DGAFMS MEDICAL MEMORANDUM
NO. 24

ALLERGIC MANIFESTATIONS FOLLOWING DRUG AND SERUM THERAPY

REVISED

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INTRODUCTION

1. The plethora of pharmacological agents in current use mandates a basic knowledge of the allergic reactions they cause. Serum therapy refers to administration of antisera containing antibodies to create passive immunity in diseases such as tetanus, rabies, diphtheria, gas gangrene and botulinism. Similar therapy is afforded by antivenin sera in snake bite. The latter are foreign proteins capable of producing anaphylaxis and serum sickness, more so if there has been prior exposure to the foreign protein.

2. The designation "drug allergy"(DA) should be reserved for adverse drug reactions caused only by immunological mechanisms. Although drug allergies are responsible for only a minority of adverse drug effects the possibility of such reactions is a daily concern of most physicians. DA has a great variety of chemical manifestations and has been attributed to most categories of therapeutic agents.

3. Certain terminologies are used loosely in connection with DA. Idiosyncratic reactions is not a form of DA. It is defined as a genetically determined abnormal reactivity to a chemical leading to a response, which is qualitatively similar in all individuals. Example is G6-PD deficiency and primaquin induced haemolytic anaemia. Anaphylactoid reactions are not immunologically mediated unlike anaphylaxis though the clinical manifestation and treatment for both is similar.

EPIDEMIOLOGY

4. An estimated 5% of adult patients have at least one drug allergy while many more incorrectly believe they have a DA. 10 to 14% of all untoward drug reactions have an allergic basis. DA is more common following multiple exposures to a drug. It is less common at the extremes of age, a reflection of fewer sensitising exposures in the very young and a decline in

immune responsiveness in the very old. Risk factors for DA are complex and include inherent differences in drug metabolism and immunologic reactivity. Topical application of drugs is associated with a higher risk of sensitisation and a topic patients may have more severe reactions.

PATHOGENESIS

5. The process of immunological sensitisation to drugs is complex and poorly understood for most drugs. To be an effective immunogen a drug must have a molecular weight greater than 4000 or for polypeptides, have at least seven amino acids. Large molecular weight agents such as antisera, vaccines and hormones are all potentially immunogenic. However, most other drugs are much smaller molecules and act as haptens to covalently combine with endogenous carrier protein to form a hapten-carrier complex, which is immunogenic. Carrier proteins may be free in the plasma; intracellular or incorporated into cell surface membranes. The hapten density on the carrier protein determines the strength of the immune response, which can be directed against the haptenated drug itself or a tissue protein conformationally changed by binding of hapten. Covalent binding of hapten to the carrier protein is necessary for it to be immunogenic. Most of the drugs on the contrary are reversibly bound to the carrier protein.

6. All categories of immunological hypersensitivity described by Gell and Coombs, have been implicated in DA (table I). The mechanism of many presumed allergic reactions is still unknown. Pseudoallergic reactions clinically resemble an allergic response but are not immunologically mediated. Histamine is released from the mast cells and basophils by inflammatory mediators and activation of the contact coagulation system and complement. Examples of pseudoallergic reactions are aspirin induced asthma, anaphylactoid reactions to radiographic contrast media and angioedema attributed to ACE inhibitors.

Table I : Classification of Immunopathological reactions

Gell and Coombs type	Description	Mechanism	Clinical Examples
I	Anaphylaxis (Reaginic allergy)	IgE mediated	Anaphylaxis Urticaria Extrinsic asthma
II	Cytolysis	IgG and IgM, complement mediated	Interstitial nephritis Cytopaenias
III	Immune complex	IgG complement mediated inflammatory response initiated by soluble antigen antibody complex.	Serum sickness Drug fever
IV	Delayed or Cellular hypersensitivity	Sensitised small lymphocytes and macrophages	Tuberculosis hypersensitivity Contact dermatitis.

CLASSIFICATION

7. Clinically DA can be classified into generalized and organ specific (Table 2). The common manifestations include urticaria, exanthems, contact dermatitis, drug fever and eosinophilia . The drugs, which frequently casuse DA are enumerated in Table 3.

Table 2 : Clinical manifestations of Drug Allergy

1. <u>Generalized</u>

Anaphylaxis
Serum sickness
Drug fever
Vasculitis
Drug-induced systemic lupus erythematosus

2. <u>Organ specific</u>

(a) Cutaneous

Urticaria, angioedema, hypersensitivity vasculitis, toxic epidermal necrolysis, Stevens-Johnson syndrome

