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ADVERSE DRUG REACTION: MONITORING MANAGEMENT AND DIAGNOSIS

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ABSTRACT

A harmful or significantly unpleasant effect caused by a drug at doses intended for therapeutic effect (or prophylaxis or diagnosis) which warrants reduction of dose or withdrawal of the drug and/or foretells hazard from future administration. If a drug has a narrow therapeutic range, samples can be taken to allow the dose to be adjusted so that the concentration remains between a minimum value for efficacy and a maximum value for safety. The diagnosis of an adverse drug reaction is part of the broader diagnosis in a patient, if a patient is taking medicines, the differential diagnosis should include the possibility of an adverse drug reaction the first problem is to find out whether a patient is taking a medicinal product, including: over-the-counter formulations; India has more than half a million qualified Doctors and15, 000 hospitals having bed strength of 6, 24,000. It is the fourth largest producer of pharmaceuticals in the world, it is emerging as an important Clinical trial hub in the world, many new drugs are being introduced in our country.

KEYWORDS: Clinical trials, concentration, diagnosis, pharmaceuticals, medicines.

INTRODUCTION

WHO's definition of an adverse drug reaction, which has been in use for about 30 years, is "a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function".[1] Adverse drug reactions, or ADRs, which are officially described as: "A response to a drug which is noxious and unintended, and which occurs at doses normally used for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function.[2,3]. "A harmful or significantly unpleasant effect caused by a drug at doses intended

for therapeutic effect (or prophylaxis or diagnosis) which warrants reduction of dose or withdrawal of the drug and/or foretells hazard from future administration.".[4] A very broad definition of a drug would include "all chemicals other than food that affect living processes." If the affect helps the body, the drug is a medicine. However, if a drug causes a harmful effect on the body, the drug is a poison. The same chemical can be a medicine and a poison depending on conditions of use, dose and the person using it. A person with drug toxicity has accumulated too much of a medication in the bloodstream.[5,6]

Adverse drug event

"Any untoward medical occurrence that may be present during treatment with a medicine but does not necessarily have a causal relationship with this treatment, that is, an adverse outcome that occurs while the patient is taking the medicine but is not, or not necessarily, attributable to it.".[7]

Adverse drug reaction

"A response to a medicine which is noxious and unintended, and which occurs at doses normallyused in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification ofphysiological function.".[8]

Examples of adverse effects associated with specific medications

1. Abortion, miscarriage or uterine haemorrhage associated with misoprostol (Cytotec), a labor-inducing drug (this is a case where the adverse effect has been used legally and illegally for performing abortions)
2. Addiction with many sedatives and analgesics such as diazepam, morphine, etc.
3. Birth defects associated with Thalidomide and Accutane.
4. Bleeding of the intestine associated with aspirin therapy.
5. Cardiovascular disease associated with COX-2 inhibitors (i.e. Vioxx).
6. Deafness and kidney failure associated with gentamicin (an antibiotic).
7. Death, following sedation in children using propofol (Diprivan)
8. Dementia associated with heart bypass surgery.
9. Depression or hepatic injury caused by interferon.
10. Diabetes caused by atypical antipsychotic medications (neuroleptic psychiatric drugs)
11. Diarrhea caused by the use of orlistat (Xenical).
12. Erectile dysfunction associated with many drugs, such as antidepressants.

13. Fever associated with vaccination (in the past, imperfectly manufactured vaccines, such as BCG and poliomyelitis, have caused the very disease they intended to fight).

14. Glaucoma associated with corticosteroidbased eye drops.

15. Hair loss and anemia may be caused by chemotherapy against cancer, leukemia, etc.[9,10,11]

Classification of adverse drug reaction

reactions and constitute true drug hypersensitivity, with IgE-mediated drug allergies falling into this category [Drug reactions can be classified into immunologic and nonimmunologicetiologies. The majority (75 to 80 percent) of adverse drug reactions are caused by predictable, nonimmunologic effects.[1] The remaining 20 to 25 percent of adverse drug events are caused by unpredictable effects that may or may not be immune mediated.[1] Immune-mediated reactions account for 5 to 10 percent of all drug.[12,13]

