

Cutaneous drug reactions in children

Sandipan Dhar, Raghbir Banerjee, Rajib Malakar

Department of Pediatric Dermatology, Institute of Child Health, Kolkata, West Bengal, India

ABSTRACT

Cutaneous drug reactions (CDR) are common in pediatric age group and can be important not only for further therapeutic strategy but also for future of the child. CDR can be classified based on the pathogenesis, morphology, dose relation and predictability. About 3% of patients admitted in hospital have adverse drug reaction. CDR can be due to both immunological and nonimmunological reactions, with nonimmunological reactions being more common. Morphologically CDR in children is divided into five subtypes with exanthematous type being most common. Meticulous history and examination are the basis of diagnosis of CDR. Management is primarily withdrawal of the offending agent and supportive and symptomatic care. Such patients should be advised to carry a drug diary so as to maintain a record of the offending drug/drugs and also to guard against future adverse events.

Key words: Adverse cutaneous drug reaction, adverse drug reaction, children

INTRODUCTION

Cutaneous drug eruptions are seen commonly and these in the pediatric population have an important role to guide the patients' further therapeutic strategy. A "rash" in childhood is often remembered and help the doctor to avoid certain implicated drugs. Early diagnosis and treatment are essential for preventing the spread of the reaction, and preventing further exposures.

It is an undesirable clinical manifestation resulting from administration of a particular drug either due to overdose, predictable effects or unanticipated adverse manifestations. An adverse drug reaction (ADR) is defined by the World Health Organization as "a response to a medicine which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function."^[1]

Adverse cutaneous drug reactions (ACDRs) vary from milder forms to more severe types and are often seen in our day-to-day practice. Cutaneous adverse drug

reactions (CADRs) are a commonly reported type of ADR. CADRs account for the majority of ADRs in hospitalized children. It can be estimated that 2.5% of children who are treated with a drug, and up to 12% of children treated with an antibiotic, will experience a CADR. It has been found that 80% of drug allergies attributed to beta-lactam and sulfa antibiotics and only 30% of the cases were related to opioid analgesics.

They encompass a full spectrum from localized skin involvement to more widespread systemic conditions. The immunology of severe reactions is not very clearly documented though role of T cell-mediation is thought to play the pivotal role. The limitation of laboratory testing for drug hypersensitivity makes clinical observation the mainstay specially when the subject is on multiple drugs.^[2]

CLASSIFICATION

ACDRs can be divided into different classes based on pathogenesis and clinical morphology. On the basis of dose relation and predictability, there can type A (augmented), which is on account of excessive pharmacological effects despite dosage being within therapeutic range and type B (bizarre) which is unpredictable and is not at all dependent on dosage or pharmacological effects.^[3,4]

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ADDRESS FOR CORRESPONDENCE

Dr. Sandipan Dhar

Flat 2A2, Block II, 5, NSC Bose Road, Kolkata - 700 040, West Bengal, India.

E-mail: drsandipan@gmail.com

CADRs in children are often type B ADRs and can be unpredictable, complex, and difficult to pinpoint. A simple classification for regular clinical usage divides them into immediate and non-immediate reactions (NIRs)-accelerated or delayed type reactions.^[5] The immediate type manifest in an hour's time manifesting as angioedema or anaphylaxis. NIRs manifest by hours, days, or even weeks of taking the drug.^[4]

Mediation by immunologic and non-immunologic mechanisms are found to account for most reactions. The reactions which are immunologic (Coombs and Gel) need a host response resulting from IgE-dependent, immune complex-initiated, cytotoxic, or cellular immune mechanisms. The non-immunologic reactions may be initiated by non-immunologic pathways, excess dosage, idiosyncrasy (pharmacogenetic), cumulative toxic effects, drug interactions and so on.^[6]

The major types can also be classified as-non-immune cutaneous reactions like photosensitivity eruptions pigmentation changes, warfarin necrosis of skin, pruritus and so on.

