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ADVERSE DRUG REACTIONS AND ITS SAFETY MEDICATION

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ABSTRACT

Adverse drug reactions are common, Identifying true drug allergy, however, can be challenging. Complicating factors of drug reactions include the myriad clinical symptoms and multiple mechanisms of drug-host interaction, many of which are poorly understood. In addition, the relative paucity of laboratory testing that is available for drug allergy makes the diagnosis dependent on clinical findings. Drugs typically throw up newer side effects than were known during clinical trials once they begin to be administered across large groups of patients. Collecting this data is crucial for patient safety as well as fine-tuning medical research. Adverse drug event Pharmacology Any noxious, undesired, or unintended response to a drug, which occurs at dosages used for prophylaxis, diagnosis, therapy, or modification of physiologic functions; ADEs do not include therapeutic failures, poisoning, or intentional overdoses; ADEs occur in 1-15% of all drug administrations, but are rarely fatal. The meaning of this expression differs from the meaning of "side effect", as this last expression might also imply that the effects can be beneficial. The study of ADRs is the concern of the field known as pharmacovigilance. Because of a rapid increase in the list of newer drugs launched in the market in the last few decades; adverse drug reaction monitoring of these drugs has assumed prime importance. The Adverse Drug Reactions (ADRs) are the fourth to sixth leading cause of death among hospitalised patients and it occurs in 0.3 per cent to 7 per cent of all hospital admissions. The incidence of serious ADRs is 6.7 per cent and 30 per cent to 60 per cent of these ADRs are preventable.

Keywords: Adverse drug reaction, pharmacovigilance, ADR, Side effect.

INTRODUCTION

Adverse drug reactions are defined as any noxious unintended and undesired effects of a drug that occur at doses used for prevention, diagnosis or treatment. Adverse drug reactions (ADR_s) are diverse, any organ can be the principal target or several systems can be involved simultaneously. Knowing this it becomes very difficult to prescribe a medicine safely. FDA Definition in ADR, Any adverse event associated with the use of drugs in

humans whether or not considered drug related including the following: an adverse event occurring in the course of the use of drug in professional practice, an adverse event from drug overdose whether accidental or intentional, an adverse event occurring from drug abuse, an adverse event from drug withdrawal, any significant failure of expected pharmacological action. Although many drug reactions are preventable. Such as those associated with prescription errors while others are not preventable. The adverse drug reactions are often not discovered until after the drug has been marketed. Pharmaceutical companies strive to work out the adverse effect profile of a drug before it is marketed, but because the complete range of adverse effects is not known, therefore, most severe drug induced reactions cannot be elucidated before licensing, therefore efficient post marketing surveillance is needed. However, even if improved surveillance is carried out the problem will not be resolved. As more drugs are marketed and as more individuals take multiple drugs, the occurrence of adverse drug reactions will probably continue to increase. Therefore, better approaches must be devised for reporting and for assessment and management of individuals who present with drug induced diseases. Some of the patients are allergic to only one drug but many others state that they have multiple drug "allergies". Here the Physicians become confused because they do not know that which medicine can be prescribed safely. The purpose of this review is to provide feasible approaches for prescribing the drugs safely to these difficult patients. Since India is a country, which caters to the maximum number of human population for the final assessment of drug safety as a part of post marketing surveillance studies, it becomes necessary to report any untoward reaction of any pharmaceutical product. The drugs, which are marketed in India, are pretested on very small population groups of European countries in an optimal environment and the data about the drug safety collected from that population could not be applied straight in our population because of the climactic and corporal differences. The database of Sweden-based Uppsala Monitoring Centre, which carries out WHO's international drug monitoring programme, shows no ADRs were reported from India between 2005 and 2007, a near impossibility, say experts, given India's population, and the massive number of medicines and combinations being introduced into the market. The early 1900s, German scientist Paul Ehrlich described an ideal drug as a "magic bullet." Such a drug would be aimed precisely at a disease site and would not harm healthy tissues. Although many new drugs are aimed more accurately than their predecessors, none of them, as of yet, hit the target precisely. Most drugs produce several effects, but usually only one effect the therapeutic effect is wanted for the treatment of a disorder. The other effects may be regarded as unwanted, whether they are intrinsically harmful or not. For

