

Adverse drug reactions: An Overview

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Abstract

Adverse drug reactions (ADR's) are defined the effects created by drugs producing unintended or noxious response. Also, an ADR is 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 a physiological function. The evaluation of ADRs adapts various factors that can predispose patients to adverse reactions. The types of adverse reaction can be studies in two main headings, i.e., more common ADRs including type A and B reactions; and less common ADRs which include type C, D and E reactions. The present review article explains about the various types and mechanisms of adverse reactions.

Key words: Adverse drug reactions, Types

1. Introduction:

Adverse drug reactions (ADR) represent one of the prime topics to be assessed in the modern times.¹⁻² According to world health organisation (WHO), an ADR can be defined as any response of a drug which is noxious and unintended, that occurs at doses used in humans for the prophylaxis, diagnosis or therapy of disease; or for the modification of physiologic function purposely excludes therapeutic failures, overdoes, drug abuse, non compliance, and medication errors.³⁻⁴ Moreover, it has been regarded as an appreciable harmful reaction which results from an intervention related to the use of a medical products. An adverse effect, which occurs as overstate of the desired therapeutic effect, forms a part of ADR, whereas, side effects are generally related to the therapeutic activities of a drug which may be beneficial as well as harmful.⁵⁻⁷ Thus, it may be suggested that an ADR is a harmful reaction or unwanted reaction that is followed by the administration of a medicinal product or a combination of drugs under normal conditions of use. However, various type of ADRs have been reported which include type A, type B and type C adverse reactions.⁸⁻⁹ Type A ADRs are commonly related to dose which enhance the normal therapeutic effect of drug, with common reasons of overdose and alteration of the dose, whereas type B have been considered as the idiosyncratic responses that are usually uncommon, unpredictable and not related to the pharmacological actions of the drug; and type C ADRs have been suggested to be connected with long-term drug therapies in which both serious and common effects on public health takes place.⁸⁻¹² The present review article has been aimed to discuss about the various type of adverse drug reactions.

2. Mechanisms of adverse drug reactions

An ADR can be defined as an unpleasant and harmful reaction resulting from an intervention after receiving the medication. The mechanism of adverse reactions can be divided into direct toxicity studies and hypersensitivity reactions that occur due to the pharmacokinetic and pharmacodynamic alterations of the drug products.⁹ Direct toxicity reactions may be attributed to the toxic effects of a compound or its metabolites which are apparent in various organ systems, inducing noxious chemical reactions, physiological dysfunction, DNA damage or injury to cellular structures and tissues.¹³⁻¹⁴ On the other hand, hypersensitivity reactions can be determined after the immune system of the individual shows an exaggerated response to a drug or its metabolites, which include allergy and anaphylactic reactions.¹⁵ It has been suggested that the results of direct cytotoxicity and excessive immune reaction are noticeable in various organs like skin, liver, lungs, bone marrow and kidneys.¹⁶⁻¹⁷

3. Types of adverse drug reactions

The types of adverse reaction can be studies in two main headings, i.e., more common ADRs including type A and B reactions; and less common ADRs which include type C, D and E reactions (Table 1).^{9,12} Type A adverse reactions have been commonly related to dose which enhance the normal therapeutic effect of drug. Moreover, the pharmacokinetic or pharmacodynamic factors of the drugs have been found to be responsible for type A ADRs. The pharmacokinetic causes of

type A reactions may be attributed to the genetic variations in order to cause ADRs.¹⁸ Moreover, hepatic diseases have been noted to cause pharmacokinetic variations that induce subsequent changes in the distribution and metabolism of drugs resulting in ADR.⁹⁻¹¹ The raised half lives of the drugs alongwith reduced glomerular filtration rates (GFR) has been suggested to cause pharmacokinetic variations. Moreover, the adverse effects have been detected with drugs extensively rejected by the kidney. In addition, the diseases have been noted to cause ADRs due to impaired absorption due to mucosal oedema, poor renal perfusion, or changes in apparent volume of distribution.¹² Also, in conditions like hypothyroidism and thyroid disease, the hepatic metabolism of the drugs get reduced which further have been suggested to lead pharmacokinetic variations ultimately causing type A adverse reactions.

