Review Article

A review on Adverse drug reactions monitoring and reporting

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ABSTRACT

Adverse drug reactions (ADRs) are considered as one among the leading causes of morbidity and mortality. Around 10% of hospital admissions are estimated to be due to ADRs and about 5-20% of hospitalized patients experience a serious ADR. Reporting of ADRs has become an important component of monitoring and evaluation activities performed in hospitals4. Such ADR reporting programs encourage surveillance for ADRs, promote the reporting of ADRs and stimulate the education of health professionals regarding potential ADRs. This article reviews about ADR reporting and monitoring, Classification of Adverse drug reaction, Contrast between Adverse Effects and Adverse Reactions, Methods of monitoring adverse drug reactions.

Keywords: Bizarre, Augmented, Karch and Lasagna, Predictable, Unpredictable.

INTRODUCTION

American society of health-system pharmacists(ASHP) defines a significant ADR as any unexpected, unintended, undesired, or excessive response to a drug that, (I) Requires discontinuing the drug (therapeutic or diagnostic), (ii)Requires changing the drug therapy, (iii) Requires modifying the dose (except for minor dosage adjustments), (iv) Necessitates admission to a hospital, (V) Prolongs stay in a health care facility, (vi)Necessitates supportive treatment, (vii)Significantly complicates diagnosis, (viii)Negatively affects prognosis, or results in temporary or permanent harm, disability, or death.Consistent with this definition, an allergic reaction (an immunologic hypersensitivity, occurring as the result of unusual sensitivity to a drug) and an idiosyncratic reaction (an abnormal susceptibility to a drug that is peculiar to the Individual) are also considered ADRs. Several other definitions of ADRs exist, including those of the WHO, Karch and Lasagna, and the Food and Drug Administration (FDA).**WHO**: Any 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 physiological function" **Karch and Lasagna**:"Any response to a drug that is noxious and unintended, and that occurs at doses used in humans for prophylaxis, diagnosis, or therapy, excluding failure to accomplish the intended purpose."**FDA**: For reporting purposes, FDA categorizes a serious adverse event (events relating to drugs or devices) as one in which "the patient outcome is death, life-threatening (real risk of dying), hospitalization (initial or prolonged), disability (significant, persistent, or permanent), congenital anomaly, or required intervention to prevent permanent impairment or damage." The perspective, it may be helpful to note events that are not classified as ADRs. A side effect is defined by ASHP as an expected, well-known reaction resulting in little or no change in patient management (e.g., drowsiness or dry mouth due to administration of certain antihistamines or nausea associated with the use of antineoplastics). An ongoing ADR-monitoring and reporting program can provide benefits to the organization, pharmacists, other health care professionals, and patients. These benefits include (but are not limited to) the following,

(I) Providing an indirect measure of the quality of pharmaceutical care through identification of preventable ADRs and anticipatory surveillance for high-risk drugs or patients.

(II) Complementing organizational risk-management activities and efforts to minimize liability.

(III) Assessing the safety of drug therapies, especially recently approved drugs.

(IV) Measuring ADR incidence.
(V) Educating health care professionals and patients about drug effects and increasing their level of awareness regarding ADRs.
(VI) Providing quality-assurance screening findings for use in drug-use evaluation programs.
(VII) Measuring the economic impact of ADR prevention as manifested through reduced hospitalization, optimal and economical drug use, and minimized organizational liability.

Some of the academic institutions in cities, like Delhi, Bombay, Vellore and Mysore, have their own systems of reporting and monitoring ADRs. These are helping in improving the knowledge about ADRs in Indian population and collecting data for future reference. ADR monitoring system is lacking in most of the government and non government health care setup.

A Review on ADR reporting and monitoring

Adverse drug reactions (ADRs) are unintended, common, and important con- sequences of medical therapy.

Classification of Adverse drug reaction

Type-A (Augmented): Commonest (up to 70%)-Dose dependent, severity increases with dose. Preventable in most part by slow introduction of low dosages. Predictable by the pharmacological mechanisms, e.g., hypotension by beta-blockers, hypoglycemia caused by insulin or oral hypoglycemic, or NSAID induced gastric ulcers.

Type-B (Bizarre): Rare, idiosyncratic, genetically determined, unpredictable, mechanisms are unknown, Serious, can be fatal; unrelated to the dose, e.g., hepatitis caused by halothane, aplastic anaemia caused by chloramphenicol, neuroleptic malignant syndrome caused by some anaesthetics and antipsychotics.

Type-C (Continuous drug use): Occurs as a result of continuous drug use. May be irreversible, unexpected, unpredictable, e.g., tardive dyskinesia by antipsychotic, dementia by anticholinergic medication.

Type-D (Delayed): Delayed occurrence of ADRs, even after the cessation of treatment e.g, corneal opacities after thioridazine, ophthalmopathy after chloroquine, or pulmonary/peritoneal fibrosis by methyserzide.