example, certain antihistamines cause drowsiness as well as control the symptoms of allergies. When an over-the-counter sleep aid containing an antihistamine is taken, drowsiness is considered a therapeutic effect. But when an antihistamine is taken to control allergy symptoms during the daytime, drowsiness is considered an annoying, unwanted effect. Most people, including health care practitioners, refer to unwanted effects as side effects; another term used is adverse drug event. However, the term adverse drug reaction is technically more appropriate for drug effects that are unwanted, unpleasant, noxious, or potentially harmful. Not surprisingly, adverse drug reactions are common. Most adverse drug reactions are relatively mild, and many disappear when the drug is stopped or the dose is changed. Some gradually subside as the body adjusts to the drug. Other adverse drug reactions are more serious and last longer. About 3 to 7% of all hospital admissions in the United States are for treatment of adverse drug reactions. Adverse drug reactions occur during 10 to 20% of hospital admissions, and about 10 to 20% of these reactions are severe. Digestive disturbances—loss of appetite, nausea, a bloating sensation, constipation, and diarrhea are particularly common adverse drug reactions, because most drugs are taken by mouth and pass through the digestive tract. However, almost any organ system can be affected. In older people, the brain is commonly affected, often resulting in drowsiness and confusion. Some industry observers see this as evidence of India's lax monitoring of so-called adverse drug reactions, or ADRs, in patients, or pharmacovigilance. Such adverse reactions are believed to be the fourth largest cause of mortality and morbidity globally.

TYPES OF ADVERSE DRUG REACTION

ADRs may be classified by e.g. cause and severity.

Cause

- Type A: Augmented pharmacologic effects - dose dependent and predictable
- Type B: Bizarre effects (or idiosyncratic) - dose independent and unpredictable
- Type C: Chronic effects
- Type D: Delayed effects
- Type E: End-of-treatment effects
- Type F: Failure of therapy

Types A and B were proposed in the 1970s, and the other types were proposed subsequently when the first two proved insufficient to classify ADRs.

Seriousness and Severity

The American Food and Drug Administration define a serious adverse event as one when the patient outcome is one of the following:

- Death
- Life-Threatening

- Hospitalization (initial or prolonged)
- Disability - significant, persistent, or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life.
- Congenital Anomaly
- Requires Intervention to Prevent Permanent Impairment or Damage

Severity is a point on an arbitrary scale of intensity of the adverse event in question. The terms "severe" and "serious" when applied to adverse events are technically very different. They are easily confused but can not be used interchangeably, require care in usage.

A headache is severe, if it causes intense pain. There are scales like "visual analog scale" that help us assess the severity. On the other hand, a headache can hardly ever be serious, unless it also satisfies the criteria for seriousness listed above.

Rawlin and Thompson devised a classification scheme in 1991, which continues to be the most frequently used. Their Scheme, shown in panel–1.

Panel – I Classification of Adverse Drug Reactions

Type "A" reactions

Predictable, common and related to Pharmacological action of the drug

Toxicity of overdose	(e.g. hepatic failure with high dose Paracetamol)
Side effects	(e.g sedation with antihistamines)
Secondary effects	(e.g. development of diarrhea with antibiotic therapy due to altered gastrointestinal bacterial flora)
Drug interaction	(e.g. Theophylline toxicity in the presence of erythromycin therapy)

Type "B

Unpredictable, uncommon, usually not related to the pharmacological actions of the drug.

Intolerance	(e.g. tinnitus with use of Aspirin)
Hypersensitivity	Immunological reaction (e.g. Anaphylaxis with penicillin administration.
Pseudoallergic	(Non-Immunological) reaction (e.g. radio contrast dye reaction).
Idiosyncratic reaction.	(e.g. development of anemia with the use of anti-oxidant drugs in the presence of glucose-6 phosphate dehydrogenase deficiency).

Type "C"

These reactions are associated with long-term drug therapy e.g. Benzodiazepine dependence and Analgesic nephropathy. They are well known and can be anticipated.[3]

Type "D" reactions

These reactions refer to carcinogenic and teratogenic effects. These reactions are delayed in onset and are very rare since extensive mutagenicity and carcinogenicity studies are done before drug is licensed.

About 80% of all adverse drug reactions are type A and for most prescription this type of reaction is described in handbooks such as the physician's desk reference.[5]

Type "B" reactions are not dose dependent and except one reaction type, are not usually related to the pharmacological reactions of the drug. They are often not discovered until after the drug has been marketed. Both environmental and genetic factors are then thought to be important in the development of reactions of this type. Idiosyncratic reaction is defined as an uncharacteristic, non-immunological response to a drug that is not related to its pharmacological actions, and those presumed to be immunologically mediated, the term "allergic" or "hypersensitivity reaction" is used.

There are many adverse reactions, which cannot be classified because the mechanisms responsible for them are not known. These reactions are uncommon, unpredictable and not reproducible in animal models. Unfortunately, accurate calculation of the incidence of adverse drug reactions is difficult since most of these reactions go unreported.

