CHAPTER 2

LITERATURE REVIEW

Exogenous antibody can be used as passive immunization when effective active immunization is unavailable to a high risk group or when establishment or progression of disease may occur before active immunizatio n can elicit an endogenous antibody response (e.g., hepatitis B, tetanus, rabies) (5,31).

Immunoglobulin preparations containing high antibody titers specific for certain agents or toxin are obtanied from sera of convalescent or specifically immunized human donors. Currently avialable examples include hepatitis B, pertussis, rabies, tetanus, vaccinia, varicella-zoster, and Rho (D) immune globulins. Animal sera are also used as a source of specific immunoglobulin. These are in general less satisfactory because of the shorter in vivo half life of the antibody and the markedly greater risk of iatrogenic disease resulting from the host's immune response to the foreign proteins (3,4,31). Examples of the currently avaible equine hyperimmune globulins are antisera used in treating black widow spider bites, snake bites, diphtheria, botulism, gas gangrene and rabies (1,2,3,19).

The adverse effects associated with immunoglobulin administration can also result from the host's own immune response to the exogenous proteins. These problems are much more common with immunoglobulins or sera of animal origin (1,2,3). The archetypal consequence of administration of large amount of foreign protein are serum sickness and anaphylaxis (5).

Serum Sickness

Serum sickness is the clinical syndrome derived from the injection of heterologous or foreign proteins or serum (1). The first detailed description of human serum sickness was presented by Von Pirquet and Bela Schick in 1905. The studies of Germuth and Dixon et al. found that both clinical and experimental serum sickness are related to the antibody response to the administered heterologous proteins, resulting in immune complex formation and deposition (2,33,34). Serum sickness-like reactions that are clinically indistinguishable from the classical serum sickness,can occur after the administration of nonprotein drugs (3). The most common drugs are penicillin, sulfa, thiouracils, cholecystographic dyes, hydantoins, aminosalicylic acid and streptomycin (14).

In addition, serum sickness-like reactions can occur after or in conjunction with various diseases (such

as malaria, typhoid, hepatitis B) and neoplasms (such as lymphoma, renal cell carcinoma) (2).

Incidence and etiologic agents

True serum sickness reaction in man is now considerably less common than in the past because of the adequate immunization coverage, the development of effective antibiotic therapy and the replacement by specific human immune globulin (3,15). Moreover, technical refinements in the manufacturing process of equine hyperimmune globulins have eliminated unnecessary but potentially harmful proteins, components of proteins and aggregated proteins (35). With some antisera, further reduction of the risk of serum sickness can be accomplished by the use of (Fab)'2 preparations, eliminating the highly immunogenic areas on the Fc portion of the gamma globulin molecules (15).

The incidence and severity of reactions are directly related to the volume of foreign serum administered and the type of serum employed (1,3,13,17, 36,37,38). Heterologous serum is still occasionally used in the treatment and prophylaxis of rabies, venomous bites, botulism, gas gangrene and diphtheria (3,4,15,39). At present, heterologous antilymphocyte globulin which is used for the prophylaxis and

treatment of allograft rejection is another potential source of serum sickness (40,41,42,43,44).

The incidence of serum sickness-like reactions resulting from nonprotein drugs is more difficult to ascertain (1). It was estimated that 5% of medical hospital admissions were due to drug reactions and at least 15% of hospitalized patients had at least one adverse drug reaction (15).

Pathogenesis

The studies on "one-shot" serum sickness in rabbits by Germuth and Dixon clarified the pathogenesis of human disease to which it appears to be similar immunologically (16,33,34). When a large dose of protein antigen is introduced (5), IgM and IgG antibody responses are elicited after a latent period of four to ten days, lead into formation of soluble immune complexes that deposit on vascular endothelium in various organs where they may initiate fixation and activation of complement (1,3,16,45,46,47,48,49,50,51,52). Activation of complement via the classic pathway generates chemotactic factors that localize inflammatory cells in and around blood vessels where the proteolytic enzymes released from their lysosomal granules can mediate tissue damage (1).

Failure of mononuclear phagocytes to effectively clear immune complexes is probably an important factor in disease expression because the complexes remain in circulation for a longer period of time (1,35). Animal experimental data suggest that IgE-dependent release of vasoactive amines may facilitate deposition of soluble immune complexes at vascular walls (1,3,53,54,55,56). Complement activation by immune complexes can result in the formation of anaphylatoxins, substances that are capable of stimulating mast cells to release histamine and other mediators, even in the absence of IgE. Mast all mediators further result in increased vasopermeability that allows for immune complex deposition in the vascular walls (2).

