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Drug allergy – Review article

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ABSTRACT

Drug allergy is an immunologically mediated adverse reaction that can lead to substantial mortality and morbidity. However, there is no published literature on the incidence in India. Knowledge and management of drug allergies are imperative in day-to-day practice. Drugs elicit immune responses in several ways and are also capable of producing immunological reactions that may vary from Type I to Type 4 hypersensitivity reactions. There are risk factors that make certain people more vulnerable to such reactions. A systematic approach to a suspected drug allergy can help in better management of the same.

Keywords: Drug allergy, Hypersensitivity, Immunological reactions

DEFINITION AND INTRODUCTION

Adverse reactions to drugs lead to substantial mortality and morbidity and are a major hazard in the practice of medicine more so in case of children.

Adverse drug reactions (ADRs) have been classified into two types:

- Type A – Predictable reactions based on the pharmacologic properties. The type of reaction can be either due to overdose, side effects, or drug interactions. Example – Diarrhoea due to antibiotics, drowsiness due to first generation antihistaminic, reduced effectiveness of oral contraceptives when taken with carbamazepine
- Type B – Drug hypersensitivity – unexpected or unexplained reactions which are restricted to a specific vulnerable population and this can be due to intolerance, idiosyncratic or immunological reactions.

The term 'drug allergy' refers to specific immunologically mediated drug hypersensitivity reactions. These are again classified as immediate or delayed depending on the appearance of the symptoms within an hour of the dosing or later than that. The idiosyncratic reactions are usually unexplainable and are qualitatively distinct from the known pharmacologically toxicity profiles. They do not have an underlying immune mechanism though they are clinically indistinguishable from allergic reactions.[1,2]

INCIDENCE OF DRUG ALLERGY IN INDIA

Worldwide 10–20% of hospitalised patients and up to 25% of outpatients have reported ADRs. Most of them have been in Type A and the estimated frequency of Type B has been less common. However, there has been no published literature on the incidence of reported adverse reactions in India.[1]

In a systematic review of the incidence of drug-induced anaphylactic reactions published in 2014 from India, there have been no reports of cohort or case-control studies and only case reports have been published. The age groups reported had been predominantly in the adult population. The peak incidence of anaphylaxis has been in the 3rd to 4th decades of life with female preponderance. Antimicrobials were commonly reported as offending agents.[3]

Most of our epidemiological data is based on studies from developed countries, and hence, the real burden on children is still unknown and requires further studies.

In this article, we would discuss the immunologically mediated ADRs.

IMMUNE RECOGNITION OF THE DRUGS

The antigen presented to the immune system must first elicit an immune response – sensitisation and then cause activation of immunopathologic mechanisms further – effector mechanism. There are multiple mechanisms through which drugs are recognised and elicit immune responses.

1. ***Macromolecules*** – Most of the drugs that elicit an immune response are multivalent by virtue of their large molecular weight with multiple repeating epitopes
2. Certain molecules have ***repetitive motifs*** which virtue of the same become complete allergens and potentially cross-link immune receptors. for ex: succinylcholine
3. ***Hapten–carrier complex*** – Most medications have small molecular weights and they bind to host molecules (carrier) forming a complex called hapten–carrier conjugate which elicits a drug-specific immune response. A classical example of this model is the beta-lactam antibiotic penicillin. The beta-lactam ring itself is unstable and readily acrylates lysine residues in the protein. This results in the penicilloyl epitope which is immune dominant and capable of producing urticaria. The beta-lactam ring further conjugates through the carboxyl and thiol groups which are non-dominant or minor determinants. However, these are of major clinical importance as they can cause anaphylactic reactions. Thus, penicillin has both major and minor determinants capable of eliciting different immunological reactions through this model
4. ***Pro-hapten model*** – some medications can form reactive intermediates during drug metabolism before they can undergo detoxification. These intermediates can act as haptens which are referred to as prohapten. An example is sulphonamide antimicrobials which can form sulfamethoxazole nitroso molecules that are highly reactive with host proteins
5. ***p-i concept*** – In this model, a chemically inert drug not capable of covalently binding to peptides or proteins activates the immune system by directly and reversibly binding to HLA molecule forming the HLA-drug complex which is capable of stimulating strong T-cell response. Furthermore, some drugs can bind to 10^{12} of the T-cell receptors available and elicit cytokine production, proliferation, and cytotoxicity. The drug reactive – TCRs interact with major histocompatibility complex and elicits the reaction. The clinical manifestations due to p-i mechanisms are T-cell orchestrated inflammation and account for severe reactions occurring even on first exposures
6. *Danger hypothesis – Altered self-repertoire* – The threshold of activation of the immunological reactions can further be lowered due to certain virus infections – Epstein–Barr virus (EBV), cytomegalovirus, Human Herpes Virus, Human immunodeficiency virus (HIV) and during exacerbation of autoimmune diseases. The bacterial and viral products can interact with pattern recognition receptors on dendritic cells and initiate antigen processing [Figure 1].[1,4,5]

TYPES OF IMMUNOLOGICAL REACTIONS ELICITED CAUSING THE REACTIONS

Allergenic drugs can induce the entire spectrum of immune pathologic reactions. These types of reactions can be as follows [Table 1].