Type-E (End of dose): Withdrawal reactions. Occurs typically with the depressant drugs, e.g., hypertension and restlessness in opiate abstainer, seizures on alcohol or benzodiazepines withdrawal; first dose hypotension caused by alpha-blockers (Prazosin) or ACE inhibitors.

Type-F (Failure of therapy): Results from the ineffective treatment (previously excluded from analysis according to WHO definition), e.g., accelerated hypertension because of inefficient control. If adverse drug reactions are considered as any other medical illness and approached in the same way, then many questions would appear like:

1. What is an adverse drug reaction (Definition)?
2. What is its importance in the current medical practice (Epidemiology)?
3. What are the factors related to its occurrence (Etiology)?
4. What are the mechanisms of its causation (Pathogenesis)?
5. What can be done to prevent it (Prevention)?

Following table compares the characteristics usually associated with each type of reaction

Type A	Type B
Predictable	Unpredictable
Usually dose dependent	Rarely dose dependent
High morbidity	Low morbidity
Low mortality	High mortality
Responds to dose reduction	Responds to drug withdrawal

The Contrast between Adverse Effects and Adverse Reactions

The terms 'adverse drug effects' and 'adverse drug reactions are commonly used inter changeable'. However, there is a distinct difference, which suggests that different definitions of the two terms are necessary. The distinction between the two terms is made clear by considering how adverse drug reactions arises

1. Extrinsic moiety (e.g. a drug or metabolite, a contaminant or adulterant)
2. Intrinsic moiety (e.g a tissue protein, such as a receptor, ion channel, or enzyme)
3. The two being distributed in the same place
4. The encounter results in an adverse effect (the outcome)
5. Which results in an adverse reaction (the Sequela).

Adverse effects and adverse reactions have different manifestations by which they can be recognized: adverse effects are usually detected by laboratory tests (e.g, bio-chemical, haematological, immunological, radiological, pathological) or by clinical investigations (e.g. Gastrointestinal endoscopy, cardiac catheterization), adverse reactions by their clinical manifestations (symptoms and/or signs).

Classification scheme for adverse drug reactions:

I. Predictable: known pharmacology of a drug and are associated with high morbidity and low mortality.

a) Side effects: Undesired effects (often self-limited) that are predictable based on the pharmacologic

action of the drug (e.g., tremor associated with beta-agonist therapy). b) Secondary effects: Undesired but not inevitable effects that are predictable based on the pharmacological action of the drug (e.g., pseudo membranous colitis associated with clindamycin therapy) C) Interactions: Interactions with other drugs, foods, or diseases that alter drug clearance and Produce concentration-dependent effects (e.g. inhibition of metabolism of cyclosporine by erythromycin) d) Toxicity: Undesired effects produced by elevated drug doses (e.g., metabolic acidosis associated with salicylate overdose)

II. Unpredictable: Reactions are idiosyncratic, bizarre or novel responses that cannot be predicted from the known pharmacology of a drug.a) Intolerance: Exaggerated side effects after usual drug dosage or with usual therapeutic drug Concentrations (e.g., tinnitus in the setting of therapeutic salicylate concentrations) b) Allergic or pseudo allergic: Undesired effects of an allergic or apparently immune-Mediated nature (e.g. urticaria Associated with penicillin therapy) c) Idiosyncratic: Undesired and often severe effects that are not related to the known pharmacologic action of the drug.

Risk factors for adverse drug reactions[19]

1. Polypharmacy
2. Extreme age (very young and very old)
3. Previous history of adverse drug reactions Impairment in the organs of clearance
4. Female

Methods of monitoring adverse drug reactions

ADR monitoring for safety evaluation is a complex process. Some of the generally followed monitoring methods are as follows.

Case reports

The publication of single case reports, or case series, of ADRs in medical literature is an important means of detecting new and serious reactions; especially Type B reactions. Their importance is on the decline with reactions; especially Type B reactions. their importance is on the decline with the emergence of spontaneous reporting systems. e.g. : Halothane induced hepatitis.

Cohort studies

These are prospective studies, which study the fate of a large group of patients taking a particular drug. They can also compare the rates of events in groups of patients taking the drug of intent with a comparative group. Prescription event monitoring and different record linkage schemes are part of this prescription event monitoring-In this, prescriptions for certain drugs are identified and followed up by asking the prescriber to fill in a simple questionnaire recording any medical event from the patients. Here the prescriber does not have to judge causality between the event and the drug.

Record linkage system

Here the records from different sources such as general practice and hospital records, pharmacy records dental records, certificated cause of death, patients records etc are linked and analyzed. Such linkage becomes quite useful when seeking long term effects of drug use (e.g. : possible increased occurrence of malignancy or of mental retardation in individuals in individual's pregnancy.)

Patient questionnaires

Self administered questionnaires can be used for out-patients regularly attending clinics, though they pose a risk of recall biases. They have helped to detect many unsuspected adverse reactions. Ex: as headache and weakness in arms and legs due to metformin. They are also used to show absence of effects.

