

Safety monitoring of drugs - Where do we stand?

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Abstract

Drug related complications, a major cause of hospitalizations, lead to huge economic burden and significant human suffering. New chemical entities enter the market without sufficient safety data on patient population making rare (Adverse Drug Reactions) ADRs undetected in the clinical trials. ADR monitoring helps in detecting the occurrence of rare and unknown ADRs and helps in prevention of further occurrence. Several methods are adopted for effective monitoring of ADRs. An effective ADR monitoring program requires adequate infrastructure and trained manpower. In developed countries, the ADR monitoring system is well established. In Nepal, the concept of ADR monitoring is in the infant stage. A simple approach for ADR monitoring may be helpful in starting an ADR monitoring program in hospital setups in Nepal. Though it is difficult to prevent ADRs, a systematic approach will definitely help in minimizing the further occurrence of similar ADRs.

Key words: Adverse Drug Reactions, Causality assessment, Pharmacoeconomics, Pharmacovigilance, Safety monitoring

It is universally accepted that “No drug is absolutely free from side effects”. For example, even the so-called safe drug paracetamol is associated with significant number of Adverse Drug Reactions (ADRs). ADRs are one of the leading causes of morbidity and mortality. ADRs are responsible for a significant number of hospital admissions, with reported rates ranging from 0.3% to as high as 11%.¹ It has been estimated that approximately 2.9% to 5.6% of all hospital admissions are caused by ADRs and as many as 35% of the hospitalized patients experience an ADR during their hospital stay.² An incidence of fatal ADRs is 0.23% to 0.41%.³

In developing countries, the magnitude of ADRs is felt less and the importance of their monitoring is less understood. In this article, the authors provide an overview of ADRs in relation with Nepal and provide an approach to start an ADR monitoring system in a 100 bedded hospital based on their experience.

Definition of an ADR

World Health Organization (WHO) defines an ADR as “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.”⁴

Karch and Lasagna defined an ADR as “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.”⁵

What are the types of ADR?

There are several means of classifying ADRs. Every method has its own merits and demerits. One of the simplest means of classification is proposed by Rawlins and Thompson (1961).⁶ According to their classification, ADRs are classified into Type A and Type B reactions.

Type A: These reactions include normal and augmented response to drugs and are dose dependent. These reactions are usually predictable due to the known pharmacology of drug and thus preventable. The incidence of Type A reactions is high and they are responsible for considerable morbidity. Reducing the dosage or changing the therapy can overcome this type of reactions. Examples: Bradycardia with beta adrenoreceptor blockers, bleeding with anticoagulants.

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Type B: These reactions are unrelated to the known pharmacological action of the drug and are often caused by immunological and pharmacogenetic mechanisms. Type B reactions are generally unrelated to dosage and, although comparatively rare, they often cause serious illness and death. These reactions are often not predictable and preventable. Examples: malignant hyperthermia caused by anesthetics, acute porphyria and many immunological reactions.¹⁰

However there are several limitations of Rawlins and Thompson classification. Certain ADRs do not fit in to either category comfortably hence it is difficult to decide whether certain reactions are Type-A or Type-B. According to this classification everything that is not a Type-A reaction got classified as Type-B, rendering the latter a highly heterogeneous group with little in common.

What are the factors contributing to ADR?

Several contributing factors for ADRs have been identified. Some of them are listed below.

1. *Multiple drug therapy:* The incidence of ADRs has been shown to increase sharply with the number of drugs taken.
2. *Age:* The very old and very young are more susceptible to ADRs. In general, elderly patients have multiple problems including organ failures, which can increase the incidence and severity of ADRs.
3. *Sex:* In general, women are at greater risk of ADRs than men.
4. *Polypharmacy:* In general, patients with more number of drugs are at greater risk of developing ADRs
5. *Intercurrent diseases:* Patients with impaired kidney and liver functions are at greater risk for ADRs.
6. *Race and genetic polymorphism:* Since hereditary factors are known to affect the bioavailability of drugs, it can be one of the contributing factors for ADRs.

What is the pharmaco-economic impact of ADRs?

A study demonstrated that adverse drug events extended the hospital stay by nearly two days and increased the cost of hospitalization by about \$2,000.⁸ It has been found that the total cost of drug related morbidity and mortality exceeds the cost of medications themselves.⁹ It is now recognized that the cost associated with drug related morbidity and mortality is exceedingly high, between \$US 30.1 billion and \$US 136.8 billion annually in the US if direct and indirect costs are included.¹⁰ The limited resources of health care delivery systems in

developing countries are stretched even further by ADR-related admissions. The economic impact of ADRs is less documented from the developing countries. However, a recent South Indian study found out that majority (47%) of the reactions were moderate in severity and the total cost incurred in managing all the reported ADRs was Rs 76,564 (US\$ 1595) with an average cost of Rs 690 (US\$ 15) per ADR.¹¹

What is meant by pharmacovigilance?