Certain drug reactions which do not exactly come under the above classification are

1. **DRESS syndrome** – Drug rash with eosinophilia and systemic syndrome – which is a hypersensitivity leading on to fever, skin eruptions, and internal multiorgan damage. It is potentially life-threatening. The drugs implicated are antibiotics – vancomycin, beta-lactams, fluoroquinolones, dapsone and sulphonamides
2. **Drug-induced lupus erythematosus** – which presents such as fever, arthralgias, vasculitis and glomerulonephritis and cutaneous manifestations. Mechanisms are unclear. Common drugs implicated are procainamide, phenytoin, isoniazid, amiodarone, penicillamine and minocycline
3. **Acute interstitial nephritis** – drug-induced renal disease. Mechanisms are poorly understood and present with rash, fever, eosinophilia and glomerulonephritis. Common drugs implicated are methicillin, nafcillin, gold, penicillamine and allopurinol
4. **Pulmonary-specific drug hypersensitivity** reactions producing acute pneumonitis and pulmonary fibrosis. Common drugs implicated are bleomycin and methotrexate
5. **Anticonvulsant hypersensitivity syndrome** – caused by aromatic anticonvulsant drugs such as phenytoin, phenobarbital and carbamazepine.

RISK FACTORS FOR DRUG HYPERSENSITIVITY

- The risk factors are due to the drug itself, the disease for which the drug is being used or due to individual

Table 1: Types of immunological reactions.

Type of immunologic reaction	Mechanism involved	Clinical features	Drugs commonly eliciting the reaction
Type 1-Immediate hypersensitivity	Immunoglobulin E mediated	Starts from minutes to hours. Can produce urticarial, angioedema and anaphylaxis	Beta lactams, anti-epileptics
Type II-Cytotoxic reactions	Complement mediated cytolysis-immunoglobulin G/immunoglobulin M	5 or more days Haemolytic anaemia, thrombocytopenia	Penicillin, sulphonamides and heparin
Type III-Immune complexes	High-dose prolonged therapy causes the same	Serum sickness, drug fever, cutaneous eruptions and vasculitis	Penicillin, infliximab, sulphonamides
Type IV-a	Activation and recruitment of monocytes and secretion of large amount of interferon-gamma, tumour necrosis factor-alpha, interleukin-12 and CD8 cells activation	Arthralgias, myalgias, fever, malaise Fixed drug eruptions due to activation of CD8	Procainamides, hydralazine, isoniazid, angiotensin-converting enzyme inhibitors
Type IV-b	Activation and recruitment of Eosinophils	Chronic asthma. allergic rhinitis and maculopapular exanthema with eosinophilia	
Type IV-c	Cell associated antigen or direct cell stimulation – T cells	Contact dermatitis along with type 4a, Maculopapular and bullous exanthems – SJS and TEN	Topical agents-bacitracin, neomycin, steroids, local anaesthetics and antihistamines – contact dermatitis Allopurinol. Sulphonamides, antiepileptics and NSAIDs – cause SJS and TENs
Type IV-d	Antigen presented by cells or direct T-cell stimulation - neutrophilic	T cells produces chemokine CXCL8 and GM-CSF producing manifestations involving sterile neutrophilic inflammation - AGEP, Behcet's disease	

SJS: Steven–Johnson syndrome, AGEP: Acute generalise dexanthematous pustulosis, GM-CSF: Granulocyte macrophage – colony-stimulating factor, TEN: Toxic epidermonecrolysis, NSAIDs: Non-steroidal anti-inflammatory drugs, CXCL8: C-X-C Motif Chemokine Ligand 8

characteristics of the patient in which the drug is being used.

- The characteristics of the drugs that enhance immunogenicity are protein reactivity, contamination with other macromolecules, exposure to cross-reactive epitopes, frequency and duration of drug treatment
- The disease characteristics like a need for prolonged treatment – cystic fibrosis, immunodeficiency diseases, concomitant medications usage and diseases such as EBV and HIV
- The individual characteristics of the patient such as prior reaction, history of atopy, familial propensity, female sex and HLA alleles.

