Allergy and Anaesthetics

Dr Peter Cooke

Department of Anaesthesia and Perioperative Medicine [Auckland Anaesthetic Allergy Clinic]
Auckland City Hospital, New Zealand

Allergic Disease and Anaesthesia

My talk reviews a range of allergic diseases and their anaesthetic implications.

Towards the end of the talk brief mention is made of two other topics.

- The recently released NAP 6 report
- The current controversy surrounding selection of the prophylactic antibiotic in patients with penicillin and or cephalosporin allergy

Introduction

The immune system is principally about defence of the body against invasion either from pathogens.

There are anatomical (intact skin for example) and physiological barriers. These defences are interlocked with other cellular and humoral elements that have been categorised as belonging either to the innate or the adaptive immune systems. Needless to say, these systems are interrelated.

The cellular elements in the innate system are derived from progenitor lymphoid tissue that includes macrophages, neutrophils, mast cells, natural killer cells and dendritic cells. Dendritic cells also become antigen presenting cells. These cell either phagocytise to destroy or produce chemicals such as cytokines that either destroy or help destroy invaders. Natural killer cells also control cells that have become altered such as cancer cells. The main humoral elements in the innate system are complement, mannose binding lectin, LPS binding protein, C reactive proteins and antimicrobial peptides. Lipopolysaccharide binding protein attaches itself to the bacterial cell wall and this facilitates destruction of the bacteria by monocytes. Macrophages and adipose tissues induce the release of C reactive protein (an acute phase protein) by the liver and this activates complement and binds to lysophosphatidylcholine expressed on dying cells and some bacteria. Mannose binding lectin recognises the carbohydrate pattern on many microbes, bacteria, viruses, protozoa and fungi and activates complement. Antimicrobial peptides have cell wall and cytoplasmic targets. Complement enhances or helps phagocytic cells, promotes the overall immune response and can also attack invaders directly.

The adaptive immune systems are comprised of cellular and humoral elements. The cellular elements T cells that confer specific cell mediated defense and the B cells produce antibodies that confer humoral specific defense.

The immune system can go wrong in at least three ways resulting in either an inability to protect, a misguided war on self or an overzealous reaction to foreign antigen. These malfunctions result in infection as a result of immunodeficiency, autoimmune disease or allergic disease respectively.

The most common allergic diseases are IgE mediated diseases. Plasma cells manufacture IgE to an allergen that is then distributed to mast cells and basophils. There is a strong genetic predisposition as well as environmental influences that result in allergic conditions. It is no surprise then that many of the diseases involve anatomical locations that in which mast cells are found.

For example in pollen induced rhinitis the pollen amount exceeds the mucosa's ability to remove it, and a small percentage of it gains entry to the sub mucosa. An interaction then occurs with a number of different types of antigen presenting cells that include macrophages, lymphocytes, monocytes and dendritic cells. The pollen antigen is then presented to circulating T cells that react with the antigen and transforms into an antigen specific T helper 2 cells. The T helper 2 cell then releases its signature cytokines that result in eosinophils production being increased

and mast cells being stimulated. The antigen specific T helper cell induces a class switching of B cells that now produce antibody to the pollen antigen that is redistributed to mast cells where it binds to high affinity receptors. The stage is now set for mast cell release by further antigen exposure. The mast cell releases preformed and newly generated substances and certain specific transcription processes take place that result in specific cytokine and chemokine releases. The symptoms of allergic rhinitis result.

T helper 2 cells are involved in IgE allergic disease as well as parasitic infections. T helper 1 cells are more involved with response to infection by bacterial pathogens. Some animal work suggest that general anesthesia may reduce Th-2 activity and recent study has shown that the incidence of allergic disease was reduced in a cohort of patients exposed to anaesthesia before the age of 1.

Food allergy
Reactions to food can be classified as either toxic or immune mediated or non-immune mediated.