Immune cutaneous reactions: Benign may present as maculopapular eruptions urticarial, angioedema, fixed drug eruptions (FDEs). Immune cutaneous reactions: Severe varieties occur such as vasculitis, pustular eruptions: Acute generalized exanthematous pustulosis (AGEP), hypersensitivity syndrome: Drug reaction with eosinophilia and systemic symptoms (DRESS) Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Drugs reactions can also be divided considering dose relatedness, timing and patient susceptibility.

Dose relatedness points to the doses above, below, or the common therapeutic range (toxic, hypersusceptibility, and collateral adverse reactions).

The significance of time relatedness considers time between first use and the appearance of the adverse reaction and hence are-immediate, first dose, early, intermediate, late and delayed. The role of susceptibility factors consider several factors that enhance the susceptibility to the adverse reaction such as genetic, age, gender, physiological changes, exogenous drugs and diseases.^[7]

Another comprehensive mechanistic format attempts to classify taking into account 5 different factors-Extrinsic chemical species (E) that starts the effect, Intrinsic chemical species (I) that it affects, Distribution (D) of these species in the body,

(physiological or pathological) Outcome (O) and Sequela (S), which is the adverse event. This system is called EIDOS, describes the mechanism initiating the adverse reaction.^[8]

EPIDEMIOLOGY

ACDRs are now quite common and some can be lethal and life-threatening. Reactions to different drugs affect almost about 3% of patients admitted in hospitals. Reaction rates from different studies show a range from 0 to 8% and are more for antimicrobials and for anti HIV drugs (amoxicillin: 5.1%, ampicillin: 4.5%, cotrimoxazole: 3.7%). The most common skin presentation being morbilliform rash (91%), urticaria (6%) severe reactions occur in about 1 in 10,000 to 1 in 1 million users-SJS and TEN. Sulfonamide antibiotics, allopurinol, amine antiepileptic drugs (phenytoin and carbamazepine) are commonly implicated for these severe reactions.^[9,10]

Epidemiological studies on ADRs use varied definitions for ADR, some do not differentiate between immunologically and non-immunologically mediated reactions, study different populations, or use different methods of assessment and final result analysis.^[11] Hotchandani reported cases of ACDRs from outpatient and inpatient departments of dermatology, age group was of 11-50 years, male patients had predominance, most cases had reaction time 1-7 days and the common reaction types were FDEs (37.1) and maculopapular rash (28.6%); Antimicrobials (61.4%), non-steroidal anti-inflammatory drugs (NSAIDs) (22.9%) and antiepileptic drugs (10%) were the common drugs found responsible for the adverse events. An analysis in 50 children and adolescents up to 18 years of age showed that 26% patients had a maculopapular rash, 22% a FDE, 20% erythema multiforme (EM), 12% TEN 10% SJS, 6% urticaria and 4% erythroderma. Cotrimoxazole, was the most common antibacterial responsible for eruptions and antiepileptics were the most common drugs in EM, TEN and SJS. FDE affecting the oral mucosa only and increasing incidence with ciprofloxacin as the offending agent was reported as early as 1992-1993.^[12-16]

Chatterjee *et al.* noted in a study in an outpatient based setting that incidence of ACDR was 2.66%, female patients constituted 61.16% of the total with common offenders being antimicrobials (34.10%), anticonvulsants (32.88%), antiinflammatory drugs (21.51%). The morphological skin reaction variants were urticaria (27.19%), fixed drug rashes (25.16%)

and macular and morbilliform eruptions (25.43%). In a recent study by Zaraq it was seen that women (70%) were more affected; mean age: 44.8 years; responsible drugs: Anticonvulsants (28%), antibiotics (28%), and NSAIDs (15%). Commonest dermatoses noted were maculopapular rash (50%). Fever (76%), lymphadenopathy (31.5%), eosinophilia (35%), and visceral involvement (50%) were also seen in these patients.^[17,18]