NON-ALLERGIC DRUG HYPERSENSITIVITY REACTIONS

Drug reactions that lack an immunologic basis but resemble an immunological reaction are non-allergic drug hypersensitivity reactions. It is important to differentiate the same as the management differs in both. The reactions that qualify as anaphylactoid or pseudo-allergic reactions involve the same clinical findings. Examples are shock after radiocontrast media that augments basophil and mast cell histamine release, aspirin as well as other non-steroidal anti-inflammatory drugs producing aspirin-exacerbated respiratory diseases – causing asthma, nasal polyposis, rhinosinusitis and exacerbated asthma symptoms as well as chronic urticarial, vaso vagal syncope following local anaesthetics, flushing during vancomycin infusions.

APPROACH TO DRUG ALLERGY IN CLINICAL PRACTICE

1. Careful history – It is important to take a detailed history. History involves the time of correlation to the ingestion of drug and the reaction, type of reactions, family history and previous reactions. We need to differentiate whether it was Immunoglobulin E (IgE) mediated where reactions are expected within 2 h or

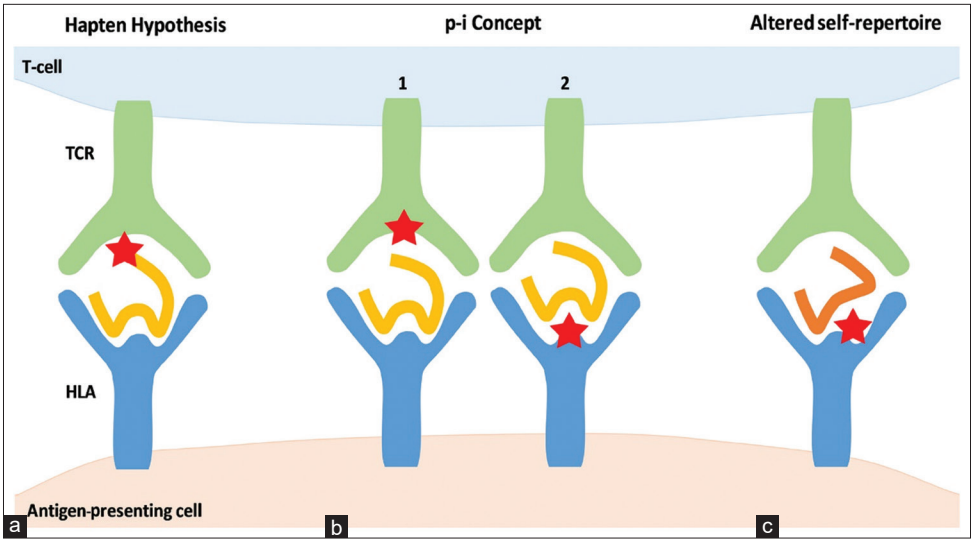

Figure 1: Various mechanisms by which the drug activates the immunological mechanisms (a) The hapten is covalently bound to a peptide and presented according to the hapten hypothesis. (b) Pharmacological interaction (p-i) concept: (1) The T-cell receptor (TCR) molecule itself is modified in the site of human leukocyte antigen (HLA) interaction or (2) the HLA molecule itself is modified in a region exposed to the TCR. (c) The drug binds to the peptide binding groove of empty HLA in endoplasmic reticulum altering the specificity of the molecule, resulting in presentation of novel peptides, as in the altered self-repertoire hypothesis.

a delayed type of reaction where reactions take days or weeks to manifest. Most common finding is skin eruptions and anaphylactic reactions. It is imperative to differentiate between allergic and non-allergic reactions