WHO defines pharmacovigilance as “science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems”. Pharmacovigilance, previously referred to as adverse drug monitoring or drug surveillance can now be regarded as the quality control system of the society. Its broader aim is to check if medicines fulfill their intended role in alleviating human suffering, reducing disease related economic loss, with the best acceptable safety in use. The ultimate aim of pharmacovigilance is to ensure safe and rational use of medicines once they are released for general use in the society. A most important outcome of pharmacovigilance is the prevention of patients being affected unnecessarily by negative consequences of pharmacotherapy.¹²

Why ADR monitoring is needed?

New Chemical Entities (NCE) as well as new formulations of existing medications is increasing at rapid rate. NCEs are marketed after phase 3 trials. In phase-I trials the drug is tested on normal volunteers to determine their pharmacodynamic effects and possible toxic effects. In phase -II trials, the new compound is compared either with a placebo, or with an existing compound with similar pharmacological effects in a limited number of subjects. Phase-III trials involve a much larger number of patients, are carried out in several centers often situated in several countries. Trials up to this point may be sufficient to detect ADRs that may occur with a relatively high frequency, but rare events may go undetected. Some of these will manifest as ADRs during phase 4 or post-marketing surveillance.¹³ An ageing population will be more likely to have cardiovascular, pulmonary, musculoskeletal and metabolic disorders that necessitate several medications. Recent studies have shown that ADRs are much common in patients taking more than one medications.¹⁴ With advancing age physiological reserve is also reduced. This makes the older patients more vulnerable to the effect of ADRs compared to younger patients, and a greater degree of disability.¹⁵

Exclusion criteria of many of these studies eliminate patients with multiple disease states or other contributing factors to ADRs. Moreover special patient population such as pediatrics and geriatrics are not studied well in the clinical trials. Also most of the studies are of short term drug use and thus eliminate the ability to recognize any ADR associated with long term use.

What are the methods to monitor ADRs?^{16,17,18}

Several methods that can be adopted for ADR monitoring. The choice of the method depends upon the objective of the program, the setup, availability of manpower etc. Some common methods to monitor ADRs are listed below.

1. Case reports: The publication of single case reports, or case series, of adverse drug reactions in the medical literature is an important means of detecting new and serious reactions, particularly type B reactions. For example, halothane induced hepatitis was first noticed through case reports.

2. Anecdotal reporting: The majority of first reports of ADRs still come mostly through anecdotal reports from individual doctors that a patient has suffered some peculiar effect. Such reports need to be verified by further studies, and sometimes fail to confirm the problem.

E.g.: Variation in serum levels and efficacy of Tricyclic Antidepressants (TCAs).

3. Spontaneous reporting system: Spontaneous reporting continues to be the principal method for monitoring the safety of marketed drugs. In the United Kingdom (UK), United States of America (USA) and Australia, the ADR programs in use are based on spontaneous reporting system. Clinicians are encouraged (or, in some countries, mandated) to report any or all reactions that they believe may be associated with drug use. Usually, attention is focused on new drugs and serious ADRs, the reporting of which is mandatory in some countries. These systems are generally inexpensive, simple to operate and do not interfere with clinical practice to any great extent.

4. Intensive event recording: Certain hospital based ADR reporting schemes designate a group of individuals to screen a defined population specifically to detect ADRs and relate them to specific drugs. These schemes have not generally been effective in detecting anything new, that is partly because the population studied in such schemes is relatively small and more importantly, each patient is studied for only a short period of time.

5. Cohort studies (prospective studies): In these studies, patients taking a particular drug are identified and events are then recorded. The weakness of this method is the relatively small number of patients likely to be studied, and the lack of suitable control group to assess the background incidence of any adverse events. Such studies are expensive and it would be difficult to justify and organize such a study for every newly marketed drug.

E.g.: A group of people who smoke and a group of people who do not, and follow them forward through time to see what health problems they develop.

6. Case-control studies (retrospective studies): These studies compare drug usage in a group of patients with a particular disease with use among a matched control group who are similar in potentially confounding factors, but who do not have the disease. The prevalence of drug taking is then compared between the groups and a significant excess of drug takers in the disease may be evidence of an association with the drug. This is a useful retrospective method which can provide valuable information on the incidence of type B reactions and the association between drugs and disease.

E.g: A study on which lung cancer patients are asked how much they smoked in the past and the answers are compared with a sample of the general population.

7. Case-cohort studies: It is a hybrid of prospective cohort study and a retrospective case control study. Patients who present with symptoms or an illness that could be due to an ADR are screened to see if they have taken the drug. The results are then compared with the incidence of the symptoms or illness in a prospective cohort of patients who are taking the drug.