Common drugs found to cause cutaneous reactions in a study by Marfatia were NSAIDs (21%) followed by the sulfa group (14%), whereas Pudukadan *et al.* in their study have reported cotrimoxazole (22.25%) followed by dapsone (17.7%) as the most common offenders.^[19,20] In human immunodeficiency virus (HIV)-infected persons trimethoprim-sulfamethoxazole cause severe reactions in up to 40% of patients when used in higher doses. Anti-HIV medications were frequently associated with $\geq 10\%$ drug eruptions (Nevirapine, Abacavir). The risk of reaction increases with the number of drugs taken, age of the patient and viral infections. Patients at risk are those with transplants, HIV infection and those suffering from collagen vascular diseases. Drugs with higher molecular weight and structural complexity are likely to produce a higher incidence of drug reactions. Genetic ability of an individual to detoxify toxic metabolites predispose to the development of drug reaction. Human leukocyte antigen (HLA) genes HLA-B*1502 predispose to Carbamazepine-associated SJS and TEN and HLA-B*5701 to Abacavir hypersensitivity syndrome.^[21,22]

ETIOPATHOGENESIS

In drug reactions, in many cases the mechanism of action is unknown. Drug eruptions due to hypersensitivity reaction relies on an immune mechanism. Reactions on account of non-immunological mechanism are more common. Drugs, may behave as haptens by combining with peptides and hence become immunogenic. Immunologic reactions result from IgE-dependent, immune complex-initiated, cytotoxic, or cellular immune mechanisms. The four Coombs' and Gell immune mechanisms may have their involvement.^[23]

Gell and Coombs classification of immunological reactions.

Delineates 4 types of immunological reactions:

- Type I: Acute IgE-mediated reactions that cause mast cell degranulation like anaphylactic and urticarial reactions

- Type II: Cytotoxic reactions, due to antigen-antibody interactions leading to production of anaphylotoxin (C5a), polymorphonuclear leukocytes aggregation, and tissue injury by hydrolytic neutrophil enzymes as in vasculitis
- Type III: Delayed immune complex reactions, where in antigen-antibody complexes are produced and accumulate in tissues as in maculopapular lesions
- Type IV: Cell-mediated or delayed hypersensitivity reactions where T-lymphocyte sensitization is brought about by a hapten-protein complex as in contact dermatitis.^[6,23]

Non-immunologic reactions occur in the form of non-immunologic activation of effector pathways, overdose, cumulative toxicity, interactions between drugs, metabolic alterations. Urticaria, photosensitivity eruptions, EM, pigmentation, morbilliform reactions, fixed drug reactions, TEN and bullous reactions are some of the clinical manifestations. Non-immunologic activation of effector pathways is also an important mechanism. Drugs release mediators from mast cells and precipitate anaphylaxis or urticaria. Some drugs may activate complement in absence of antibody. Phototoxicity starts when the drug/chromophore absorbs radiation to elicit a reaction.^[24]

Severe cutaneous adverse reactions encompass DRESS or drug-induced hypersensitivity syndrome (DIHS) and SJS/TEN.^[25] The interlink between HLA alleles and these syndromes, including abacavir-hypersensitivity reaction, allopurinol DRESS/DIHS and SJS/TEN and SJS/TEN with amine anticonvulsants. HLA associations help in prevention through screening. HLA-B * 5701 routine genetic screening test to prevent abacavir hypersensitivity provides the initiation for further such tests. The role of genetic screening to identify patients at potential risk for severe CADR is now well-established. These may be fatal and idiosyncratic as in the cases of SJS and TEN overlap and DRESS. Advanced research in genomics have identified genes that have increased propensity to cause ADRs specific to drug and phenotype.^[26]