2. Diagnostic tests
    a. Serum beta tryptase is useful in the diagnosis of drug-induced anaphylaxis. Paired samples, one taken within 1.5 h of the reaction and other after normalcy has returned to determine the baseline levels will be helpful for retrospective confirmation of the allergic nature of the reactions. The level of beta-tryptase >1 ng/mL total tryptase level of >10 ng/mL suggests systemic anaphylaxis.[1,6]
    b. Skin testing – Helps to determine IgE-mediated reaction to drugs which havee been made on clinical grounds. When skin testing is done both the drug and its metabolites need to be tested. However, penicillins are the only agents for which validated testing is available in certain countries. Skin testing with non-irritant concentrations of non-beta-lactam antibiotics is not standardised. Positive skin testing is more relevant than negative testing as sensitivity is limited. In case of negative testing, it cannot exclude a drug allergy. Hence, progress in this field is required before skin testing can be made as a part of routine investigation of drug allergy evaluation.[7]
    c. Intradermal testing is used when there is negative puncture tests and it is essential to confirm the drug reactions
    d. Patch testing is used for diagnosis of type IV contact dermatitis and involves application of the drug directly to skin surface for 24–72 h. Most useful in diagnosing reactions causing maculopapular exanthems or in fixed drug eruptions
    e. Flow cytometry – is being increasingly used for confirmation. It involves measuring basophil activation by means of increased surface markers such as CD63 and CD203c lymphocytic activation tests
    f. Provocative drug test – when the diagnosis is in doubt and the reactions had not be life-threatening drug stimulation/challenge test can be performed with a graded increase in the concentration of the suspected drug in controlled settings. In general, from a European perspective it is accepted as a 'gold standard' for diagnosis of hypersensitivity, whereas, in USA, it is considered as a cautious method of introduction of drugs to prevent severe reactions. However, to date, it is the only resource available to confirm or exclude drug hypersensitivity. The precise challenge procedure may vary from centre to centre.[4,8-10]

MANAGEMENT OF DRUG ALLERGY

1. Acute management involves identification and stopping of the offending agent, introduction of supportive and suppressive therapies. H1 antihistamines have been used for suppression of symptoms. Anaphylaxis has to be

treated vigorously with adrenaline and other measures. The use of wallet cards, medic alert badges, is mandatory for future prevention of episodes
2. Severe drug eruptions and late reactions involving systemic symptoms may warrant hospitalisations
3. Alternatives for drug allergy patients may involve – usage of alternative unrelated medications, administration of potentially cross-reactive medication in incremental dosages in cases where reactions had not been severe or life-threatening and re-administration of the offending drug by desensitisation protocols where it is imperative to continue the medications.[1]

CASES FOR DISCUSSION

Case 1

One-year-old A was started on amoxicillin for the 1st time and had several epsiodes of loose stools. His mother is now frightened now to give the same and each time she informs the doctor that her child is allergic to the same.

Management

It is imperative that we need to make the parents understand that this is an expected side effect of the drug, and hence, the drug can be used safely when it is imperative to give the same as the alternatives are costly and may not be rationale in certain situations.

Case 2

Mr. B was posted for surgery and routine testing which included an intradermal testing for lignocaine, was done. However, on table when the anaesthetic agent was administered, he developed severe cutaneous eruptions and had hypotension. The attenders were very agitated that something was overlooked by the hospital.

Management

It is imperative to understand that intradermal testing with non-standardised dosages is not a gold standard to rule out drug hypersensitivity. Hence, proper precautionary measures and effective management of the anaphylaxis episode are essential. A good clinical history for previous such reactions even a minor one is very helpful. Further, explanation of the same to the patient and attenders is mandatory. If the surgery has to be done, it is wise to use alternative drugs in this condition after certain safe period. Referral to an allergist for evaluation can be done if surgery can be postponed for a while.

Case 3

Five-year-old boy Master C was brought by his parents for evaluation of skin lesion following administration of acetaminophen. The parents initially noted that there was a skin reaction that had come after an episode of fever at the age of three which they attributed to some infection. However, the reaction was much bigger when he had fever the second time. After that during the next episode of fever, when the parents where on a travel and fever had occurred for the boy they had given only tepid sponging for 12 h. However, as soon as, they gave the acetaminophen the child had recurrence of the skin reaction in the same place which was severe than previous episodes and this time they had also noticed some mucosal erosion in corner of the mouth which darkened later. They wanted confirmation of the same and also was wondering that child was asymptomatic when the drug was given during his infancy.

Management

The history is very classical of acetaminophen hypersensitivity. Though the condition is rare, isolated case reports have been reported in literature. The reaction has been initially a fixed drug eruptions and now becoming systemic. The basis for both is delayed type of hypersensitivity. The reason for late manifestation could have been due to a viral trigger and is not explainable. As the reactions are progressive and has now involved the mucosa, it is not advisable to do drug provocation testing and as there are safe alternative drugs available that it is better to use them in case of need. There are also no standardised confirmatory tests available for the same.

CONCLUSION

Drug allergy involves a complete spectrum of immunologic reactions and its clinical manifestations are varied. It needs a high degree of suspicion and careful evaluation as labelling a patient in condition where the patient is not allergic may involve huge costs and usage of unnecessary higher antibiotics and if the patient is allergic the subsequent reactions may be life-threatening. Hence, it is imperative that the primary care paediatrician is aware of the various aspects of the same.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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