Neutrophils play a major role in the vasculitis observed in serum sickness by releasing proteolytic substances that promote vessel destruction. Netrophils are reruited to the sites of inflammation through chemotactic factors derived from complement activation, and through specific receptors on immune complexes (2). Monocytes and macrophages may play a role in the glomerulonephritis of animal serum sickness, however, this mechanism has not been demonstrated in humans (1,2,57,58).

Clinical manifestations

The classic serum sickness reactions after injection of heterologous serum consist of fever, cutaneous eruptions, lymphadenopathy and joint symptoms (1). Some would insist that at least two or three of these symptoms be present before the diagnosis is made (3).

Primary serum sickness occurs 6 to 21 days (typically 7 to 14 days) after the administration of the causative agent. The initial dose of antigen serves both to sensitize and then to elicit the symptoms. The latent period reflects the time required to synthesize appropriate quantities of antibodies (3). The onset of the disease is often heralded by pain, pruritus and erythematous swelling at the injection site. This is a valuable diagnostic finding (1,3,15). Skin eruptions occur in 90% of patients and often are the earliest manifestations (3). Urticaria is particularly common and usually lasts only 2 to 3 days but is often supersed by a generalized erythematous maculopapular rash (15). A diagnosis of this syndrome without a skin eruption must be questioned (1).

Fever is usually slight to moderate, but may be considerable in more severe cases (3). Lymphadenopathy is another very common clinical manifestation of serum

sickness and may initially be localized near the size of the offending antigen injection and then may become generalized (2). Arthritis and arthralgia occur in 10 to 50 percent of patients (1). Diffuse facial edema or angioedema may occur (2). Renal involvement may be reflected by proteinuria and microscopic hematuria. Significant renal disease usually does not develop (15).

Although less common, neurologic manifestations can occur and may present as peripheral, plexus or cranial nerve involvement (2). A rare, but very serious sequelae of serum sickness is the development of the Guillain-Barre syndrome (1).

Accelerated serum sickness develops within a short time (usually 2 to 4 days) following administration of the agent, indicating prior sensitization of the host (3). These reactions may be more severe than primary serum sickness, but are basically similar in nature (15).

Laboratory findings

Laboratory findings in serum sickness include an elevated erythrocyte sedimentation rate, variable changes in leukocyte count with either slight leukopenia or leukocytosis with or without eosinophilia (15). Hyper gamma globulinemia with free circulating light chains and

plasmacytosis may be present (3,16). Urinalysis may reveal slight proteinuria and/or microscopic hematuria in addition to an occasional cast (1). Serum complement levels may be reduced, providing some evidence that an immune complex mechanism is operative (3). Elevation of complement activation products such as C3a has been documented (2). Assay for circulating immune complexes may be positive (18,23,24,52). Electrocardiographic abnormalities may occur Cryoglobulins and rheumatoid factor are sometimes observed (2).

Forssman antibodies may be detected and can be distinguished from heterophil antibody observed in infectious mononucleosis by absorption with guinea pig tissue (3,15). Hemagglutinating antibodies to horse serum can be demonstrated (59). Precipitating IgG antibodies are found less consistently, but may be present in more severe cases (3). IgE antibodies to horse serum and horse danders are frequently present, and may be detected by skin tests (60).

Diagnosis

The classic clinical manifestations within the appropriate time frame following exposure to heterologous proteins or nonprotein drugs make the diagnosis of serum sickness rather obvious. There is no specific diagnostic

laboratory tests for serum sickness. However, the demonstration of IgG antibody to offending antigen in some patients where this is feasible helps confirm the diagnosis (15).

The signs and symptoms of serum sickness or serum sickness-like reactions may be similar to other inflammatory or infectious diseases such as rheumatic fever, SLE, rheumatoid arthritis (2). Persistence of symptoms for longer than one month militates strongly aganist the diagnosis of serum sickness (15).

Treatment and Prevention

Most cases of serum sickness or serum sickness-like reactions are mild and usually spontaneously resolve within a few days to weeks. Initial treatment should discontinue the suspected antigen. Antihistamines and aspirin will be given for pruritis and arthralgias (1,2,15). Antihistamines may reduce the incidence of serum sickness perhaps by negating the action of vasoactive amines, and consequently preventing the increased vascular permeability so the deposition of circulating immune complexes may be minimized (1,2). In more severe cases, corticosteroids should be administered and tapered over a 10 to 14 day period because of the frequency of symptomatic relapse during drug withdrawal

when shorter course is used and it may be more difficult to alleviate the recurrent symptoms (15).

