REVIEW ARTICLE

ADVERSE DRUG REACTIONS: CLINICAL ASSESSMENT OF DRUG INDUCED DISEASE

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Physicians are often confronted with patients who state that they are "allergic" to a drug. The goal of this review article is to help physicians to develop management plans for patients who present with drug induced diseases. It provides information that allows physicians to differentiate between reactions that are truly allergic in nature and those that are not immunologically mediated. The suggestions which may be helpful in the assessment are discussed and guidance is provided whether a drug may be safely readministered. Unfortunately until we are unable to thoroughly understand the mechanisms responsible for drug induced reactions, our management tools will remain limited.

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[1].

Adverse drug reactions (ADRs) 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.

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.

CLASSIFICATION OF ADVERSE DRUG REACTIONS

Rawlin and Thompson[2] 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[4] 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.[6] 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.

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.[7]

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.

BACKGROUND INFORMATION IS IMPORTANT IN THE ASSESSMENT OF DRUG INDUCED DISEASE

Physicians are asked to assess drug reactions while reactions are in progress or afterwards when all clinical evidence of the events has resolved. If the patient is in the midst of a reaction, medical history, physical findings and laboratory information can all be used to find the responsible drug, as well as to help elucidate the reaction type. In many instances, however, the drug reaction has long resolved and the physicians have no objective information upon which to base a decision about whether or not to re-administer the drug in question. Even here, much useful information can be obtained if a detailed history is taken.

Since patients often cannot recall important details clearly, so all relevant medical records should be visualized. This information is not only vital to the physicians but it also makes patients less anxious, since they can become frustrated and embarrassed if they cannot recall specific details.

Questions a physician should ask when assessing a patient with a suspected drug induced disorders.

Is there any history of drug-induced reaction?

- What were the characteristics of the previous reactions?
- At what stage during therapy did the current reaction occurred?
- At the time of reaction, which drugs was the patient taking, when were they started and what were the doses of each drug?
- Had the patient been exposed to any of these drugs previously?
- What are the other medical problems of patients?
- What were the clinical manifestations of the drug induced reaction and could these manifestations help to determine that which drug was responsible for the reaction?
- Were there any laboratory abnormalities that could be explained by a drug induced reaction?

- When the drug was discontinued, did the reaction cease?

Almost all drugs are capable of causing numerous adverse type reactions. Therefore, when an individual presents with a drug-induced reaction, a careful physical examination focused on the organ systems involved in the reaction should be done, and then the adverse-reaction profile of all administered drugs should be reviewed to pinpoint the most likely culprit.

LIST OF THE DIAGNOSTIC TESTS FOR DRUG INDUCED REACTIONS

A. Depending on the organ system involved.

a. Liver functions tests.

b. Blood Urea nitrogen.

c. Blood Creatinine.

d. Complete blood picture (Eosinophilia).

e. Urine analysis.

f. Bio-chemical immunological markers which confirms the activation of certain immunopathological pathways.

B. Depending upon the reaction type.

a. Hemolytic complement concentrations.

b. Antinuclear antibodies (LE cells)

c. 24 hours urine histamine metabolites.

d. Bio-chemical markers for disorders that involve systemic mast cell activation.

e. Skin testing can be done to find out whether drug specific IGE antibodies exist.

f. A marked proliferative response is seen in lymphocytes when they are cultured in the presence of the suspected drug, but this finding & its clinically relevance is not yet clear.

g. Patch test.

Management Plan

If it is non-immune adverse drug reaction (i.e. toxicity, side effects, secondary effect, drug interaction, Drug intolerance, drug idiosyncrasy, Pseudoallergic reaction etc)

Then for management one can think about.

- Modifying dose of drug

- Use of alternative drug
- Can consider prophylactic regimen (if seen to be effective)
- Patient /physician education

But if immune adverse reaction is suspected and after laboratory tests if diagnosis of drug Hypersensitivity is confirmed then management includes.

- Avoidance of drug, if possible
- Consider desensitization if presumed **IgE** mediated
- Consider prophylactic regimen (if seen to be effective)
- If re-administration of implicated drug is absolutely contra indicated then it should be stopped
- Prudent use of all drugs in future
- Patient / physician education

CONCLUSION

ADRs represent a huge challenge in terms of their initial recognition, and even when they have been well described such reactions can be difficult to diagnose.

Thus the physicians must anticipate, avoid, recognize and respond to ADRs promptly so that morbidity and mortality is decreased.

SUGGESTIONS

In order to minimize adverse drug reaction, the prescriber should carefully consider the following questions:

- Are the risks of with holding treatment greater than the risks of the treatment it self?
- Is the proposed drug the safest amongst the alternatives available?
- Is the patient already receiving a drug which might interact with the one proposed?
- Is the patient already receiving a drug which might interact with the one proposed?
- Has the patient an under lying condition which might predispose to therapeutic failure of toxicity?

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