditionally they have been described as either major or minor determinants, depending on their degree of protein binding. Harle and Baldo have suggested that fine structural differences between the molecules may be more important in determining their antigenicity [39]. With a recently developed RAST test, only four of 132 patients with a history of allergy to penicillin had evidence of specific antibodies. When the remaining 128 patients were challenged with oral penicillin there were no adverse effects [96].

It has been suggested that patients previously exposed to protamine zinc insulin may develop antibodies to protamine. However, Weiler and colleagues, in their prospective study of 243 patients, found no increased risk of reaction to protamine in patients exposed to insulin [105]. Similarly, because protamine is derived from salmon sperm, it has been suggested that vasectomized patients may become sensitized by developing autoantibodies to sperm. In addition, fish allergies have also been suggested as a possible sensitizing mechanism. Vezina found that 13 of 20 vasectomized patients had anti-sperm antibodies and five had anti-protamine antibodies [100]. However, because of the small numbers, this was not deemed to be significant.

The water soluble polypeptide molecules derived from natural latex are believed to be the antigenic substances of latex [72]. Manufacturing chemicals, the cause of contact dermatitis, are not thought to be associated with histaminoid reactions. Patients are usually RAST positive, indicating antibody involvement and there is an association with fruit allergy [62], especially bananas [73].

Clinical features
The clinical manifestations of a histaminoid reaction are many and can usually be inferred from a knowledge of the mediators involved.

Cardiovascular system
Ninety percent of reactions involve cardiovascular collapse and in 10% may be the only presenting feature [28]. Initially, there is usually an increase in cardiac output, resulting from increased endogenous catecholamine production. There follows profound arterial hypotension through the variety of mechanisms listed in table 6. Arrhythmias are common with supraventricular tachycardia occurring in more than 80% [24]. Cardiac arrest occurs in 11% of patients [57] but overt cardiac failure is rare. Membranous pulmonary oedema occurs in 3% of patients and may be the only presenting feature [27].

The haemodynamic changes in a reaction to cefazolin in humans have been documented. Decreases in mean arterial pressure, pulmonary capillary wedge pressure, pulmonary and systemic vascular resistance and left ventricular end-diastolic pressure occur, while cardiac index, stroke volume, heart rate and ejection fraction increase (fig. 2) [6].

In patients with pre-existing cardiac disease, serious arrhythmias and cardiac failure are more likely [24,25].

Respiratory system
Bronchospasm occurs in up to 50% of patients which may be either transient or severe [27] and in 3% may be the only presenting feature [28]. Prolongation of expiration may occur because of loss of elastic recoil of the lungs and may be a limiting factor during resuscitation. Bronchospasm is almost inevitable in patients with pre-existing asthma [28].

Table 6 Mechanisms of cardiovascular depression during anaphylactic reactions

<table>
<thead>
<tr>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral vasodilatation</td>
</tr>
<tr>
<td>Decrease in cardiac contractility because of:</td>
</tr>
<tr>
<td>Hypercapnia</td>
</tr>
<tr>
<td>Hypoxia</td>
</tr>
<tr>
<td>Acidosis</td>
</tr>
<tr>
<td>Loss of intravascular fluid</td>
</tr>
<tr>
<td>Pooling of blood in regional vascular beds</td>
</tr>
<tr>
<td>Cardiac arrhythmias</td>
</tr>
<tr>
<td>Coronary vasoconstriction</td>
</tr>
<tr>
<td>Increased pulmonary vascular resistance</td>
</tr>
<tr>
<td>Bronchoconstriction</td>
</tr>
</tbody>
</table>

Figure 2 Haemodynamic and echocardiographic changes before (15 min after intubation (15 min), 3 min after incision (3 min)), during and after an anaphylactic reaction to cefazolin (C). MAP = Mean arterial pressure, HR = heart rate, PCWP = pulmonary capillary wedge pressure, LVEDA and LVESA = left ventricular end-diastolic (●) and end-systolic (△) cross-sectional areas, EF = ejection fraction (LVEDA - LVESA)/LVEDA, CI = cardiac index (litre min⁻¹ m⁻²), SI = stroke index (ml beat⁻¹ m⁻²), SVRI = systemic vascular resistance index (dyn s cm⁻⁵ m²), PVRI = pulmonary vascular resistance index (dyn s cm⁻⁵ m²) (reproduced with permission [6]).
Histaminoid reactions in anaesthesia

Twelve percent of reactions involve upper airway oedema and this may be an immediate life-threatening problem.