Prevention of serum sickness reactions can be accomplished by avoiding the use of foreign proteins and not readministering the drug to patients with a history of an adverse reaction to the drug. Assuring that appropriate primary immunization is accomplished and employing specific human immune globulins when indicated will also reduce the occurence of this illness (1).

The most serious adverse effect of heterologous immune globulin administration is anaphylaxis (31).

Anaphylaxis

Anaphylaxis is a manifestation of immediate (Gell and Coomb type I) hypersensitivity. It is an immunologic tissue injury mediated by IgE antibodies which occurs within minutes after the interaction of antigen and the basophil or mast cell bound IgE antibodies (6,61). The reaction may be local or systemic (6,7,8,9,10).

Systemic anaphylaxis is a serious and life-threatening allergic reaction (7). It occurs as a result of the sudden release of mediators from mast cells and/or basophils into circulation affecting several organ systems simultaneously (8).

Local anaphylaxis may occur in any specific target organs such as the gastrointestinal tract, nasal mucosa or skin manifested as gastrointestinal symptoms, rhinitis or urticaria respectively (6,61).

Mechanism of anaphylaxis

Human anaphylaxis is most frequently mediated through IgE antibodies whose Fc region can specifically bind to the receptors on mast cells or bosophils (7,9). Human IgG_4 also binds to the mast cell receptors but more weakly and disperses from the injection site within a day whereas IgE antibodies can be detected for several weeks after injection into the skin (62). These antibodies (IgE and IgG_4 are termed homocytotropic antibodies) also referred previously as reagins (9).

Degranulation of the mast cell occurs when bound homocytotropic antibodies are cross-linked either by specific antigen or by the corresponding divalent anti-immunoglobulin (e.g. anti-IgE or anti-light chain) but univalent (Fab) anti IgE is inactive (9,62,63). This bridging brings together 2 IgE receptor molecules which triggers an enzymatic cascade at the cell surface leading to an influx of calcium ions and changes in cyclic nucleotide levels. A fall in cAMP or a rise in cGMP favours degranulation of mast cell resulting in release

of histamine, serotonin and different chemotactic factors of anaphylaxis (6,9,61,64). In addition to degranulation, a rapid sequential oxidative metabolism of arachidonic acid occurs resulting in synthesis of several other pharmacologically active mediators, including leukotrienes, prostaglandins, and platelet aggregating factor (64,65,66).

The effects of these phamacological mediators are summarized in Table 1 and Table 2 (8).

Allergens

Allergens are the antigens that give rise to allergic sensitization of the IgE antibody class. Their molecular weights appear to be restricted in the range of 10,000 - 70,000 (6). The most frequent cause of anaphylaxis is penicillin and the synthetic penicillin derivatives. In the past, this role was played by heterologous antisera used for prophylaxis and treatment of tetanus, diphtheria, rabies, botulism and snake bites. Insulin, ACTH and enzymes are other significant causes of anaphylaxis (7,67). The common causes of IgE-mediated anaphylaxis are summarized in Table 3 (8).

Pathophysiology of anaphylaxis and anaphylactoid reactions

Anaphylaxis is IgE-mediated reaction whereas anaphylactoid reactions are non-IgE-mediated reactions

clinically mimicking anaphylaxis. Both can activate mast cells and basophils, resulting in the same clinical syndrome. Thus, the distinction between anaphylaxis and anaphylactoid reactions has little clinical meaning, because the clinical presentation and treatment are identical. (7,8)

The primary manifestations of anaphylaxis occur in areas where mast cell concentrations are highest, such as the skin, lungs, and gastrointestinal tract. Therefore, urticaria, airway edema, vascular collapse, asthma, abdominal pain and diarrhea are common clinical signs and symptoms (8).

Clinical manifestations

Anaphlaxis may affect multiple organ systems or be confined to one organ system such as skin. Anaphylactic reactions are commonly preceded by a breif prodrome of nasal, ocular, and genital itching or burning. The first sign is usually a generalized flush, which may progress to urticaria and angioedema. Upper airway obstruction causes inspiratory stridor, hoarseness and dysphagia. Lower airway obstruction is experienced as chest tightness,noted as wheezing and can develop into severe, acute asthma. Airway obstruction is usually associated with hypoxaemia. (7,8)

Cadiovascular collapse and shock result from severe hypovolemia secondary to postcapillary venular leakage and myocardial depression, complicated by cardiac arrhythmias. (8)

Nausea, vomiting, abdominal cramp and diarrhoea are of less clinical importance. (7)