Intensive monitoring

These are hospital based intensive programs. In this all patients admitted to a designated ward are included in the analysis. Specially trained personnel obtain the necessary information from the patients and their records such as demographics, medical history, drug exposure, known side effects of the drugs, any lab test reports and outcome of treatment. This method has the potential to follow up and investigate adverse reactions suggested by other systems of detection such as isolated case reports in medical journals, Also, frequency of side effects can be studied more cheaply compared to a clinical trial. Basically, intensive monitoring provides information about relatively common and early reactions to drugs used under hospital conditions. It is not possible to identify delayed reactions since the patients are not hospitalized long enough for their detection.ADR monitoring is an important part of post marketing surveillance which helps in generating data on safety of medications. The short term goals and methodology of an ADR monitoring system depends on the clinical setup where it is being done, but in general "ADR monitoring" aims at:

1. Promoting rational use of drugs.
2. Safe use of Medicine.
3. Promote safety in all medical and paramedical interventions.
4. Improving patient care/improving public health.
5. Assessment of benefit/harmful.
6. Effectiveness and risk of medicines.
7. Improving the cost effective use of medicines.
8. Promoting awareness, understanding of ADRs in the public.
9. Disseminating the drug information and its effective communication to all other healthcare professionals and general public.

Conclusion

ADR monitoring in any clinical set up can thus be able to provide solutions to the problems resulting from irrational drug use, overdoses, poly pharmacy, drug interactions, and concomitant use of traditional and herbal medicines with medication errors, failure of pharmacotherapy. This ADR reporting helps in improving the patient health and the identification of ADR is very useful for physicians so that the misuse,

over doses, drug interactions and repeated ADR's will be reduced and ultimately it results in patient's health improvement.

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References

1. Ditto AM. Drug allergy. In: Grammer LC, Greenberger PA, editors. Patterson's allergic diseases. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2002. P. 295.
2. Jick H. Adverse drug reactions: the magnitude of the problem. J Allergy Clinlmmunol 1984; 74:5557.
3. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. Journal American Medical Association 1998; 279:1200-5.
4. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp pharm1992; 49:2229-32.
5. American Society of Health System Pharmacists. ASHP guidelines on adverse drug reaction monitoring and reporting. Am J Hosp Pharm1989; 46:336-7.
6. Murphy BM, Frigo LC. Development, implementation, and results of a successful multidisciplinary adverse drug reaction reporting program in a university teaching hospital. Hosp Pharm 1993; 28 (12):1199-204,1240.
7. Moride Y, Haramburu F, Requeyo AA, Begaud B. Underreporting of adverse drug reactions in general practice. Br J Clinpharmacol1997; 43 (2): 177-81.
8. Alvarez-Requejo A, Carvajal A, Begaud B, Moride Y, Vega T, Martin Arias LH. Under reporting of adverse drug reactions. Estimate based on a spontaneous reporting scheme and a sentinel system. Eur J Clin Pharmacol 1998; 54:483-8
9. Gallelli L, Ferreri G, Colosimo M, Pirritano D, Flocco MA, Pelaia G, et al. Retrospective analysis of adverse drug reactions to bronchodilators observed in two pulmonary divisions of Catanzaro, Italy. Pharmacol Res2003; 47 (6): 49
10. Wu WK. Evaluation of outpatient adverse drug reactions leading to hospitalization. Am J Health-Syst Pharm 2003; 60 (3): 253-9.
11. Regal B. Finally a pharmacovigilant India. Uppsala Rep 2004; 25:7-8.
12. Adithan C. National pharmacovigilance program. Indian J Pharmacol 2005; 37:347.
13. Requirements for adverse reaction reporting. Geneva, Switzerland: World Health organization; 1975.
14. Karch FE, Lasagna L. Adverse drug reactions-a critical review. Journal American Medical Association. 1975; 234:1236-41.
15. Kessler DA. Introducing Medwatch, using FDA form 3500, a new approach to reporting medication and device adverse effects and product problems. Journal American Medical Association. 1993; 269:2765-8.
16. Bhatt AD. Drug related problems and adverse drug events: Negligence, litigation and prevention. Journal of the Association of Physicians of India 1999; 47:715-20.
17. Ferner RE, Aronson JK. EIDOS: a mechanistic classification of Adverse drug effects. Drug Saf. 2010; 33 (1): 13-23.
18. Patterson R, DeSwarte RD, Greenberger PA, et al. Drug allergy and protocols for management of drug allergies. Allergy proc. 1994; 15:239-264.
19. Av Kiran R, Ratan JL, Mangala L, Umni C, Swaroop K. Bamah A Study on Adverse Drug Reactions In Hiv Infected Patients At A Art Centre of Tertiary Care Hospital In Guwahati, India Asian J Pharm Clin Res, Vol 6, Suppl 2, 2013,102-104.