The immune mediated ones can be broken down into the IgE and non-IgE mediated. Food protein induced entercolitis is the most common non-IgE related cell mediated allergy. Symptoms may be acute or chronic and mainly involve vomiting and dehydration. Some of these children may be seen referred as "an acute abdomen". IgE mediated food allergy is associated with dermatitis, asthma, allergic rhinitis. Milk, egg, soy, wheat usually start in childhood, and often resolve whereas peanut and tree nut allergy can develop at any point. Fish and shellfish allergy is more common in adulthood. Peanut and tree nut allergies account for 90% of fatalities from food allergy.

Obtaining and documenting the history of food allergy is important because patients need food and may otherwise inadvertently be offered the wrong food whilst in hospital. If the patient has had anaesthesia or sedatives, the patient's self-policing ability may be impaired. The occurrence of a food allergic episode prior to elective surgery might result in delay. Food allergy patients as mentioned above may have associated conditions such as asthma so these conditions need to be identified. There has been a case of cross contamination from anaesthetist to patient in a patient with peanut allergy who then developed a reaction. Many food allergy patients have an "Epipen". They are likely to bring it to hospital and we at least need to identify whether they have or not and work out whether they or the staff will administer adrenaline in case of a reaction.

There have been concerns about cross reactivity of certain anaesthetic drugs or substances cross reacting with food allergy patients. The most well-known and valid concern relates to kiwifruit, banana, avocado and chestnut allergy and all of these can be associated with latex allergy. Kiwifruit allergy patients are usually sensitive to birch pollen as well. There are 200 epitopes in Latex and similarities with the epitopes in the various fruits have been identified.

Anaesthetists have had concerns about egg, soy and peanut allergy being related to propofol allergy but the consensus is that the risk of allergy to propofol is no more that the populations risk in these patients. Seafood and shellfish allergy are not thought to be at risk of allergy to either radio-contrast media or povodine iodine but in patients with a definite and serious allergy to fish consideration should be given to protamine testing before its use.

Gelofusin is now not used so often but there is an association between red meal allergy and Gelofusin allergy with a number of cases. The patients were all positive for the specific IgE alpha gelatin.

Atopic dermatitis
The main features of this condition are pruritus and eczematous rashes. The dermatitis is chronic. It is associated with asthma, allergic rhinitis and food allergy. The condition is strongly hereditary but the traits are multifactorial. The barrier function of the skin is impaired and there is a general overexpression of T helper cell cytokines in this patient group. Patch testing is often positive for pollen and house dust mite. In addition there are hormonal, emotional, seasonal, dietary and climatic factors that contribute. There are diagnostic criteria where 3 of the major and 3 of the minor criteria are required in order to make the diagnosis. But In experienced hands diagnosis is straightforward. Recurrent conjunctivitis and keratoconus are two on the manifestations of atopia and the disease has a wide variety of expressions. The mainstay of treatment is topical corticosteroids. In severe cases systemic T-cell-suppressing therapies, such as azathioprine, methotrexate, mycophenolate mofetil and cyclosporine, are effective but limited by side effects. A new humanised monoclonal antibody, dupilumab, that targets interleukin-4

receptor alpha (IL-4R-alpha) is finding a place for severe cases with great improvements being described in very severe cases.

As anaesthetists we may have a role in ensuring that the skin condition and or related infection is under control prior to surgery. There is a risk of potential contamination of procedures such as an IV insertion from surrounding skin disease and a higher risk of staphylococcal infection. There is some evidence that atopic patients are more likely to have perioperative anaphylaxis in response to latex, propofol and ketamine exposure.

Urticaria

The medical condition urticaria is characterized by the development of wheals, angioedema or both. It is not urticaria caused by anaphylaxis, auto inflammatory syndromes, urticarial vasculitis or bradykinin mediated hereditary angioedema. The wheal in a patient with urticaria has 3 typical features: central swelling of variable size surrounded by erythema, itching and the fact that each individual wheal lasts a variable period of time, usually no longer than 24 hours. Angioedema in urticaria patients is a sudden swelling in the lower dermis, sub-cutis or mucous membranes, pain and a resolution that takes longer than the urticaria, typically up to 72 hours. Urticaria is regarded as acute if the rashes occur for less than six weeks and chronic if they continue to occur for a longer period. Urticaria can be classified as spontaneous or inducible and the inducible forms are induced by a number of different agents including cold, pressure, the sun, heat, water, and vibration. It is a mast cell driven disorder with release of histamine, platelet activating factor and cytokines.