Commonly offending drugs are variable in diverse ethnic populations. SJS and TEN are mostly found to be precipitated by NSAIDs and sulfonamides in the Western literature whereas carbamazepine is found to be the major implicated agent for SJS in Southeast Asia. The role of carbamazepine in the west is more in causation of drug-induced hypersensitivity syndrome. Allopurinol often plays the causal role in SJS but has no obvious ethnic bias. Pharmacogenetic studies now

point to an association between HLA alleles and drug hypersensitivity. HLA typing has significantly reduced the incidence of abacavir hypersensitivity on account of its association with HLA-B*5701. Susceptibility to nevirapine hypersensitivity was noted in Caucasian Australians having HLA-DRB1 * 0101 with high CD4 + T-cell counts carbamazepine hypersensitivity and HLA-B*1502 has been observed in Han Chinese and allopurinol-induced severe cutaneous adverse reactions are positive for HLA-B*5801.^[27,28]

Considering the linkage of HLA-B*1502 and carbamazepine, HLA-B*1502 allele was found in 100% of people with carbamazepine-induced SJS/TEN and only 3% of carbamazepine-tolerant people in a study from Taiwan. The same was further substantiated in cohort of Chinese descent originating from different geographic regions. This association was not found among people with European descent. The allele hence is ethnically relevant.^[28] Allele with functional effect in the pathogenesis of reaction will be observed consistently in populations. The variability of Chinese and European population maybe due to the fact that pharmacogenetic studies have positive results in a population with a high incidence of such an allele. HLA-B*1502 allele is 4.8-12.8% in Southeast Asians in contrast to 0-0.1% noted in white people. The increased susceptibility of disease from genetic polymorphism is influenced by the prevalence as noted in HLA-B*1502 having lower incidence in Caucasians.^[27-29]

SJS is mostly polygenic. Polymorphisms in the proapoptotic gene Fas-L, the toll-like receptor 3 gene and the IL-4 receptor/IL-13 signaling pathway is documented in most studies.^[30] Screening for HLA-B*1502 in a high-risk population has a 100% sensitivity and 97% specificity for carbamazepine-induced overlapping SJS and TEN, A high-resolution genetic testing using a sequence-specific primer assay for this allele from blood or buccal swabs is now in vogue.^[31]

Associating HLA-B*5801 and allopurinol in a study involving Han Chinese participants revealed the presence of the HLA-B*5801 allele in all patients with allopurinol associated severe CADRs. HLA-B*5801 allele, in comparison to HLA-B*1502, is equally distributed in ethnic groups. The allele maybe established by high-resolution, sequence-based HLA genotyping which is quite an expensive method.^[22,32]

SJS and its association with HLA-B molecules indicate an obvious role in its causation. This presents the drug to CD8 cells resulting in clonal expansion of

CD8 cytotoxic lymphocytes. This cytotoxic effector response leads to apoptosis of keratinocytes. These pathways are not specific to overlapping SJS and TEN. Chung found that granulysin, a cytolytic protein from CD8 cells, occurs in blister fluid in significant levels and correlates disease activity.^[32,33]

CLINICAL SPECTRUM

Common CADR pattern in children are five types. Exanthematous cutaneous eruptions (ECEs) are the most common kind of CADR in children. Acute urticarial in children is usually mild, and self-limiting. FDE have been associated with drugs such as sulfamethoxazole and trimethoprim. Almost 8% of cutaneous drug eruptions are photosensitivity reactions, including phototoxic and photoallergic both. A serum sickness reaction, occurs when antibody-antigen complexes deposit in the microvasculature of the skin and joints and activate a complement cascade.

Serious drug-induced cutaneous eruptions, erythema, urticaria, skin necrosis Blisters, positive Nikolsky's sign have been observed.

Some general symptoms like fever, lymphadenopathy, joint pains may also occur.