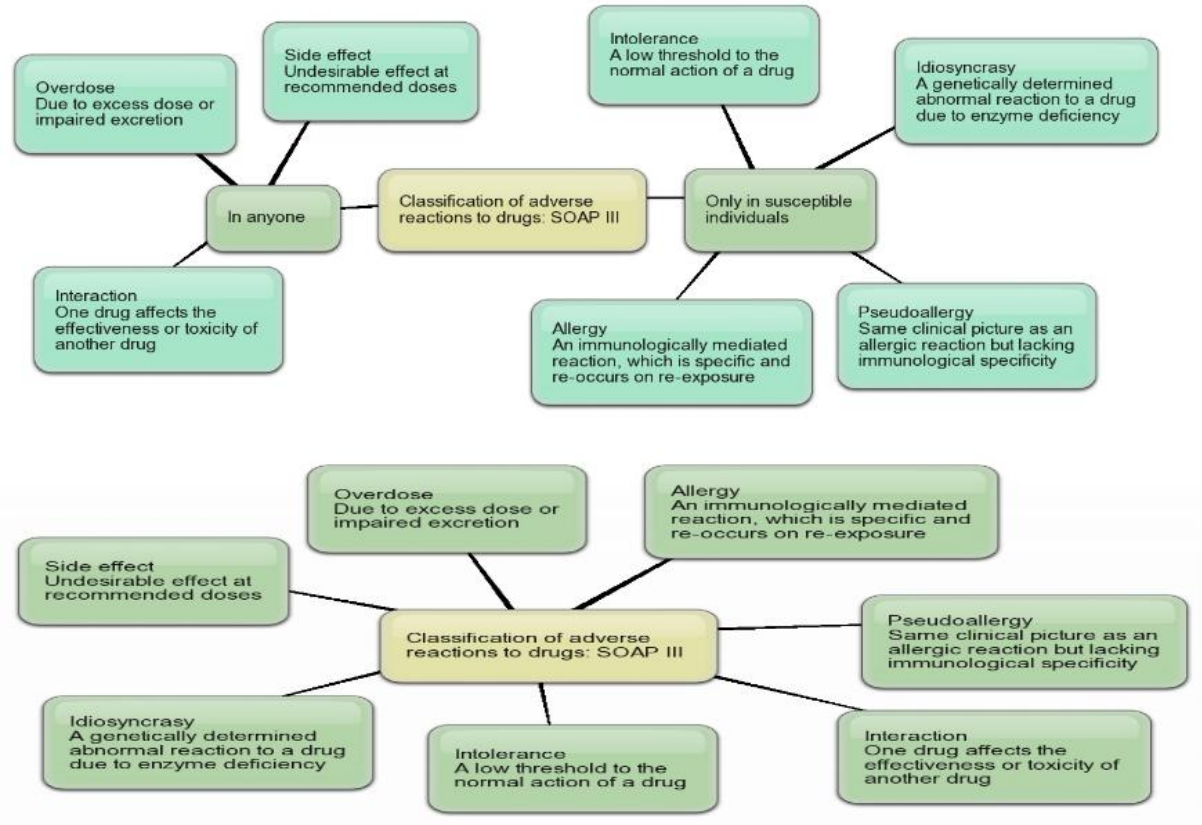

Figure-1. classification of ADRS to Drugs.

ALLERGIC REACTIONS TO MEDICATIONS

True allergic reactions to medications typically follow certain features:

- The first time the medication was taken there was no reaction.
- The medication is either taken for a period of time (usually at least 1 week) without problems or there is at least a week before the medication is taken again.
- The reaction that occurs from the medication is different from expected side effects.
- The reaction is suggestive of allergy or anaphylaxis.
- The symptoms of the reaction disappear within a few days of the medication being stopped.

SYMPTOMS OF ALLERGIC AND IMMUNOLOGIC REACTIONS

Skin rashes are the most common symptoms occurring from adverse drug reactions. Urticaria and angioedema suggest an allergic cause, while blistering, peeling and sun-burn like reactions suggest non-allergic immunologic causes. When a rash blisters and peels, is painful or involves sores in the mouth and mucous membranes, Stevens - Johnson syndrome or toxic epidermal necrolysis is the likely diagnosis, which can be life-threatening. Other non-allergic immunologic symptoms can include fever, kidney failure, hepatitis and blood problems (such as anaemia).

ALLERGY TO COMMON MEDICATIONS

People can experience allergic reactions to just about any medication, although some are more common than others. Here is a list of the most common medication allergies (or non-allergies, in some cases):

1. **Penicillin** (and all related antibiotics). About 1 in every 10 people reports a history of an "allergic reaction" to penicillin. It turns out that much less than 10% of those who think they are allergic to penicillin actually are. However, people with a true allergy to penicillin could have life-threatening anaphylaxis as a result, it is important to tell your doctor about your past reaction to the medication. Skin testing to penicillin can help determine if the past reaction was a true allergy or some other side effect.

