DRUG IDIOSYNCRASY IN OPHTHALMIC PRACTICE

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ABSTRACT
Idiosyncratic drug reactions, denoting non-immunological hypersensitivity to a substance, have been a neglected entity. The idiosyncrasy, more often than not, is confused with hypersensitivity, which is an undesirable reaction of normal immune system. The present article gives an insight of the various aspects of idiosyncrasy and idiosyncratic responses of drugs commonly used in ophthalmic practice.

Key words: Idiosyncrasy, Hypersensitivity, Hypersensitivity, Ophthalmic.

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INTRODUCTION

Drug idiosyncrasy in ophthalmic practice, being uncommon or better said being under-emphasized, has been a neglected entity. The term idiosyncratic drug reaction means different things to different people, but in this perspective, it will be used to indicate an adverse drug reaction that does not occur in most patients at any readily achieved dose of a drug and does not involve the known pharmacologic effects of the drug**.** Once the idiosyncrasy is diagnosed, the only best approach is to withdraw the drug to avoid any idiosyncratic response going wild. It is important to know about the entity and also the commonly used drugs in ophthalmic practice known to show idiosyncrasy.

Idiosyncrasy defined the way physicians conceived diseases in the nineteenth century. They considered each disease as a unique condition, related to each patient. This understanding began to change in the 1870s. In contemporary medicine (as of 2007) the term "Idiosyncratic Drug Reaction' denotes a non-immunological hypersensitivity to a substance, without connection to pharmacological toxicity. Idiosyncrasy stresses here the fact that other individuals would react differently, or not at all and that the reaction is an individual one, based on a specific condition of the one who suffers from it (1).

Idiosyncrasy is defined as a genetically determined abnormal reactivity to chemicals. The observed response is qualitatively similar in all individuals, but the idiosyncratic response may take the form of extreme sensitivity to low doses or extreme insensitivity to high doses of chemicals. These genetic polymorphisms can be due to inter-individual differences in drug pharmacokinetics, such as phase I and phase II biotransformation enzymes. The polymorphisms also can be due to pharmacodynamic factors such as drug-receptor interactions (2).

Idiosyncratic drug reactions are type B reactions, which occur rarely and unpredictably amongst the population. They frequently occur with exposure to new drugs, as they have not been fully tested and full range of possible side-effects have not been discovered. This is not to be mistaken with idiopathic which implies that the cause is not known (3).

Idiosyncratic drug reaction does not appear to be concentration dependent. A minimal amount of drug will cause an immune response, but it is suspected that at a low enough concentration, a drug will be less likely to initiate an immune response. The dose of a drug to produce the same effect may vary by 4-6 folds among different individuals. This is mainly because of differing rates of drug metabolism as the amount of microsomal enzymes is genetically controlled. There are also differences in target organ sensitivity. A continuous variation with Gaussian frequency

distribution is seen in the case of most drugs. However, there are some specific genetic defects which lead to discontinuous variation in drug responses (4), e.g;

1. Atypical pseudo cholinesterase
2. G-6-PD deficiency
3. Acetylator polymorphism
4. Acute intermittent porphyria
5. CYP2D6 abnormality
6. Precipitation of an attack of angle closure glaucoma by mydiatrics in individuals with narrow iridiocorneal angle.

MECHANISM OF IDIOSYNCRASY

In adverse drug reactions involving overdose, the toxic effects is simply an extension of the pharmacological effect (Type A of adverse drug reactions), on the other hand, clinical symptoms of idiosyncratic drug reactions (Type B adverse drug reactions) are different from the pharmacological effect of the drug.

The proposed mechanism of cellular damage in case of idiosyncratic drug reactions are immune mediated toxicity either from toxic drug/drug metabolite or it may come from an injury or infection. To create an immune response, you must have a foreign molecule that antibodies combine to (i.e. the antigen) and you must have cellular damage. Very often, drug will not be immunogenic because they are too small to bind to antibodies, however a drug can cause a immune response if the drug binds a larger molecule. The second criteria of cellular damage can come either from a toxic drug/drug metabolite or it may come from an injury/ infection. These will sensitize the immune system to the drug and cause a response (3).