The pharmacodynamic causes of type A reactions include hepatic disease, altered fluid and electrolyte balance, altered sensitivity, and long-term effects.¹⁹ The hepatic disease have been shown to affect pharmacodynamic response of a drug and cause ADR due to production of clotting factor. Also, the drug have to be escaped which impair clotting or affect bleeding by causing ulceration. Hypokalemia and hypercalcemia, the consequences of cardiac glycoside, have been noted to get potentiated, causing pharmacodynamic variations ultimately causing type A adverse reactions. In addition, type A adverse effects have been documented to be related to the pharmacological effects of the drug. However, type A effects can usually be replicated and studied experimentally. Also, type A adverse reactions have been detected by spontaneous reporting during the original clinical trails.²⁰⁻²¹ Hence, marketing the quantitative and controlled determination is needed in order to certify the relationship and major persistence with type A effects of low specificity.

Type B adverse effects have been noted in marginal number of patients and are often sensitive or idiosyncratic reactions.²² Moreover, type B adverse reactions have been suggested to be unforeseen and unpredictable; showing less or no relationship with the dosage. However, the relationship with time and low background frequency are generally the chief reasons to suspect the drug in type B effects. Furthermore, type B ADRs can be classified as non-immunological ADR's, that are further categorized as predictable and unpredictable reactions which are due to over dose, collective effects, slow toxicity, drug interaction, metabolic modification, teratogenicity, aggravation of disease, drug induced chromosomal disturbance, and intolerance; and immunological ADR's, which are unpredictable and occur due to immunoglobulin (Ig) E-dependent drug reactions, immune complex dependent drug reactions, cytotoxic drug-induced reactions, and cell mediated reactions.^{12,19}

The pharmacokinetic causes of type-B ADRs remains scarce, that can be an aspect to bizarreness of absorption or distribution, which suggests that the bio-activation of drugs yield reactive species responsible for a significant preparation of type-B adverse effects. Also, the direct or immune mediated toxicity has been noted to result in binding of such reactive metabolites. The type-B reactions propose to occur as a result of bio-activation of reactive metabolites includes hepatotoxicity, agranulocytosis, and hypersensitivity reactions.^{9,23} Moreover, the pharmacodynamic causes affecting type B reactions depend on response of individually patients to specific drugs. There has been a variation between individuals even after allowance has been made for patient's age, gender, body weight, disease state and concurrent drug regimens. The genetic, immunological, neoplastic, and teratogenic have been considered in qualitative difference in the target organ response to drugs. Also, the idiosyncratic reactions have been labelled in genetic causes for abnormal response for many type-B adverse reactions.²⁴

The type C adverse reactions have been attributed to both serious and common effects having notable outcomes on public health from chronic disease toxicities. Moreover, type C reactions have been regarded as the reactions with chronic effects related to long-term drug use, such as analgesic nephropathy or extrapyramidal effects. These reactions have been found to relate to the cumulative toxic effects of a drug used over time, in which the adverse effects increase gradually. In addition, the type C reactions have been suggested as the long-term drug effects including adaptive changes and withdrawal effects.⁹ Type C adverse reactions have been known to be chronic in nature associated with long-term drug therapy, which can be evidenced by the fact that the induction of iatrogenic hyperadrenocorticism occurs with chronic use of prednisolone or other corticosteroids. In addition, studies have reported the adaptation on discontinuation of the drug, commonly referred to as abstinence syndrome.²⁵ Type D reactions, also termed as delayed ADRs, are the reactions that have been found to be apparent after sometime of the treatment.

The development of secondary cancers in patients treated with alkylating agents like cyclophosphamide is the best example of type D adverse reactions. In addition, type E ADRs have been known to occur when drug treatment has been terminated suddenly, the examples of which include withdrawal seizures on terminating anticonvulsant therapy and adrenocortical insufficiency subsequent to glucocorticoids termination.^{9,12,19}

Table 1. Types of Adverse Drug Reactions

Type of ADRs	Characteristics	Examples
Type A	-Dose-related -Related to a pharmacological action of drug -Predictable from known pharmacology	-Nephrotoxicity caused by aminoglycosides -Anticholinergic effects of tricyclic antidepressants
Type B	-Not dose-related -Uncommon -No relation to a pharmacological action of the drug	-Penicillin- induced urticaria -Anticonvulsant hypersensitivity syndrome reaction
Type C	-Uncommon -Long term exposure of drugs	-Hypothalamic-pituitary-adrenal axis suppression by corticosteroids
Type D	-Prolonged exposure to a drug	-Tardive dyskinesia caused by antipsychotic medication
Type E	-Termination of treatment	-Tachyphylaxia

4. Conclusion

Adverse drug reactions have been regarded to arise due to pharmacokinetic and pharmacodynamic variations of drug products. ADRs have been reported to exist in various types and mechanisms, depending on the health status and environmental factors of the individual. However, extensive research in the area of factors affecting the incidence and tendency of ADR's have been performed but effective integration of theory and practice is needed to safeguard the patients requiring drug therapy.

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