The non-immune cutaneous reactions include photosensitivity from fluoroquinolones and cycline antibiotics, pigmentary changes from oral contraceptives, minocycline. Necrosis of skin occurs between the third and 10th days of warfarin initiation. Nonscarring alopecia is often noted with antineoplastic agents. The target organ commonly involved in NIRs is the skin where there is a wide spectrum of manifestations like maculopapular exanthema (MPE), urticaria, AGEP, DRESS/DIHS, SJS, TEN, EM and FDE.^[4,34] NIRs are mainly less severe diseases like exanthematic reactions and MPE, and urticaria. Severe forms like DRESS/DIHS and bullous reactions with mucosal involvement are often noted. EM, mostly of viral etiology presents with target lesions. The most severe are SJS and TEN characterized by widespread epidermal detachment and mucosal erosion and are mainly due to a drug etiology. Evidence now implicates that SJS and TEN are a single disease spectrum and difference appears in the extent of detachment <10% in the case of SJS and more extensive >30% in TEN. SJS and TEN are usually associated with a higher mortality rate of about 20%.^[35]

A study has put forward the view that a new variety of lesion occurs in addition to EM, SJS and TEN,

namely “flat typical target”. The classical lesions are the raised type target lesions. The EM has been proposed to consist of raised typical targets and raised atypical targets and the SJS/TEN flat targets, flat atypical targets and macules with or without blisters. The lesions in EM group are raised, lesions in SJS/TEN spectrum are usually flat with blisters.^[36]

DIAGNOSIS

The drug history forms the cornerstone in the diagnosis and allergology examination and tests further substantiate it. Prick, intradermal and patch tests are the common forms of allergy tests. Specific IgE level is a popular *in vitro* method for immediate reaction detection. Basophil activation test and lymphocyte proliferation assays also add to the investigation basket. Some cases need provocation tests for a complete work up.

On completion of a thorough clinical history, patients with drug allergy are tested. An accurate medication history, details of recent medication, over-the-counter medicines, herbal and homoeopathic preparations, vaccines or contrast media has to be documented. A common feature of NIRs is that in many cases symptoms appear 24 to 48 h after drug intake, the time of onset of symptoms is vital in the evaluation process. Characteristic time lags between onset of treatment and reaction are: 4-14 days for maculopapular eruptions, 7-21 days for SJS/TEN, 14-48 days for DRESS, Fixed drug reactions and generalized exanthematous pustulosis often occur early (within 48 h).^[37]

On the basis of the drugs suspected, patients may undertake skin tests like prick tests, intradermal tests, *in vitro* tests and allergen challenges. Topical medications usually need patch tests for confirmation. Patients having severe drug reaction like TEN are not subjected to drug challenge for the risk serious outcomes.^[37,38]

The laboratory findings in serious drug-induced cutaneous eruptions are eosinophil count >1000/ μ L, lymphocytosis with atypical lymphocytes and abnormal liver function test results. Tests for IgE are available for the drugs like penicillins, cephalosporins, peptide and protein drugs (insulin). In some patients, such as antiretroviral therapy in human immunodeficiency virus, the need for HLA typing before initiating abacavir is routinely recommended.^[37,39] Skin tests like intradermal tests with delayed-reading and cutaneous patch tests are the usual modality. Patch test for drug is easily executed with almost any

available drug. Intradermal tests has the advantage of higher sensitivity but has technical and procedural complexities. The use of intradermal and patch tests for confirmation of NIRs to betalactams, has yielded a sensitivity of 2.6% as a positive reaction to patch tests in 8 of 298 patients tested with phenoxymethyl penicillin. In some recent studies, 37.8% and 9% positive results were noted and so it pointed to the fact that sensitivity of skin test is low as with beta lactam induced exanthema. The usefulness of Patch testing was again established in reactions by cardiovascular or antiepileptic drugs in similar studies.^[39]