Immunologic and Nonimmunologic Drug Reactions

TABLE-1[12,13]

TYPE		**EXAMPLE**
Immunologic		
Type I reaction (IgE-mediated)		Anaphylaxis from β-lactam antibiotic
Type II reaction (cytotoxic)		Hemolyticanemia from penicillin
Type III reaction (immune complex)		Serum sickness from anti-thymocyte globulin
Type IV reaction (delayed, cell-mediated)		Type IV reaction (delayed, cell-mediated)
Specific T-cell activation		Morbilliform rash from sulphonamides
Fas/Fas ligand-induced apoptosis		Stevens-Johnson syndrome, Toxic epidermal necrolysis
Other		Drug-induced, lupus-like syndrome, Anticonvulsant hypersensitivity syndrome
2.	**Nonimmunologic**	
	Predictable	
	Pharmacologic side effect	Dry mouth from antihistamines
	Secondary pharmacologic side effect	Thrush while taking antibiotics
	Drug toxicity	Hepatotoxicity from methotrexate
	Drug-drug interactions	Seizure from theophylline while taking erythromycin
	Drug overdose	Seizure from excessive lidocaine (Xylocaine)
B.Unpredictable		
Pseudoallergic		Anaphylactoid reaction after radiocontrast media
Idiosyncratic		Hemolyticanemia in a patient with G6PD deficiency after primaquine therapy
Intolerance		Tinnitus after a single, small dose of aspirin
G6PD = glucose-6-phosphate dehydrogenase.		

MONITORING AND THERAPEUTICS

Monitoring in the sense described is used in three different aspects of the therapeutic process. Clinicians and patients themselves, can monitor response to treatment of a specific condition – for example, monitoring the temperature during antibacterial treatment. If a drug has a narrow therapeutic range, samples can be taken to allow the dose to be adjusted so that the concentration remains between a minimum value for efficacy and a maximum value for safety.[14] Monitoring for adverse effects by repeated laboratory testing seems to have begun with the observation that the antibacterial drug chloramphenicol could cause bone-marrow toxicity of two types, one of which occurred at high dosage and was reversible, and the other of which could occur at any therapeutic dosage and generally resulted in fatal aplastic anaemia.[15] Monitoring is a process of checking a system that changes with time, in order to guide changes to the system that will maintain it or improve it. A recent article discussing the monitoring of disease in medicine has drawn attention to the more general problem of monitoring the health of patients suffering with chronic disease.[16] These examples illustrate monitoring by observing directly the quantity of interest, but indirect (surrogate or proxy) measures are also widely used. The choice of surrogate measure is important, as the surrogate needs to reflect closely the reaction of interest. Development of better surrogate measures to aid monitoring of disease and its response to therapy is dependent upon an understanding of the chain of events in the pathogenesis of disease through to its final clinical end-point.[17] The advice on haematological monitoring given to prescribers might be expected to reflect difficulties such as these, noted over 25 years ago. However, many Summaries of Product Characteristics provide instructions for monitoring for haematological adverse reactions that are incomplete or impractical in modern clinical settings.[18]

Management

Rapid action is sometimes important because of the serious nature of a suspected adverse drug reaction, for example anaphylactic shock. Otherwise, using clinical benefit-risk judgment, together with help from investigations, one decides which medicine or medicines should be withdrawn as a trial.[19] The patient should be observed during withdrawal. The waiting period will vary, depending on the rate of elimination of the drug from the body and the type of pathology. For example, urticaria usually disappears quickly when the drug is eliminated, whereas fixed psoriatic skin reactions can take weeks to resolve. If the patient is clearly getting better,[20] If the patient cannot manage without a medicine that has caused an adverse reaction, provide symptomatic relief while continuing the essential treatment.[21]

PENICILLIN ALLERGY

Cross reactivity between a β-lactam ring and penicillin restricts the use of carbapenems in patients who are allergic to penicillin.[22] 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.[23]