SKIN
A generalized erythema or flushing is the most common skin manifestation. The characteristic irregular, raised, erythematous wheals that are intensely pruritic are unmistakable but are uncommon. Occasionally a diffuse rash may appear, often on the lower half of the body. Conjunctival swelling and inflammation, eyelid oedema and lacrimation may also occur. More than one skin manifestation may appear at one time.

GASTROINTESTINAL SYSTEM
Nausea, vomiting, haematemesis, abdominal pain, bloody diarrhoea and melaena have been described. Occasionally they may be the only presenting symptoms and are often prodromal.

OTHER FEATURES
Disseminated intravascular coagulation may occur. Leucopenia, hypothermia and a watery vaginal discharge have been described [27].

Differential diagnosis
Anaesthetic misadventure may masquerade as a histaminoid reaction and it is important to differentiate a true reaction from other conditions causing bronchospasm, hypotension, or both, during anaesthesia. With a full-blown multisystem reaction, the diagnosis may be relatively easy, but with single system reactions (14%) [28] the diagnosis can be difficult. Mechanical and neurogenic factors, inhalation of gastric contents and direct drug effects should always be considered in the differential diagnosis. Similarly, hypotension after induction may be caused by hypovolaemia, relative or absolute overdosage of anaesthetic agents and decreases in cardiac output caused, for example, by arrhythmias or myocardial infarction. However, if in doubt the patient should be treated as for an anaphylactic reaction and investigated appropriately.

Reactions to preservatives, solubilizers and incipients can occur. In the past, reactions to alphadalone–alphadalone and propanidid were examples of such reactions. Polyethoxyethylated castor oil (Cremophor) was the antigenic substance and although these drugs are no longer used in humans, Cremophor is the solubilizing agent in i.v. cyclosporin (Sandimmune), vitamin K (Konakion) and i.v. miconazole (Daktarin). Reactions have been reported with cyclosporin [47].

Other common additives include metabisulphites and hydroxybenzoates. Metabisulphites in both oral and parenteral preparations induce bronchospasm in asthmatics as does for example, the parenteral form of doxycycline [67]. Methylparaben, an ester of para-hydroxybenzoic acid, is the preservative used in multi-dose vials of local anaesthetics and in one preparation of suxamethonium (Anectine). Reactions may occur to methylparaben, but are probably uncommon [64].

Risk factors
Ultimately, anaesthetists should aim to identify patients at risk, but as yet the only clear predictor of a reaction is a history of a previous one. However, many risk factors have been proposed and several authors have suggested modifying the anaesthetic technique, drugs, or both, in such cases.

Reactions are rare in children, probably because of their relatively immature immune systems and the lack of previous exposure to allergens. A reaction during anaesthesia in a neonate has been reported [80]. Reactions are said to occur more frequently in young adults and Galletty and Treuren found the peak incidence to be in the fourth decade [34].

There is overwhelming evidence to suggest that females are affected more often than males, particularly with neuromuscular blocking agents. Again, Galletty and Treuren found that 77% of reactions occurred in females [34]. Simpson and colleagues noted that of 10 patients reacting on first exposure to Althesin, eight were pregnant [91]. Similarly Shkutin, Naresha and Donchenko [87], examining pathological changes in the lungs of 51 patients dying from drug-induced reactions, found pregnancy to be a frequent concurrent condition.

Many studies have found that reactions occur more commonly in patients with an atopic history [17]. However, Fisher, Outhred and Bowey investigated the likelihood of a reaction in patients with an allergic history. They found that a history of allergy was not predictive of severe clinical anaphylaxis [31].

Rats subjected to an audio–visual signal coupled with an antigenic stimulus developed anaphylactic shock. On presentation of the signal alone, the rats again reacted, suggesting that mediator release can be learned [83]. However, there is no evidence to suggest that anxious patients react more frequently. With antibody-mediated reactions there is little evidence to suggest that the dose or rate of administration affects the severity of the reaction.