(b) Renal

Acute interstitial nephritis, glomerulonephritis

(c) Pulmonary

Asthma, acute infiltrates

(d) Haematologic

Haemolytic anaemia, granulocytopenia, thrombocytopenia, eosinophilia

(e) Hepatic

Cholestatic hepatitis, hepatocellular damage

Table 3 : Drugs Frequently Causing Allergic and Pseudoallergic Reactions

Antimicrobials Beta-lactams Sulphonamides Nitrofurantoin Antituberculous drugs
Anticonvulsants Phenytoin Carbamazepine Barbiturates
Cardiovascular agents Procainamide Hydralazine Quinidine Methyldopa ACE inhibitors
Macromolecules Heterologous antisera Enzymes Hormones
Anti-inflammatory agents Aspirin Other nonsteroidal anti-inflammatory drugs Gold Salts Penicillamine
Antineoplastic agents Azathioprine Procarbazine Asparaginase Cis-platinum
Others Allopurinol Radiographic contrast media Opiates Sulphasalazine Neuromuscular blocking drugs Antithyroid drug

8. Anaphylaxis (immediate or Type I hypersensitivity) is typically noted 1 to 30 minutes following exposure to drugs like antisera, amphotericin, penicillin and local anaesthetic like procaine. A generalized flush with tingling sensation followed by a "feeling of impending doom" can proceed to life threatening airway compromise (upper airway obstruction, bronchospasm, angioneurotic edema) and circulatory collapse. It is a medical emergency, which can be fatal within minutes. Prompt administration of injection adrenaline with other supportive measures helps reverse this condition (for details see treatment).

9. Cytolytic reactions (Type II hypersensitivity). The target issue here is the blood cells. Penicillin and cephalosporin can induce coombs positive haemolytic anaemia; quinidine, quinine and rifampicin can induce thrombocytopaenic purpura; sulphonamide induced granulocytopaenia and drug induced systemic lupus erythematosis by procainamide and hydralazine. These reactions reverse within weeks to months of drug withdrawal.

10. Serum sickness ("Arthus" reaction or Type III hypersensitivity). Noted commonly following therapy with Beta-lactam antibiotics, antisera, antilymphocytic globulin and sulphonamides. Fever, urticaria, skin rash, lymphadenopathy and polyarthritis, often in this order constitute the common presentation. Less frequently splenomegaly, myocarditis, leucopaenia and mental changes can occur. Serum sickness appears 6 to 12 days after drug exposure and disappears within two weeks of elimination of the offending agent. Steven – Johnson syndrome is a more severe form associated with sulphonamide therapy and is characterised by erythema multiforme, arthritis, hepatitis, CNS abnormalities and myocarditis.

11. Local hypersensitivity at site of drug administration and thermal reactions are common but not alarming. They respond to local measures and symptomatic therapy.

DIAGNOSIS

12. It takes 7-10 days for allergic manifestations to appear. A more rapid onset suggests prior sensitization (often inadvertent with no

historical record), cross reactivity (e.g. penicillin and cepholsporins) or pseudoallergy. The reaction does not appear to be dose dependent or suggestive of a toxic effect of the drug.

13. The reaction has characteristics of a hypersensitivity response in form of skin rash, fever and eosinophilia. Clinical improvement is evident within 48 to 72 hours of drug withdrawal.

14. Specific tests to evaluate DA include skin tests, measurement of serum antibody levels and challenge administration of the offending drug. Challenge tests, however, are inherently dangerous and should be avoided especially when there is possibility of anaphylaxis.

PREVENTION

15. A careful history should review possible sensitivity to the type of protein being injected. A complete record of previous "serum" injections of any type and allergic manifestations, if any in the the patient should be documented. Administer animal serums with caution even in individuals with a negative sensitivity test.

16. **SKIN TESTS** can predict a type I hypersensitivity response to some drugs and is done routinely before administering penicillin and heterologous antisera. It is important to simultaneously do a control test using normal saline at a comparable site. False positive reactions due to nonspecific skin irritation can occur and doing a control test makes interpretation more reliable.

[a] **Scratch test** is done prior to the intradermal test. Make a ¼ inch skin scratch through a 1:100 dilution in normal saline of the drug on the volar surface of the forearm or lateral surface of the upper part of the arm. Use a 26 G sterile needle to do the scratch test. To serve as a control, make a similar scratch through a drop of normal saline on a different but comparable skin site. After 20 minutes compare the two sites. A positive scratch test consists of an urticarial wheal with or without pseudopods, surrounded by a halo of erythema. A negative test should occur at the control site.

[b] **Intradermal test** is done only if scratch test is negative. Inject 0.02 ml of a 1:100 saline diluted antisera intradermally. Inject a separate but comparable skin site with normal saline to serve as a control. After

15 to 30 minutes compare the two sites. A positive test consists of an urticaria wheal, with or without pseudopods, surrounded by a halo of erythema. A negative test should occur at the control site.

[c] **Conjuctival test** ("eye" test) has been used to test for allergy to heterologous antisera. Instil a drop of 1:10 saline diluted serum into the conjuctival sac of one eye and a drop of normal saline into the other eye. A positive reaction consists of itching, burning, redness and lacrimation appearing within 10 to 30 minutes; these symptoms can be relieved by instilling a drop of adrenalin solution. The control eye should remain normal.