Acute urticaria may have an underlying cause such as type 1 (IgE) food allergy, a response to NSAIDS or anaesthetic drugs. Morphine is a potent trigger of urticaria.

There are a number of similar looking but different disease conditions that need to be excluded and there may be underlying causes of chronic urticaria such as bacterial or fungal infection, H pylori infection. Underlying malignancy is not common. Diagnosis of the condition will require expert dermatology and immunology input, but not necessarily a raft of tests.

Treatment of chronic urticaria consists of avoidance of environmental triggers, in the case of inducible forms, reducing physical and emotional stress, and symptomatic pharmacological treatment. Second generation, non-sedating antihistamines such as loratadine and cetirizine are often used continuously for long periods, with little apparent risk of harm. Omalizumab which is a recombinant DNA-derived humanized IgG1k monoclonal antibody that specifically binds to free human (IgE) in the blood and interstitial fluid and to membrane-bound form of IgE (mIgE) on the surface of mIgE-expressing B lymphocytes. Cyclosporine reduces mast cell release but side effects limit its use. Montelukast a leukotriene inhibitor has been used in conjunction with antihistamines. Antihistamines may also be of value in preventing inducible urticaria prior to planned exposure to the inducing agent such as excercise of cold. Higher dose antihisamines have also been found to be helpful for some patients.

As anaesthetists we see urticaria in response to our medications. Antihistamines should be continued in cases of chronic urticaria and selection of medications with less propensity to produce urticaria may be helpful. Documentation of prior assessement by a dermatologist or allergologist would be valuable with a view to ensuring that treatment is optimised. Avoidance of physical factors that could induce urticaria in particular patients is important. This is particularly important in cases of urticaria that are associated with angioedema. Tranexamic acid and steroids are also helpful.

Allergic Rhinosinusitis

This is a common and costly condition, often associated with conjunctivitis and asthma with a prevalence approaching 40%. The nose acts as a barrier to inhaled particles so is an easy target for immunodysfunction.

Allergic rhinitis is a 2 type inflammatory disorder of the nasal mucosa and is IgE mediated. Dendritic cells located within the nasal mucosa capture the allergens and present them to T lymphocytes in the draining lymph nodes. This precipitates B cell switching, IgE to the allergen and distribtion to the mast cells. Eosinohils, CD4+T cells and basophils also are drawn to the submucosa in response to mast cell release. Important mediators are PGD2, LTC, leukotriene C4 and cytokines that include tumour necrosis factor alpha.

Symptoms of allergic rhinitis tend to build up over a period of prolonged exposure, a process known as priming. The major symptoms are nasal blockage, rhinorrhea, sneezing and itching, disturbed sleep, and reduced ability to learn and work. Many patients have identifiable allergies on skin prick or specific IgE testing, but in some the allergen is not identified.

Other causes of nasal congestion include preganancy, oral contraceptives, hypothyroidism and rhinitis medicamentosa. Unilateral nasal blockage may signal Wegeners granulomatosis, foreign body in the nose or deviated nasal septum.

Acute rhino-sinusitis is most frequently caused by infection with respiratory viruses, but some progress to bacterial infection. Chronic rhino-sinusitis, is most frequently an inflammation secondary to allergic rhinitis and the consequent blocking of the ostea to the sinuses with impairment of mucociliary clearance. The common symptoms of sinusitis are anosmia, facial pain and pressure.

There are a number of other variants including eosinophilic rhinosinisitis, allergic fungal sinusitis and aspirin-exacerbated disease. Nasal polyps form to a variable extent with these conditions.