Reactions, particularly to latex, are more common in patients with neural tube defects [97] probably representing recurrent exposure to rubber products such as catheters.

Treatment
Treatment is aimed at modulating the effects of released mediators and inhibiting mediator production and release. As it is virtually impossible to identify the offending agent at the time of reaction, all drugs, therapy and surgery should stop unless it is obviously impossible to do so. Theatre staff and surgeons should be enlisted to help until experienced anaesthetic staff are available.

Oxygen 100% should be administered and consideration should be given to early intubation because of the possibility of rapidly developing angio-oedema. In addition, control of the airway
allows the anaesthetist "two hands free" until help arrives. If intubation proves difficult then cricothyroidotomy should be considered. Because a reduction in peripheral resistance and loss of intravascular volume are the initial pathophysiological changes, fluid therapy should be an early resuscitative measure, but pharmacological resuscitation is the priority.

Adrenaline is the drug of choice in the management of hypotension, bronchospasm and angioedema. Initially, 1 ml of a 1:10000 solution is injected i.v. and repeated every minute until there is a satisfactory clinical response. Ventricular arrhythmias have been associated with adrenaline, especially in patients who had received halothane [24]. However, the undeniable efficacy of adrenaline should not preclude its use on the above grounds, especially if electrocardiographic monitoring is available. Adrenaline may be ineffective if the intravascular volume is low and therefore fluids must be administered concurrently. Colloids are more effective than crystalloids in restoring the circulation during a reaction [21,30]. Reactions have not been described when colloids are administered for shock [28]. If reactions recur or are difficult to treat, an adrenaline infusion may be required.

Noradrenaline has been advocated, especially in conditions where low peripheral perfusion predisposes to intrapulmonary shunting. Calcium salts, as inotropes, should be avoided because of the potential enhancement of mediator release. Low output states may occur with apparently benign arrhythmias, and under such circumstances external cardiac massage must be instituted to ensure an adequate cardiac output. Arrhythmias should be treated symptomatically and calcium antagonists are probably the drugs of choice, as they are known to antagonize some of the arrhythmogenic effects of histamine in vitro [58].

In the presence of sympathetic block produced by either β blockers or regional anaesthesia, reactions are usually refractory to treatment [38]. In such cases, high-dose dopamine or other adrenoreceptor agonists (alpha or beta as appropriate) may be required. With cardiac failure a cardiac assist device may be necessary [82]. Serial haematocrits, urea and electrolyte concentrations, blood-gas tensions and lactate measurements may be used to monitor the reaction. Coagulopathies may occur [92].

Bronchospasm is the most difficult clinical manifestation to treat. Adrenaline is usually effective, but for persistent bronchospasm, aminophylline and nebulized bronchodilators can be used. If the patient is haemodynamically stable, isoprenaline is effective. Halothane, ketamine and ether may be used for persistent bronchospasm. Intratracheal and perihilar infiltration of local anaesthetics have also been advocated. In extreme cases cardiopulmonary bypass may be required. The expiratory resistance of the lung may be greater than its elastic resistance, so that lung deflation may not occur and external chest compression may be needed to facilitate expiration [27].

Steroids are probably ineffective in the acute reaction, but by increasing lipocortin synthesis and thereby inhibiting phospholipases [16], they inhibit the late component of reactions [85]. Additionally, steroids may decrease IgE receptor expression.

The use of antihistamines is controversial. In some studies a beneficial effect was observed, but not in others. H₂ antagonists have been reported to be effective in refractory anaphylaxis, as they block some of the desirable effects of histamine, such as positive inotropy and coronary vasodilatation, they should be used with caution. In addition, the H₂ receptor exerts negative feedback on histamine release and H₂ block may enhance histamine release [44]. High-dose atracurium (1.5 mg kg⁻¹) decreased mean systemic arterial pressure, a change which was associated with an increase in plasma histamine concentrations and which was attenuated by both H₁ and H₂ receptor block. However, H₂ block alone further decreased mean arterial pressure.

In severe cases, central venous and pulmonary artery catheterization should be considered. After stabilization, the patient should be transferred to the intensive care unit and monitored for 24 h because of the risk of recurrent reactions.