Most commonly, this is caused by enzymopathy, congenital or acquired, so that the triggering substance cannot be processed properly in the organism and causes symptoms by accumulating or blocking other substances to be processed(1). Enzymopathy-comprise a large class of genetic diseases involving disorder of metabolism. The majority are due to defects of single gene that codes for enzymes which facilitate conversion of various substances into other products, resulting either in accumulation of substance or reduced ability to synthesize sensational compounds (5).

Idiosyncrasy response should not be confused with hypersensitivity reactions which refer to undesirable reactions produced by normal immune system. Hypersensitivity requires a pre-sensitized (immune) state of the host. Various forms of hypersensitivity reactions have been recognized in humans which are often referred as allergies; collectively.

An Idiosyncrasy causing symptoms like allergy is also called pseudoanaphylaxis and its presentation is similar to that of anaphylaxis. It however does not involve an allergic reaction but is due to direct mast cell degranulation.

There is no clinical difference between allergy and idiosyncrasy, both can be self-limiting. Broadly Idiosyncrasy is treated symptomatically and its general prophylaxis includes a good family history of patient, as it may suggest strong hypersensitivity to a particular drug. Mode of delivery of a drug should be properly checked, as the drug, when used systemically may cause idiosyncrasy but not when used topically or vice-versa(6).

Table 1: Differences between Idiosyncrasy and Hypersensitivity

Idiosyncrasy	Hypersensitivity
Type B adverse drug reaction	Type A adverse drug reaction
Direct mast cell degranulation	Reactions require a pre-sensitized immune state of the host
Uncharacteristic or Bizarre drug effect due to peculiarities of an individuals	Stereotype symptoms which are unrelated to pharmacodynamic profile of drug
Genetically determined abnormal reactivity to chemical	An Immunological mediated reaction

Table 1: Differences between Idiosyncrasy and Hypersensitivity	
Idiosyncrasy	**Hypersensitivity**
Extreme sensitivity to low doses or extreme insensitivity to high doses of chemicals	Independent of dosage
Genetic polymorphisms can be due to inter-individual differences in drug pharmacokinetics	No genetic predisposition as well as no role of drug pharmacokinetics

Table:2 Drugs commonly used in ophthalmic practice causing idiosyncrasy	
Drugs	**Idiosyncratic Manifestations**
Sulpha group (a)- Sulfonamide(7-9)	Conjunctival chemosis, corneal epithelial edema, Acute periocular edema, acute hemolysis.
(b)- Acetazolamide (10)	Drowsiness
Atropine (11)	Periocular puffiness, Dermatitis, Conjuctival chemosis
Homatropine(11)	Same as Atropine
Phenylephrine(12)	Lid retraction, Photosensitivity
Chloramphenicol(13)	Optic neuritis , Acute hemolysis (aplastic anaemia), Digital paresthesias
Mild mercuric Chloride(14)	Irritative conjunctivitis
Yellow mercuric oxide(14)	Irritative conjunctivitis
Iodine(15)	Periocular pigmentation, conjunctival irritation.

CONCLUSION AND FUTURE PROSPECTS

RNA interference is an area of intense, upfront basic research and holds the key to various technological applications in future due to their higher silencing efficiency and shorter time requirements for screening and to analyses functions of wide variety of genes in different organisms. The RNA silencing technology apart from being highly sequence specific is also technologically facile and economical. Therefore, this technique has great potential in agriculture specifically for nutritional improvement of plants and the management of various plant diseases. Future directions will focus on developing finely tuned RNAi-based gene silencing vectors that are able to operate in a temporally and spatially controlled manner. In coming years better and comprehensive understanding of RNAi would allow the researchers to work effectively and efficiently in order to work more on improvement of crop plants nutritionally and in managing various diseases of crop plants. Finally, the discovery of RNAi has not only provided us with a powerful new experimental tool to study the function of genes but also raises expectations about future applications of RNAi in medicine.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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