2. **Cephalosporins** (and all related antibiotics). Severe reactions to cephalosporins are much less common than with penicillins. However, there is a small chance that someone with a true penicillin allergy could also react to cephalosporins, since the drugs are related. An allergist may be able to help determine if these antibiotics are safe for you.

3. **Sulfonamides** (including antibiotics, oral diabetes medications and some water pill diuretics). It is unclear whether these reactions are truly allergic or due to another immunologic process. There is no reliable test available to determine is a person is allergic to this class of medications.

4. **Non-Steroidal Anti-Inflammatory Drugs** (NSAID), including aspirin, ibuprofen and naproxen. This class of medications can cause allergic and non-allergic flares of hives/swelling, worsen asthma, and result in anaphylaxis. There

is no reliable test available for most people with reactions to these medications.

5. **IV Contrast Dye**. This reaction is non-allergic but can result in anaphylaxis because the high concentration of the dye causes mast cells to release their contents, which mimics an allergic reaction. While there is no test available for reactions to IV contrast, most patients can take the dye safely by taking oral steroids and anti-histamines hours before the contrast is given. The contrast is usually given in a less concentrated form to these patients. Let your doctor know if you've had a past reaction to IV contrast before receiving it again.

6. **Local Anesthetics**. True allergic reactions to local anesthetics (novocaine, lidocaine) are extremely rare, and usually due to other ingredients in the medication, such as preservatives or epinephrine (present in the local anesthetic to make the medication last longer once it's injected). An allergist can perform testing to various local anesthetics and find one that works for almost everybody.

7. **General Anesthesia**. Some medications used during surgery are very common causes of true allergic reactions and anaphylaxis. If you think you experienced an allergic reaction during or shortly after surgery, an allergist may be able to help determine the cause.

8. **Anti-Seizure Medications**. Many medications used for treatment of epilepsy can cause non-allergic reactions as a result of certain enzyme deficiencies in the person taking the medication. Symptoms can include a rash, fever, body aches and hepatitis. There is no test available for this type of reaction.

NATIONAL PHARMACOVIGILANCE PROGRAM

Even though pharmacovigilance is still in its infancy, it is not new to India. It was not until 1986 that a formal adverse drug reaction (ADR) monitoring system consisting of 12regional centers, each covering a population of 50 million, was proposed for India. However, nothing much happened until a decade later when in1998, India joined the World Health Organization (WHO) Adverse Drug Reaction Monitoring Programme based in Uppsala, Sweden. The program has three-tier structure-2 zonal centers 5 regional centers and various peripheral centers. Pharmacovigilance centers pursue four objectives: to detect ADRs, to evaluate them, to study them what is the difference between evaluate and study? and to inform prescribing physicians.

The Central Drugs Standard Control Organization (CDSCO) launched the National Pharmacovigilance Program in November 2004 under the aegis of Directorate General of Health Services, Union Ministry of Health and Family Welfare. The basic purpose of this program is to collate, analyze and archive adverse drug reaction data for making regulatory decisions regarding drugs marketed in India. The National Pharmacovigilance Programme will have the following goals:

- To foster a culture of notification

- To engage several healthcare professionals and NGOs in the drug monitoring and information dissemination processes.
- To achieve such operational efficiencies that would make Indian National Pharmacovigilance Programme a benchmark for global drug monitoring endeavours.

The programme shall be coordinated by the National Pharmacovigilance Centre at CDSCO, New Delhi. The National Centre will operate under the supervision of the National PharmacovigilanceAdvisory Committee to recommend procedures and guidelines for regulatory interventions.

Specific objectives of the Programme:

- To create an ADR database for the Indian population
- To create awareness of ADR monitoring among people
- To ensure optimum safety of drug products in Indian market
- To create infrastructure for ongoing regulatory review of PSURs (periodic safety update reports)

ADR Monitoring and Detection

Adverse drug monitoring and detection is carried out in our hospital by the prescription audit department as a part of their routine checking of prescriptions for drug name, strength and route of administration, doses, frequency and duration. The computerized drug order entry is screened here for events related to adverse drug reaction and a detailed investigation is done if any clue is found.

- Medication order screening
- Abrupt medication discontinuation.
- Abrupt dosage reduction.
- Orders for tracer substances.
- Orders for special tests or serum drug concentrations.
- Orders for high risk drugs, which are likely to cause ADRs are screened and their use is monitored

Examples of high risk drugs are aminoglycosides, amphotericin, antineoplastics, corticosteroids, digoxin, heparin, lidocaine, phenytoin, theophylline, thrombolytic agents, and Warfarin.