Surveillance

Surveillance methods for drug reactions, and population methods for proving associations are summarised in Outside of formal surveillance systems, all health-care professionals have a responsibility to inform their colleagues about clinically important adverse drug reactions that they detect, even if a well-recognised or causal link is uncertain.[24]

TABLE-2[25]

Method		Advantage	Disadvantage
Anecdotal (eg, in journals) Simple		cheap	Relies on individual vigilance and astuteness
Voluntary organized reporting* (doctors, pharmacists pharmaceutical companies)		Simple	Under-reporting; reporting bias by “bandwagon” effect
Intensive eventmonitoring		Easily organised	Selected population studied for a short time
Cohort studiesCan be prostive		good at detecting effects	Very large numbers required; very expensive
Casecohort studies		Good for studying rare effects with high power	As for cohort and case-control studies; complex
	Population statistics	Large numbers can be studied	Difficult to coordinate; quality of information may be poor;
	Record linkage	Excellent if comprehensive	Time-consuming; expensive; retrospective
	Meta-analysis	Uses data that have already been obtained	Need to obtain unpublished data; heterogeneity

Method Advantages Disadvantages

Anecdotal (eg, in journals) Simple; cheap Relies on individual vigilance and astuteness; Voluntary organized reporting* (doctors, pharmacists, Simple Under-reporting; reporting bias by “bandwagon” effect pharmaceutical companies).

Intensive eventmonitoring Easily organised Selected population studied for a short time Cohort studies Can be prospective; good at detecting effects Very large numbers required; very expensive.

Case-control studies Excellent for validation and assessment Will not detect new effects; expensive.

Case-cohort studies Good for studying rare effects with high power As for cohort and case-control studies; complex.

Calculations

Population statistics Large numbers can be studied Difficult to coordinate; quality of information may be poor; Record linkage Excellent if comprehensive Time-consuming; expensive; retrospective; Meta-analysis Uses data that have already been obtained Need to obtain unpublished data; heterogeneity.

FACTORS AFFECTING ADVERSE DRUG REACTION

1. **Patient related factors**

a Age

All drugs can produce ADRs, but not all patients develop the same level and type of ADRs. Age is a very important factor which affects the occurrence of ADRs. Elderly patients with multiple medical problems who are taking multiple drugs, those who have a history of ADRs, and those with a reduced capacity to eliminate drugs are at high risk for ADRs.[26] Infants and very young children are at high risk of ADRs because their capacity to metabolize the drug is not fully evaluated. The following are some factors that might affect the development of ADRs in neonates.[27]

1. Neonates have immature renal tubular function when they are below the age of 8 weeks, avoiding digoxin, aminoglycosides, ACE inhibitors, NSAIDs is a must.[28]
2. Physiologic hypoalbuminemia in neonates affects drug dosing. Caution is recommended when dealing with high protein binding drugs such as NSAIDs.[29]
3. Neonates, have low body fat; they might be affected by fat soluble drugs.[30]
4. Increasedanesthetic effects due to immature blood brain barrier at <8 weeks of age.[31]
5. Predisposition to hypotension due to poor cardiac compliance and immature baroreceptors.[32]

b. Gender

The biological differences of males and females affect the action of many drugs, the anatomical and physiological differences are body weight, body composition, gastrointestinal

tract factors, liver metabolism, and renal function, women in comparison to men have lower bodyweight and organ size, more body fat, different gastric motility and lower glomerular filtration rate.[33] They also suggested that women are more prone than men to develop torsade de pointes ventricular tachycardia during the administration of drugs that prolong cardiac repolarization. Women restrict their activity because of acute and chronic health problems approximately 25% more days per year than do men, spending approximately 40% more days in bed each year than men.[34]

c. Maternity status

Pregnancy has an impact on drug treatment. Not only are women affected by the drug, but the fetus will also be exposed to ADRs of the drug, acidity and tone of GIT are decreased during pregnancy and this might interfere with drug absorption or excretion and finally drug metabolism may be affected at certain stages of pregnancy.[35] Many drugs for example, antihypertensive drugs such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers pose a risk to the health and normal development of a fetus.[36]