Drug provocation tests are useful on account of the fact that intradermal or patch testing has low sensitivity, some patients are given the drug to confirm a causal association. Provocation testing is an useful method, however a very careful administration in a specialized center is recommended. This test is generally not recommended and contraindicated in cases of severe eruptions. Patients having exanthematous reaction after betalactam have negative skin tests but tolerate drug provocation tests better. A recent study noted 2 of 22 adult patients with exanthema to betalactams confirmed by provocation testing had a positive delayed intradermal skin test thus indicating that drug provocation is very much an important diagnostic method.^[37,40]

In-vitro diagnostic tests like the lymphocyte transformation test banks on the principle-T cells can proliferate when exposed to a specific antigen, this theory has been utilized to detect T-cell sensitization to a drug. This test has sensitivity rates of 60% to 70% and relatively low specificity (85%).

Role of dendritic cells in amoxicillin-specific lymphocyte proliferation studies showed dendritic cells improved LTT sensitivity.^[41]

Immunohistochemistry-skin biopsy from the acute reaction site with immunohistochemistry data help in the investigation of the immunologic mechanisms involved and not the drug involved. Mononuclear cell infiltrate composed mainly of activated T cells expressing DR antigens, CD69 activation markers, is an usual finding.^[37]

SOME POINTS TO NOTE IN CHILDREN

The risk factors in children are more or less classified into drug and patient factors. Antibiotics and infections are frequently associated with CADR. In addition, anticonvulsant agents (phenytoin, phenobarbital)

appear frequently as implicated medicines in pediatric reactions.

Risk factors include infection and the possibility of a genetic variation leading to altered metabolism of drugs. Some children with parents who have a true drug allergy are at a 15-fold relative risk for allergic reactions to the same drugs.

MANAGEMENT

Suspected agents should be immediately with-drawn and not repeated although the risk benefit ratio needs to be evaluated in case of necessary medicines. Symptomatic management is usually required. Calamine lotion or oral antihistamines usually relieve pruritus and topical corticosteroids reduce inflammation and itching. Systemic corticosteroids are needed for more severe reactions.

Commonly drug eruptions are reversible, abating spontaneously after the offending drug is withdrawn. The drug half-lives serve as a guide to resolution, as with long half-lives, the time to resolute may be much longer.^[42]

The fact that SJS and TEN are due to dermal cell apoptosis, intravenous immunoglobulin is advocated to block apoptosis through the Fas pathway. Studies on the use of intravenous immunoglobulin in TEN have reported good results. A study of ten consecutive patients with TEN of moderate severity were treated with different doses of IVIG (0.2 to 0.75 g/kg of body weight per day for 4 consecutive days); there was recovery in all cases. Blood transfusion in cases of SJS and TEN helps in many ways as-toxic metabolites, Cytotoxic T cells and autoantibodies get diluted by hemotransfusion, supplies immunoglobulins to fight infections. A benefit of plasmapheresis for treatment of TEN/SJS is also reported. Cyclophosphamide was also claimed to produce good results. A retrospective comparative study showed cyclosporin was safe and produced good re-epithelialization rate and a lower mortality. Tumor necrosis factor is a mediator of cell death in TEN, and control of the progression of TEN with intravenous anti-tumor necrosis factor antibody infliximab yielded better outcomes.^[2,42-45]

COUNSELING

When the responsible drug is pinpointed, it is prudent to avoid that drug later on by the patient. The patients is instructed to carry a record of the drugs to which

he has allergies or had a severe drug reaction. Drugs that are cross-reactive have also to be notified to the patient and avoided. Penicillin allergic patients often have cross-reactivity with cephalosporins group, and sulfonamide allergic subjects cross-react with other sulfa group drugs.^[46,47] These facts are to be particularly emphasized when the patient is counseled.

The diagnosis based on the typical clinical presentations is still the mainstay for pinpoint classification which will lead to prompt therapeutic intervention. Timely diagnosis of the condition and identification of the offending drug and its omission forms the cornerstone of management to prevent more serious outcomes.

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