- Medication utilisation review.
- Computerised screening.
- Chart review and concurrent audits.
- Lab tests & checklist.
- Standard laboratory tests.
- Adverse drug event questionnaire-extensive checklist of symptoms categorized by body system.

Severity scale of ADRs

The ADRs are classified into severity levels and all the ADRs with a severity level of 5 and 6 are investigated in detail by doing a Root-Cause-Analysis (RCA).

Level 1- ADR occurred but required no change in treatment with suspected drug.

Level 2- Drug held, discontinued or changed but no antidote or additional treatment needed.

Level 3- Drug held, discontinued or changed and/or antidote or additional treatment.

Level 4- ADR required patient transfer to an intensive care setting.

Level 5- ADR caused permanent harm to the patient.

Level 6-ADR either directly or indirectly led to the patient's death.

DRUG METABOLISM AND DRUG REACTIVITY

To work out the underlying pathophysiology of drug reactions, the chemical properties of the drug and its metabolism must be analyzed. Metabolism is a type of detoxification process, whereby lipid-soluble, non-polar compounds are converted to compounds that are easily excreted. Drug metabolism is usually a two-step process involving the oxidation, reduction or hydrolysis (phase-I) followed by conjugation with glucuronyl, sulphate, or acetyl groups (phase-II) that results in the formation of inactive compounds that are water soluble and easily excreted by the kidneys. In some instances, reactive drug metabolites that are not promptly detoxified may be formed, which may cause direct cytotoxicity leading to direct tissue damage and necrosis. It may bind to nucleic acids to produce an altered gene product or it may covalently bind to a larger macromolecule inducing an immune response

Pharmacodynamics

Antipsychotics – women greater impairment & increased ADR and therefore much lower doses are advocated.

Imipramine – men respond better.

Panic attacks - better with tricyclics in males

- MAO inhibitors in women.

Platelets of men have fewer receptors sites than females in binding paroxetine (5HT antagonist)

CVS drugs – Increased ADR in women and increased antithrombic effect.

Atracurium – increased response in omen.

Mehtyl prednisolone gender based differ, in PCK is offset by pharmacodynamic response because if increased sensitivity in females with mehtyl prednisolone.

Antiinflammatory activity with naproxen, piroxicam women shows greater ADR.

Clinical significance

Drugs with wide T.I because of greater magnitude does not necessitate dose adjustment and only with narrow TI dose adjustment is necessary.

Sex specific disease

Menopause estrogen and/or progesterone therapy reduces risk of osteoporosis, reduce cardio-vascular disease and reduce risk of endometrial cancers. Aging in women is significant than men.

Alfentanil clearance in female has inverse correlation (CYP3A4 is reduced menopause). Reduced estrogen metabolism in

old age and reduced prednisolone clearance in postmenopausal women. Estrogen replacement in menopause does not reverse the enz status but affect PCK differently Ex: Prednisolone, anti-inflammatory steroids and reduced piroxicam clearance. Ca absorption is impaired by menopausal state.

Oral contraceptives can alter metabolism of other drugs

Drugs interfering with Oral Contraceptives:

1. Those increase hepatic metabolism
2. Decrease absorption from entero-hepatic circulation: Drugs interfering with Oral Contraceptives:
1. Those increase hepatic metabolism
2. Decrease absorption from entero-hepatic circulation:

a) Rifampicin, phenobarbitorne, phenytoin

b) Oral **contraceptives** steroids undergo extensive enterohepatic circulation after hydrolysis by gut flora and free hormones are released. Antibiotics reduce gut flora and reduces oral contraceptives effectiveness – penicillin, tetracycline cephalosporins reduce oral contraceptives conc.

Oral contraceptives can influence metabolism

1. Ethinyl content steroids in most Oral contraceptives are suicide inactivators of CYT P_{450} CYP3A4 and other isoenzymes inactivated reduced hepatic metabolism of cyclosporin corticosteroids the ophylline (extent of 30% or more) O.Cs increase glucoronyl transferase – Ex: paracetamol conjug 45% greater, oxazepam, temazepam and aspirin etc.

Menstrual cycle

Methaqualone clearance is increased twice in mid cycle. Methyl prednisolone also similar effect. t½ of paracetamol shorter in mid cycle. Phenytoin clearance is increased at end of cycle. Drug absorption is also influenced by cycle: Absorption of alcohol, aspirin reduced in midcycle.