Management includes avoidance of known allergens, saline douching, intranasal steroids and sodium cromoglycolate. The older steroids beclomethasone, budesonide have now been unsurpassed by new steroids, like fluticasone and mometasone, that are more potent but also more comprehensively metabolised by the liver minimising systemic effects. Oral antihistamines may be helpful. Antileukotienes are of 2 types, those that inhibit leukotriene formation and those that block the actions of leukotrienes. Nasal decongestants may be helpful - they work by reducing the swelling of the mucosa induced by vasodilation but they are safe for short term use. Systemic corticosteroids generally work well but their side effects prevent long term use. Some patients benefit from a desensitization programme.

Many anaesthetists are involved with the surgical management of these conditions and will have noted patients that these patients are frequently prescribed preoperative antibiotics and systemic steroids.

Because the nasal mucosa and sinuses have a rich capillary network, great emphasis is placed on vasoconstrictors intra-operatively and anaesthesia with a low to normal rather than higher blood pressure target. There is a literature on anaesthesia for nose and sinus surgery.

Nasal disease can contribute to OSA and patency of the nose. Should be part of every anaesthetic assessment?

Asthma

Asthma has been defined as a disorder of variable intensity, typified by sentinel symptoms, airway obstruction, inflammation and hyper-responsiveness. The primary symptoms of asthma are shortness of breath, wheeze, cough, increased sputum production and chest pain.

A recent report suggests that the term asthma should be viewed more as an overall descriptive term of the various pulmonary conditions, rather like arthritis is an overarching term that covers a variety of conditions.

This suggested approach incorporates many diseases such as emphysema, chronic bronchitis and allergic asthma under one umbrella and challenges us to think carefully about the symptoms, traits or characteristics that our individual asthma patient in front of us manifests. There are also many new bronchodilator medications, long and short acting, and many possibilities for combinations of these. Only some of our patients will benefit from bronchodilators or inhaled steroids. Patients may have other comorbidities for example asthma that impacts on respiratory function; others may have laryngeal dysfunction or remodeled restrictive bronchi with no reversibility. The Lancet commission paper is not directed at anesthetists but the thinking therein is likely to impact our practice in the future. It suggests new methods to identify patients at significant risk of severe attacks and many new diagnostic approaches.

Allergic asthma for example is characterized by eosinophilic disease that can be detected by airway sampling or in the blood. Whether or not there is bronchial smooth muscle reactivity and response to bronchodilator is also important.

How good are we at assessing our patient's asthma control prior to surgery? A useful online patient questionnaire is presented.

On average asthma patients present few problems intra-operatively but when problems arise they can be severe. Severe bronchospasm may be a manifestation of anaphylaxis, but it may also be a manifestation of asthma. Various treatments algorithms for severe bronchospasm are discussed.

Mastocytosis

This is a mast cell disorder associated with an increase in the number of mast cells and abnormality of c-kit trans-membrane mast cell wall protein in 50 to 90% of cases. This abnormality is a result of a mutation that can be identified. Mastocytosis is a heterogeneous group of disorders but can be categorized as either systemic or cutaneous depending on whether the excess mast cells are mainly in skin or internal organs. The cutaneous form presents often in childhood, the systemic in adulthood.

The majority of these patients are identified as a result of their skin disorder but others present with symptoms relating to mast cell release and occasionally with perioperative anaphylaxis. In mastocytosis there is a propensity for mast cell mediators to be released more readily usually without any requirement for IgE mediated triggered release. The mast cell tryptase is frequently chronically elevated. Release of mast cells can be triggered by stress, mechanical trauma such as a tourniquet, cold stress and drugs that are known to cause dose related mast cell release especially mivacurium and atracurium. Many other drugs have been implicated in reactions including morphine, pethidine, nefopam, NSAIDs and radio-contrast media, so a cautious approach is recommended.