d. Allergy

Drug independent cross-reactive antigens can induce sensitizations, which can manifest as a drug allergy. The existence of such cross-reactivity is supported by medical literature.[37] corresponding to the type I to IV immune reactions (Gell and Coombs Classification). Most of the drug allergies observed are type I or IV reactions; type II and III reactions are only encountered infrequently.[38]

e. Body weight and fat distribution

In the body, drugs are distributed to and from the blood and various tissues of the body (for example, fat, muscle and brain tissue), after a drug is absorbed into the bloodstream, it rapidly circulates through the body, as the blood recirculates, the drug moves from the bloodstream into the body's tissues, once absorbed, most drugs do not spread evenly throughout the body.[39] Some drugs, such as those that accumulate in fatty tissues, leave the tissues so slowly that they circulate in the bloodstream for days after a person has stopped taking the drug.[40]

2. Drug related factors

a. Polypharmacy

Taking several drugs, whether prescription or over-the-counter, contributes to the risk of having an ADR, the number and severity of ADRs increases disproportionately as the number of drugs taken increases, many definitions are applied for polypharmacy, It is different from scholar to scholar but the basic concept of taking more medications at the same time than are clinically appropriate remains constant.[41] A study among 65 year old patients and older in the United States of America found that in more than 40% of the patients involved in the study there was evidence of incorrect medication use, overuse and underuse for those treated by more than five medications.[42]

b. Drug dose and frequency

Drug dosing affects the development of ADRs in many ways; e.g. some drugs need to be given in the morning and others in the evening, some at bedtime, taking Bisphosphonates at bed time may lead to esophagitis, the antiplatelet effect of aspirin when taking in the evening is more potent that in the morning.[43]

Diagnosis and attribution of causality

The diagnosis of an adverse drug reaction is part of the broader diagnosis in a patient, if a patient is taking medicines, the differential diagnosis should include the possibility of an adverse drug reaction the first problem is to find out whether a patient is taking a medicinal product, including: over-the-counter formulations; products that may not be thought of as medicines (such as herbal or traditional remedies, recreational drugs, or drugs of abuse); and long-term treatments that the patient may forget (such as oral contraceptives).[44] The next step is to find out whether the effect could be due to a medicine, if the patient is taking several medicines, the problem is to distinguish which, if any, is causative, this problem is complex, because some of the patient's complaints might be due to other diseases or to one or more of the drugs, there are many formal methods for assigning robability of causation to a suspected adverse drug reaction.[45]

Pharmacovigilance in India

India has more than half a million qualified Doctors and15, 000 hospitals havingbed strength of 6, 24,000. It is the fourth largest producer of pharmaceuticals in the world, it is emerging as an important Clinical trial hub in the world, many new drugs are being introduced in our country, Therefore, there is a need for a vibrant pharmacovigilance system in the country to

protect the population from thepotential harm that may be caused by some of these new drugs.[46] The National Pharmacovigilance Programme was officially inaugurated by the Honorable Health Minister Dr. Anbumani Ramadoss on 23 November, 2004 at New Delhi.[47]

a. Improve patient care and safety in relation to use of medicines and all medical and paramedical interventions.
b. Improve public health and safety in relationto use of medicines.
c. Promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public.[48]

AIMS OF PHARMACOVIGILANCE

The aims of pharmacovigilance are[49]

1. The identification and quantification of previouslyunrecognized adverse drug reactions (ADR).
2. The identification of sub-groups of patients atparticular risk of ADRs (the risk relating to dose, age,
gender and underlying disease).
3. The continued monitoring of the safety of a product, throughout the duration of its use, to ensure that its
risks and benefits remain acceptable. This includessafety monitoring following significant newly approved indications.
4. The comparative adverse drug reaction profile ofproducts within the same therapeutic class.
5. The detection of inappropriate prescription andadministration.
6. The further elucidation of a product's

Future aspect of pharmacovigilence in india

With more and more clinical trials and other clinical research activities being conducted in India, there is an immense need to understand the importance of pharmacovigilance and how it impacts the life cycle of the product, given this situation at present, a properly working pharmacovigilance system is essential if medicines are to be used safely.[50]

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