Pregnancy

Antiepileptic – faster elimination – increased incidence of seizures. Phenytoin, carbamazepine, phenobarbitone faster elimination. Betalactam antibiotics faster elimination Caffeine t½ is increased by 200% clearance reduced by 705 because of reduction of xanthine oxidase and N acetyl transferase. Alternation due to changes in steroids during pregnancy: Increased progesterone inhibits CYP1A2 and increases CYP3A4.

Clinical Significance

In pregnancy, with oral contraceptives, menopause, and menstrual cycle phase there is alteration in both PCK and pharmacodynamic aspects of drug handling and therefore drugs with narrow therapeutic range dosage adjustment is necessary. A sudden change in drug efficacy or toxicity should raise suspicion

of gender phenomenon.

It is anticipated that gender difference in drug metabolism may become an important factor in deciding the dosage of drug with narrow therapeutic range probably involving an increase in incidence of ADR in man.

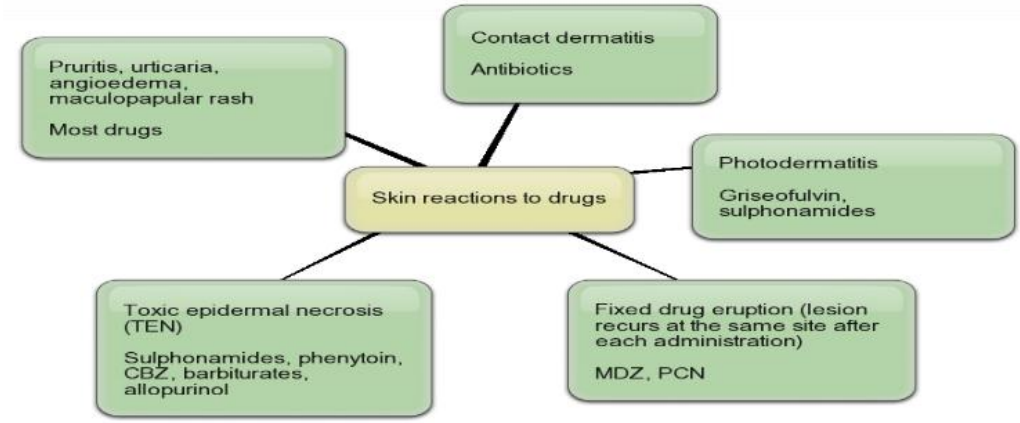

Figure-2 skin reactions to drugs

PENICILLIN ALLERGY

Cross reactivity between a *b*-lactam ring and penicillin restricts the use of carbapenems in patients who are allergic to penicillin. [Evidence level B, nonrandomized clinical trial] Aztreonam (Azactam) cross-reactivity is extremely rare in these patients. Varying degrees of cross-reactivity between cephalosporins and penicillins have been documented. However, since 1980 the rate of cross-reaction between penicillin and second- or third-generation cephalosporins has been found to be 5 percent or less. The degree of cross-reactivity appears to be greater for first-generation cephalosporins. While the incidence of true cross-reactivity between penicillins and cephalosporins is low, the possible reactions include anaphylaxis, which can be fatal. Caution is advised when administering cephalosporin therapy to patients with a history of penicillin allergy. A more conservative approach includes penicillin skin testing before initiation of cephalosporin therapy, particularly for patients with a history of serious allergic reactions to penicillin.

RISK FACTORS FOR DRUG ALLERGY

Positive penicillin skin tests do not occur more frequently in atopic individuals, but an atopic background is a risk factor for penicillin anaphylaxis.

Penicilloyl IgE immune responses progressively decline in most individuals, over 3–8 years; more than 75% of prior penicillin reactors become skin test negative.

Having an antibiotic-sensitive parent carries a 15-fold increased risk of drug sensitivity.

There is a 10-fold increased risk for allergic reactions to unrelated antibiotics in patients with antibiotic sensitivity.

Strong associations of HLA-B 5701 with a hypersensitivity to the reverse-transcriptase inhibitor abacavir.

Non-allergic hypersensitivity reactions are also called 'pseudoallergic drug reactions'

A subset of idiosyncratic reactions and must be distinguished from immunologic (allergic) reactions. They are often referred to as 'anaphylactoid,' a much-abused term.

Pseudoallergic/ anaphylactoid reactions involve the same final common pathway as type I reactions. Basophils and mast cells are activated and vasoactive mediators are released by non-immune mechanisms.

Local anesthetic agents are good sensitizers when applied topically, but antibody-mediated allergic reactions are rare.

Pseudoallergic responses to local anesthetics (e.g. in dentistry) often lead to allergy consultations. Vasovagal syncope can mimic anaphylaxis. Intradermal skin testing followed by a series of provocation dose challenges is the recommended approach.