CAUTION:- A syringe loaded with 2 ml of 1:1000 adrenalin B.P is to be kept ready at hand whenever any of the above tests are conducted. Concomitant use of antihistaminics may interfere with the sensitivity tests, hence should be avoided.

DESENSITISATION

17. Desensitisation can be carried out when administration of the drug is imperative despite a positive skin test e.g. antisera in diphtheria and tetanus; and antisnake-venins in poisonous snakebites. It is done by giving repeated injections of small amounts of the serum every 15 minutes starting with 0.1 ml of 1:100 saline diluted antisera subcutaneous and doubling the amount with each dose till 1 ml has been given, provided no reaction is noted. If a reaction occurs wait for an hour and then repeat the last dose, which failed to cause a reaction. Mechanism of desensitisation is uncertain but gradual neutralisation of IgE antibody with repeated low doses of the drug (antigen) is a possible mechanism. This procedure can result in severe allergic reaction including anaphylaxis hence is best done in the ICU setting with full back up for vetilatory and circulatory support by skilled personnel familiar with management of acute anaphylaxis. A informed consent from the patient or next of kin is taken prior to the procedure.

TREATMENT

18. **ANAPHYLAXIS** is medical emergency and can be fatal. It mandates an immediate and prompt treatment.

[a] **Injection adrenaline B.P** (Epinephrine) 1:1000 is the **FIRST** drug to be administered in a dose of 0.2 to 0.5 ml subcutaneously, when

there is no hypotension.(In children 0.01 ml / Kg body weight). Additionally 0.1 ml can be injected into the site where the offending drug was injected. The use of a tourniquet above the site of injection may slow its absorption and distribution. However, the tourniquet pressure should be appropriate (occlude venous pressure) and it should be released every 10 to 15 minutes to maintain circulation.

[b] Injection adrenaline B.P is given intravenously if there is hypotension. Dose of 0.3 to 0.5 ml of a 1:10,000 dilution (1 ml of 1:1000 + 9 ml normal saline) is given over 5 minutes and repeated every 15 minutes till a response is noted.

[c] Injection adrenaline B.P 1:10,000 dilution could be delivered as an aerosol through an endotracheal tube when no venous access is available in peripheral circulatory collapse. The drug is readily absorbed from the capillary bed of the lung.

[d] Ensure a patent airway in the patient. This is achieved by endotracheal intubation or tracheostomy if needed. Bronchospasm is treated with salbutamol nebulisation and intravenous deriphylline (220 mg in 20 ml 5% dextrose over 10 minutes).

[e] Oxygen 5 to 6 litres per minute using a mask or nasal prongs.

[f] Hypotension if present indicates the severity of the reaction and should be energetically treated with intravenous fluids (normal saline/ringer lactate), vasopressor support using drugs like dopamine, dobutamine or norepinephrine in standard doses as an infusion.

[g] Adjunctive therapy does not alter acute reactions, but can modify an ongoing or slow onset process and shorten the course of the reaction.

(i) Antihistamines: Diphenhydramine (50 to 100 mg) or chlorpheniramine (25 mg) slow intravenous followed by oral therapy for 1-2 days.

(ii) Corticosteroids take a few hours at the earliest for its action and hence have little role for the immediate emergency. Injection Hydrocortisone 100 to 200 mg is given intravenously followed by 100 mg six hourly for one day. Equivalent oral prednisolone is given for one more day.

(iii) H_2 receptor antagonists such as injection Ranitidine 50 mg intravenous eight hourly may be of value in addition to H_1 antihistamines, although this opinion is not universally shared.

19. General guidelines for treatment of other forms of DA besides anaphylaxis includes,

(a) Discontinuation of the drug

(b) Symptomatic treatment with antihistamines for pruritus, antipyretics for fever and steroids for more severe and prolonged reactions like serum sickness.

(c) Anxiety related problems come into play in patients who have suffered from DA in the past . Reassurance and close monitoring allays anxiety in these patients.

(d) The patients should be clearly explained not to consume any drug where allergy was noted. All drugs causing DA should be documented in I.A. B–64 and in the patient's hospital records (AFMSF-7A).

20. Patients with acquired immunodeficiency syndrome (AIDS), humoral immunodeficiency (e.g. I gA deficiency) and systemic lupus erythematosis (SLE) are at risk for developing multiple drug sensitivities due to the underlying immune dysregulation. AIDS patients are at increased risk for reaction to sulphonamides, amoxicillin, pentamidine, clindamycin, dapsone, quinolones, acyclovir and antituberculosis drugs. This leads to difficult management problems for opportunistic infections. However, successful rechallenge or desensitisation has been reported with acyclovir, dapsone and trimethoprim- sulphamethoxazole in AIDS patients. This procedure is inherently dangerous as mentioned earlier but this risk is sometimes justified in these patients when they have opportunistic infections.