Investigations
It is the responsibility of the anaesthetist to investigate all patients. The drug should be identified and if possible the mechanism. Additionally, the anaesthetist should determine which drugs are safe for the patient in the future. The traditional approach of regular blood sampling during the reaction is of limited value as the diagnosis cannot be made or the mechanism of reaction identified with any certainty.

During the reaction, histamine measurement would certainly establish a diagnosis. However, its measurement is technically difficult and impracticable in clinical practice. Recently, two immunoassays have been developed that may confirm histamine release [78]. Tryptase, the neutral protease, released from mast cells, is normally undetectable in serum and is elevated after mast cell degranulation [86]. Tryptase concentrations during a reaction to thiopentone are shown in figure 3. Serum tryptase appears to be a good marker for...
Histaminoid reactions in anaesthesia

severe reactions but not for mild ones [53]. N-methyl-histamine, the major urinary metabolite of histamine, may be used as an indirect marker of histamine release [50]. Both tryptase and urinary N-methyl-histamine have long half-lives and are correlated with plasma histamine concentrations. Their long half-lives allow sampling at the convenience of the anaesthetist even after the reaction. Recent evidence has suggested that urinary N-methyl-histamine may be of little value as an investigation in reactions during anaesthesia [54].

At 4 weeks, skin tests, the leucocyte histamine releasing test, or both, and specific antibody tests (RAST) are performed.

SKIN TESTS

Full resuscitative equipment must be available because of the small risk of a reaction during testing. Drugs such as antihistamines, sympathomimetics, xanthines, cromoglicate and steroids should be stopped at least 48 h before testing because of their modulating effects on the mast cell. Skin testing is thought to be of limited value in the investigation of reactions to colloids or x-ray contrast media [23].

Intradermal skin tests

The intradermal test has been the standard for assessing drug reactions. The test should be carried out according to Fisher’s procedure, where the drug responsible can be correctly identified in 90% of cases [22]. False positives may be caused by direct histamine release by the drug, preservatives or dermatographism.

Prick tests

Prick tests are becoming increasingly popular. They are technically easier to perform and perhaps safer, despite using either undiluted or a 1:10 dilution of the drug. In addition it is claimed that prick tests are easier to interpret [70]. Leynadier and colleagues claim that prick tests are more reliable than intradermal tests [63]. They showed agreement between prick and intradermal tests in 426 of 441 (96.6%) comparisons. Fourteen of the 15 discrepancies were caused by failure of the prick test to agree with a positive intradermal test. It is unclear if these positive intradermal tests were false positives or represented true drug sensitivity. Laxenaire and colleagues found that in three patients with severe reactions to propofol and a positive intradermal test only one patient had a clearly positive prick test [57]. Further studies are required to determine if diagnostically prick tests are a satisfactory alternative to intradermal tests.

LEUCOCYTE HISTAMINE RELEASING TEST

This is an in vitro test where blood from the patient is exposed to the suspected drug and the resulting histamine release assayed. The test requires elaborate laboratory facilities and is not appropriate in anaesthetic practice [35]. False negatives can occur, as up to 20% of patients with specific drug antibodies have a negative test [37].

ALLERGEN SPECIFIC IGE (RAST)

The drug or allergen is attached to an inert, stable material with a high protein binding capacity, the solid phase; for example, cellulose discs and agarose particles (Sepharose). When the patient’s serum is added, drug-specific antibodies bind to the solid phase. The specific antibody is detected by labelled anti-IgE, usually 125I. The result is expressed as the ratio of the test sample to a non-allergenic control. If duplicate samples are analysed, than a positive result is where the ratio is greater than 3.0, otherwise a ratio of 4.0 is taken to be significant [46]. The RAST test is subject to both random and systematic errors. Positive and negative controls help to eliminate random errors, but systematic errors can only be minimized by using experienced laboratory personnel. The American Academy of Allergy Committee has studied the variance of RAST results from 12 different academic laboratories and found the results to be highly variable [20]. These factors must be taken into account when analysing test results.