Nondrug-related reactions

- Vasovagal syncope after IV administration of an antibiotic
- Co-incidental symptoms, for example, viral exanthema in child who takes an antibiotic

Types Of Allergies To Medicines

In this section we will discuss the most common categories of allergy to medications, knowing that there are other reactions and are not described in the topic.

1. Urticaria

Urticaria is characterized by rash of hives or hives in size and location variables, with an evolution of 24-48 hours. In most cases is associated with angioedema (angioneurotic edema or Quincke), that instead of causing itching sensation of weight or stress, and deformation of the face.

2. Anaphylaxis

It is a general reaction of the organism after contact, application, or taking of a drug, which is an immediate (5-10 minutes) in the form of itching in the palms and soles, general warmth, rash formation of the skin with hives, a sensation of coarse language and some difficulty swallowing, difficulty breathing, coughing, wheezing in the chest, fatigue, tachycardia, vomiting, bowel movements, anxiety.

If after this picture persists and is not displayed a violet color of the lips and skin of the nail, hypotension and cardiac arrhythmia, and entry into shock, with loss of consciousness and death.

The incidence of anaphylaxis (allergic shock) is known in relation to penicillin from 10 to 50 per 100,000 live shots, and these reactions are 100 to 500 fatalities per year in USA.

Erythema multiform

It is a skin reaction with injuries at the beginning are simple or pink macules or erythematous papules, sometimes erythematous appearance and generally evolve in its central region to take a look at that level edematous and therefore high pitch dark violet and even look ampoules with persistent peripheral edge erythematosus (cockade injuries or target). There may be itching or burning sensation associated, and this is characteristic of skin lesion distribution symmetrical. The causes are various, sometimes appears as a symptom of infection or activation of certain microorganisms (herpes simplex, mycoplasma, bacteria) and other mechanisms are allergy medicines.

Toxic epidermal necrolysis (Lyell Syndrome)

It is a reaction in the form of generalized erythema, formation of large blisters (as if they were burns) Epidermal off and a high mortality. Drugs that may occur are:

- sulphonamides
- pirazolonas
- hydantoin
- penicillin

CONCLUSION

Reactions to medication are extremely common. In fact, 15-30% of all hospitalized patients will experience an unintended reaction as a result of medications. However, true allergic reactions to medications only occur in about 1 of 10 of all adverse drug reactions. Reactions which are common and predictable in any person. This would include expected side effects from medications, interactions between 2 medications that the person is taking, and reactions from using too much of the medication (overdose). This group represents the majority of all reactions to medications. Reactions which are unpredictable, and only occur in certain people. These reactions can include an unexpected side effect, medication intolerance, allergic reactions and other non-allergic immunologic reactions. An adverse drug reaction is a “response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function.” Note that there is a causal link between a drug and an adverse drug reaction. An adverse drug event is “an injury resulting from the use of a drug.

Under this definition, the term ADE includes harm caused by the drug (adverse drug reactions and overdoses) and harm from the use of the drug (including dose reductions and discontinuations of drug therapy)."1 Adverse Drug Events may results from medication errors but most do not. An allergy is an adverse drug reaction mediated by an immune response (e.g., rash, hives). A side effect is an expected and known effect of a drug that is not the intended therapeutic outcome. The term "side effect" tends to nominalise the concept of injury from drugs. It has been recommended that this term should generally be avoided in favor of adverse drug reaction Medication errors are mishaps that occur during prescribing, transcribing, dispensing, administering, adherence, or monitoring a drug. Examples of medication errors include misreading or miswriting a prescription. Medication errors that are stopped before harm can occur are sometimes called "near misses" or "close calls" or more formally, a potential adverse drug event.

REFERENCES

1) Executive summary of disease management of drug hypersensitivity: a practice parameter. Joint Task Force on Practice Parameters, the American Academy of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology. Ann Allergy Asthma Immunol 1999; 83:665-700.
2) deShazo RD, Kemp SF. Allergic reactions to drugs and biologic agents. JAMA 1997; 278:1895-906.
3) Anderson JA, Adkinson NF Jr. Allergic reactions to drugs and biologic agents. JAMA 1987; 258:2891-9.
4) Hertl M, Merk HF. Lymphocyte activation in cutaneous drug reactions. J Invest Dermatol 1995; 105 (1 suppl):95S-8S.
5) Yawalkar N, Egli F, Hari Y, Nievergelt H, Braathen LR, Pichler WJ. Infiltration of cytotoxic T cells in drug-induced cutaneous eruptions. Clin Exp Allergy 2000; 30:847-55.
6) Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (Drug Rash with Eosinophilia and Systemic Symptoms: DRESS). Semin Cutan Med Surg. 1996; 15:250-7.
7) Pramatarov KD. Drug-induced lupus erythematosus. Clin Dermatol 1998; 16:367-77.
8) Ditto AM. Drug allergy. In: Grammer LC, Greenberger PA, eds. Patterson's Allergic diseases. 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2002:295.
9) Jick H. Adverse drug reactions: the magnitude of the problem. J Allergy Clin Immunol 1984; 74:555-7.
10) Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA 1998; 279:1200-5.
11) Einarson TR. Drug-related hospital admissions. Ann Pharmacother 1993; 27:832-40.