Severe cutaneous reactions

These are reactions that anaesthetists need to be aware of in a patient's history in order to ensure that the culprit drugs are not re-administered. **DRESS syndrome** is short for Drug Reaction with Eosinophila with Systemic Symptoms. It occurs typically 6-8 weeks after exposure and the symptoms include fever, an itchy morbilliform rash, enlarged and sometimes painful lymph nodes and other symptoms due to variable internal organ involvement. Allopurinol, sulfasalazine and minocycline are the most frequent culprit drugs but it can occur after diclofenac, celecoxib or ibuprofen. It has a 10% mortality. It is a cell mediated type 4 (sub type 4b) reaction. It is T cell mediated but eosinophils play a large part in the reaction. There is a genetic predisposition and is more common in South East Asia.

Stevens Johnson syndrome and **toxic epidermal necrolysis** form a spectrum of disease with SJS being less severe. Early symptoms of SJS include fever and flu-like symptoms. A few days later the skin begins to blister and peel forming painful raw areas. Mucous membranes such as the mouth, are involved. Complications include dehydration, sepsis pneumonia and multiple organ failure. SJS and TEN most often begin between 4 and 28 days after culprit drug administration with a long list of possible drugs. The ones that anaesthetists might administer include: vancomycin, diclofenac, penicillins, valedecoxib, ibuprofen, sulphonamides and paracetamol. Other causes are viral or fungal infections. The reaction is a cell mediated, type 4 (sub type 4c), one that involves natural killer cell attack on self.

Acute generalized exanthematous pustulosis is a rare type 4 (sub type d) cell mediated skin reaction that in 90% of cases is related to medication administration. Skin eruptions occur five days after a medication is started. These eruptions are small white or red elevations of the skin that contain pus. The skin lesions usually resolve within 1–3 days of stopping the offending medication but more severe cases are associated with a more persistent disorder that may be complicated by secondary skin infections and involvement of the liver, lung and kidney. A range of drugs have been implicated but mainly antibiotics, including cephalosporins, and anti-inflammatory medication. AGEP is a type 4 d reaction, (T cell mediated) that then stimulates neutrophils to attack self-tissues.

References

1. https://www.nationalauditprojects.org.uk/NAP6home
2. Holgate S, Church M, Broide David and Martinez F et al Allergy Elsevier (2012)
3. Kuo H, et al General anaesthesia exposure in early life reduces the risk of allergic disease Medicine (2016) 95:28(e4269)
4. Fernandez P, Mikheal M, Perioperative considerations for the food allergic paediatric patient Paediatric Anaesthesia 27 (2017) 461-470
5. Allergic reaction bovine gelatin colloid Bahktiar M et al Internal Medicine Journal (2017) 47 Supplement 5 p 23
6. Dewachter P Multiple drug allergies are all drug allergies the same Current Opinion in Anaesthesiology (2011) 24:320–325
7. Leung D, et al New Insights into atopic dermatitis Science in Medicine 2004
8. Hanifin, J.M. and Rajka, G.: Diagnostic features of atopic dermatitis. Acta Derm Venereol Suppl (Stockh) 1980; 92: 44–47 Atopic Dermatitis: Five Promising Targeted Therapies
9. Graeme M. Lipper, MD June 26, 2018 Medscape Caffarelli C, Perioperative Allergy: Risk Factors International Journal of Immunopathology and Pharmacology vol 24 S pp 27-34 2011
10. EAACI guidelines for the definition, classification, diagnosis and management of urticaria. Allergy 2018 73 : 1393-1414
11. Peri-operative management of a patient with cold urticaria Agbenyefia P et al Frontiers in Medicine 18 December 2017 4: article 222 Journal of Immunopathology and Pharmacology 2011 vol 34 3 S 83-90
12. Systematic Review and metanalysis of total intravenous anesthesia and endoscopic sinus surgery De Conde A et al Allergy and Rhinology 2013
13. Woods B, Sladen R, Perioperative Considerations for the patient with asthma and bronchospasm BJA/PGA supplement: i57-i65 (2009)
14. Lancet Commission report "After asthma redefining airways disease" www.thelancet.com vol 391 January 27 2018
15. Dewachter P, Moutin-Faivre C, Emala C, Beloucif S. Anesthesiology 5(2011) 1200-1210 Case scenario: Bronchospasm during Anaesthetic Induction