Despite claims that the RAST test is specific [104], false positive and negative results do occur. A drug with a flexible structure, such as suxamethonium, may adapt to the binding site of an antibody specific for another neuromuscular blocker. This may explain the results of Didier and colleagues when suxamethonium-sensitive patients with positive skin and RAST tests were also shown to be RAST-positive to pancuronium without exhibiting a positive skin test to pancuronium [15]. Conversely, false negatives can also occur. In 61 patients who were RAST-negative to penicillin, and who were then skin tested with penicillin, 16 patients had a positive skin reaction [51]. Some false negatives are caused by IgG-blocking antibodies that even in low concentrations compete with specific IgE for its binding site. To minimize this, extraction of the allergen by the solid phase must be maximized. Sepharose-based allergosorbants can extract the allergen more efficiently than the more common solid phase (the cellulose disc, the basis of the commercial Pharmacia assay). A very high total serum IgE (greater than 1000 IU ml"1) can cause a false positive, but performing the test with an IgE myeloma control will correct for this error.

The RAST inhibition assay is used to detect the specificity of the antibodies detected by the RAST assay and examine cross reactivity between drugs. Here soluble drug is added to the RAST assay where it competes with the solid phase allergosorbant for binding to the specific serum antibody [106]. Following washing, the specific IgE is determined as before and the percentage inhibition due to the soluble drug is determined, thus allowing the specificity of the antibody to be determined.

ARRANGEMENTS FOR TESTING

Arrangements for investigation must be made with a local immunology laboratory or dermatology department. Every reaction should be reported to the Committee on Safety of Medicines via the yellow
card scheme and patients should be encouraged to carry with them evidence of their investigations, either as a letter or on a medic alert bracelet.

Management of the patient with a previous anaphylactic reaction

Obviously the offending agent must be avoided. If not contraindicated a regional or local technique would be a reasonable choice. Pretreatment with H1 or H2 antagonists, or both, may be useful [64].

Where the reaction was caused by a neuromuscular blocker, the choice of a subsequent blocker must be based on the results of skin testing. The patient should have been tested to all currently available blockers because cross reactivity occurs in 52% of patients. Care must be exercised when new blockers are introduced into clinical practice because prior sensitisation need not have occurred to the new blocker molecule itself. The value of skin tests was clearly demonstrated by Leynadier, Calinaux and Day when patients with a previous reaction were given "safe anaesthesia" based on the results of skin testing [61].

If the patient has had subsequent anaesthesia without adverse effect then those drugs used will probably be safe in any future anaesthetic. Finally, if anaesthesia proceeds uneventfully then the patient should be given a letter indicating the anaesthetic technique and drugs used in order to aid other anaesthetists in the future with their choice of drugs and techniques.

Conclusion

Reactions during anaesthesia continue to be a cause for concern. Little can be done to predict which patients may react, but a high index of suspicion, rapid diagnosis and effective management should prevent much of the morbidity and mortality associated with this condition. Patients should be fully investigated and suggestions for future management should be given to them and their GP.

Acknowledgement

We thank Professor M. Fisher for reviewing the manuscript and for his helpful suggestions.

References

20. Evans FJ. Variability in the measurement of specific immunoglobulin E antibody by the RAST procedure. Journal of Allergy and Clinical Immunology 1982; 79: 578-584.
Histaminoid reactions in anaesthesia


40. Harle DG, Baldo BA, Fisher MM. Immunoassays employing substituted ammonium compounds other than neuromuscular blocking drugs to increase the detection of IgE antibodies to these drugs. *Molecular Immunology* 1990; 27: 1039–1045.


55. Latier EG, Lang JH, Lyon SG, Hamblin AE. Contrast and contrast material reactions. *Journal of Allergy and Clinical Immunology* 1979; 64: 105–112.


60. Lewis RE jr, Curse JM, Richey JV. Effects of anesthesia and operations on the classical pathway of complement activation. *Clinical Immunology and Immunopathology* 1982; 23: 666–671.


Downloaded from https://academic.oup.com/bja/article-abstract/74/2/217/452405 by guest on 17 June 2018


84. Ryan PA, Katz M. Skin testing and incremental challenge in the evaluation of adverse reactions to local anesthetics. *Journal of Allergy and Clinical Immunology* 1984; 74: 606-616.