12) Barranco P, Lopez-Serrano MC. General and epidemiological aspects of allergic drug reactions. Clin Exp Allergy 1998;28 (suppl 4): 61-2.

13) Bayard PJ, Berger TG, Jacobson MA. Drug hypersensitivity reactions and human immunodeficiency virus disease. J Acquir Immune Defic Syndr 1992; 5:1237-57.

14) Descamps V, Valance A, Edlinger C, Fillet AM, Grossin M, Lebrun-Vignes B, et al. Association of human herpesvirus 6 infection with drug reaction with eosinophilia and systemic symptoms. Arch Dermatol 2001; 137:301-4.

15) Lang DM, Alpern MB, Visintainer PF, Smith ST. Increased risk for anaphylactoid reaction from contrast media in patients on beta-adrenergic blockers or with asthma. Ann Intern Med 1991; 115:270-6.

16) Petri M, Allbritton J. Antibiotic allergy in systemic lupus erythematosus: a case-control study. J Rheumatol 1992; 19:265-9.

17) Adkinson NF Jr. Risk factors for drug allergy. J Allergy Clin Immunol 1984; 74:567-72.

18) Holder SM, Joy MS, Falk RJ. Cutaneous and systemic manifestations of drug-induced vasculitis. Ann Pharmacother 2002; 36:130-47.

19) deShazo RD, Nelson HS. An approach to the patient with a history of local anesthetic hypersensitivity: experience with 90 patients. J Allergy Clin Immunol 1979; 63:387-94.

20) Moscicki RA, Sockin SM, Corsello BF, Ostro MG, Bloch KJ. Anaphylaxis during induction of general anesthesia: subsequent evaluation and management. J Allergy Clin Immunol 1990; 86:325-32.

21) Patterson R. Drug allergy and protocols for management of drug allergies. 2d ed. Providence, R.I.: OceanSide Publications, 1995.

22) Hamilton RG, Adkinson NF Jr. Natural rubber latex skin testing reagents: safety and diagnostic accuracy of nonammoniated latex, ammoniated latex, and latex rubber glove extracts. J Allergy Clin Immunol 1996; 98:872-83.

23) Sogn DD, Evans R 3d, Shepherd GM, Casale TB, Condemi J, Greenberger PA, et al. Results of the National Institute of Allergy and Infectious Diseases Collaborative Clinical Trial to test the predictive value of skin testing with major and minor penicillin derivatives in hospitalized adults. Arch Intern Med 1992; 152:1025-32.

24) Gruchalla RS, Sullivan TJ. In vivo and in vitro diagnosis of drug allergy. Immunol Allergy Clin North Am 1991; 11:595-610.

25) Schwartz LB. Tryptase, a mediator of human mast cells. J Allergy Clin Immunol 1990; 86:594-8.

26) Shepherd GM. Allergy to beta-lactam antibiotics. Immunol Allergy Clin North Am 1991; 11:611-33.

27) Anne S, Reisman RE. Risk of administering cephalosporin antibiotics to patients with histories of penicillin allergy. Ann Allergy Asthma Immunol 1995; 74:167-70.

28) Adams LE, Hess EV. Drug-related lupus. Incidence, mechanisms and clinical implications. Drug Saf 1991; 6:431-49.

29) Craven NM. Management of toxic epidermal necrolysis. Hosp Med 2000; 61:778-81.

30) Saxon A, Adelman DC, Patel A, Hajdu R, Calandra GB. Imipenem cross-reactivity with penicillin in humans. J Allergy Clin Immunol 1988; 82:213-7.

31) Saxon A, Hassner A, Swabb EA, Wheeler B, Adkinson NF JR. Lack of cross-reactivity between aztreonam, a monobactam antibiotic, and penicillin in penicillin-allergic subjects. J Infect Dis 1984; 149:16-22.

32) Adkinson NF Jr. Immunogenicity and cross-allergenicity of aztreonam. Am J Med 1990; 88:12S-5S.

33) Lin RY. A perspective on penicillin allergy. Arch Intern Med 1992; 152:930-7.

34) Pumphrey RS, Davis S. Under-reporting of antibiotic anaphylaxis may put patients at risk. Lancet 1999; 353:1157-8.