The anaphylactic syndrome usually begins within 10 to 20 minutes after allergen exposure and, as already mentioned, may vary from mild pruritus to irreversible shock or fatal pulmonary insufficiency. Fatalities are rare and in most instances sudden. (8)

Prevention and treatment

A negative history of a previous untoward reaction offers no guarantee that administration of a pharmaceutical agent will not produce anaphylaxis. Subclinical sensitization may result from a previous uneventful clinical exposure, for example, from the presence of the material in food such as penicillin or from contact with a cross-reacting antigen (10,68). A skin test should be performed before the administration of certain materials procucing a high incidence of anaphylaxis, such as horse serum or allergenic extract, or when the nature of a past adverse reaction is unclear (68). If there is a definite

history of a past anaphylactic reaction, even though mild, it is advisable to select another agent or procedure. In the event that an agent is to be used despite a positive history, a positive skin test, or both, the precautionary measures should include the presence of an intravenous infusion line, intubation equipment, and a tracheostomy set (10).

Rapid diagnosis and immediate initiation of therapy are essential, begining with removal or diminution of the suspected allergen. Epinephrine and othe necessary medications should be administered promptly such as intravenous fluid, vasopressors, antihistamines,etc. (7,8,10,69).

Table 1. Stored mediators of anaphylaxis

Mediator	Effector Cells	Effects
Histamine (low-molecular-weight amine)	Tissue mast cell, basophils	Dilates capillaries and venules, increases vascular permeability, and constricts nonvascular smooth muscle; causes urticaria, angioedema, hypotension, bronchospasm, and coronary vasoconstriction
ECF-A (preformed acidic tetrapeptide)	Mast cells	Chemotactic for eosinophils
NCF-A (high-molecular-weight substance found in serum during induced allergic reactions)	Mast cells, basophils	Chemotactic for neutrophils
Proteolytic enzymes (potent proteases)	Mast cells, basophils	Generate kinins, initiate intravascular coagulation, and activate complement cascade
Heparin (predominant proteoglycan in connective tissue mast cells) (associated with granule matrix)	Mast Cells	Anticoagulant; can cause urticaria, fever, chills, and occasionally bronchospasm

ECF-A, eosinophil chemotactic factor of anaphylaxis; NCF-A chemotactic factor of anaphylaxis.

Table 2. Generated mediators of anaphylaxis

Mediator	Effector cells	Effects
Prostaglandin D2 (major product of cyclooxygenase pathway of arachidonic acid catabolism)	Mast cells	Causes bronchoconstriction, increased capillary permeability, pulmonary hypertension, and peripheral vasodilation
Leukotrienes (LTB_4, LTC_4*, LTD_4*, LTE_4*) (products of lipoxygenase pathway of arachidonic acid metabolism)	Mast cells, neutrophils	Most potent bronchoconstrictors; cause cutaneous inflammation; LTB_4 chemotactic for neutrophils; LTD_4 causes coronary vasoconstriction
Platelet-activating factor	Mast cells, basophils, macrophages, polymorphonuclear cells	Causes local aggregation and degranulation of platelets, reduction of coronary flow, and negative inotropic effect

*Formerly called slow-reacting substance of anaphylaxis (SRS-A)

Table 3. Common causes of IgE-mediated anaphylaxis

Protein drugs (hormones,presumably complete antigens)

Insulin

ACTH

Relaxin

Estradiol

Vasopressin (Pitressin)

Parathyroid hormone

Nonprotein drugs (presumably haptens)

Antibiotics

Penicillin

Tetracycline

Nitrofurantoin (Furasantin,Macrodantin)

Streptomycin

Sulfonamides

Vatamins

Thiamine

Folic acid

Vaccines (allergy probably caused by cultivating tissue)

Pertussis

Typhoid

Vaccines grown on egg embryo

Venoms

Honeybee

Fire ant

Wasp

Deerfly

Snake

Foreign protein agents

Tetanus and diphtheria antitoxins

Gamma globulin

Antilymphocyte globulin

Venom antitoxin

Seminal plasma

Enzymes

Chymotrypsin

Trypsin

Penicillinase

Allergen extracts

Pollens (ragweed,June grass,Bermuda grass)

Molds

Epidermals (cat,dog,horse,bird)

Foods (cottonseed, egg white)

Foods

Milk

Egg white

Shellfish

Legumes (especially peanuts)

Nuts

Citrus fruits

Bananas

Grains

Chocolate

Fish

Cottonseed

Others

Chemicals

Ethylene oxide gas

Formaldehyde

Parasites

Hydatid cyst rupture