E.g. Dose-response relation between styrene exposure and ischemic heart disease

8. Record linkage: The idea here is to bring together a variety of patient records: general practice records of illness events, general practice records of prescriptions, hospital records of illness events and hospital records of prescriptions. In this way it may be possible to match illness events with drugs prescribed. A specific example of the use of record linkage is the so-called Prescription Event Monitoring Scheme (PEMS), in which all the prescriptions issued by selected practitioners for a particular drug are obtained from the prescription pricing authority. The prescribers are then asked to inform those running the scheme of any events seen in the patients taking the drugs. This scheme is less expensive and time consuming than other surveillance methods.

9. Meta analysis: This is a quantitative analysis of two or more independent studies to determine an overall effect and to describe reasons for variation in study results. Suggested roles for Meta analytic techniques include the establishment of associations between drugs and adverse events, estimation of the frequency of ADRs and identification of subgroups at increased risk for ADRs.

10. Use of population statistics: Birth defect registers and cancer registers can be used if a drug-induced event is highly remarkable or very frequent. If suspicions are aroused then case control and observational cohort studies will be initiated.

What are the basic requirements of an effective ADR monitoring program?

A well established ADR program requires infrastructure, funding, expertise and dedicated staff. At the minimum, an ADR monitoring and reporting program should include the following features:

1. The program should establish an ongoing concurrent (during drug therapy) surveillance based on reporting of suspected ADRs by pharmacists, physicians, nurses, or patients, concurrent or prospective (before drug therapy) surveillance system for drugs or patients with a high risk for ADRs; and a concurrent surveillance system monitoring the use of “tracer” drugs that are used to treat common ADRs (eg orders for immediate doses of antihistamines, epinephrine, and corticosteroids).
2. Prescribers should be notified regarding suspected ADRs.
3. Information regarding suspected ADRs should be reported to the pharmacy for complete data collection and analysis, including the patient’s name, the patient’s medical and medication history, a description of suspected ADR, the temporal sequence of the event, any remedial treatment required, and sequelae.
4. The cause(s) of each suspected ADR should be evaluated based on the patient’s medical and medication histories, the circumstances of the adverse event, the result of dechallenge and rechallenge (if any), alternative etiologies, and a literature review.
5. A description of each suspected ADR and outcomes should be documented in the patient’s medical record.
6. Serious or unexpected ADRs should be reported to the food and drug administration (FDA) and the drug’s manufacturer.

7. All ADR reports should be reviewed and evaluated by the pharmacy and therapeutics committee.
8. ADR report information should be disseminated to health-care professional staff members for educational purposes. Patient confidentiality should be preserved.
9. Finding from an ADR monitoring and reporting program should be incorporated into the organization’s ongoing quality assurance activities.¹⁹

What are the expected outcomes of an ADR monitoring program?

An ongoing ADR monitoring and reporting program can help to:

1. Provide a measure of the quality of pharmaceutical care through identification of preventable ADRs and anticipatory surveillance for high- risk patients.
2. Complement organizational risk-management activities and efforts to minimize liability.
3. Assess the safety of drug therapies, especially new ones.
4. Measure ADR incidence rates over time.
5. Educate health professionals on drug effects and increase their level of awareness regarding ADRs.
6. Provide quality - assurance screening findings for use in drug –use evaluation programs.

Over time, an ongoing ADR monitoring and reporting program may help to measure the economic impact of ADRs prevented, as manifested through reduced hospitalization, efficient and economical drug use, and minimize organizational liability.¹⁹

What is the role of healthcare professionals in minimizing ADRs?

An ongoing ADR program should be the objective of all the members of the healthcare team. It should be kept in mind that the program is teamwork and should not be of the personal interest of any single member. The roles of different healthcare members and the hospital Drugs and Therapeutics Committee (DTC) are discussed in brief.

Nurse’s role: A nurse is the first member to observe the patient while the patient is admitted in the hospital. Some of the responsibilities of nurses are as follows.

1. Take a through medication history in any patient assessment, including prescription medications (including any prescribed by a different clinician) and over-the-counter

medications (including vitamins, herbal remedies, and health foods).

2. Ask patients about allergies or other adverse experiences with medications. Then try to clarify which were true allergies versus unpleasant side effects. Ask especially if any side effects resulted in the patients' discontinuing the drug (either on their own decision or on advice of the prescriber).
3. In follow-up visits be sure to ask patient about any side effects and whether the patients are continuing to take the medications. If side effects are present, advise patient (if possible).
4. Use knowledge of patient's pathophysiology, other concurrent therapies, or other bases for having alterations in pharmacokinetics to adjust dosage and/ or to schedule medications in order to prevent adverse drug effects related to this patient variable.
5. Have a high index of suspicion of an adverse effect for drugs in classifications commonly known to produce adverse drug effects. (Eg. Cardiovascular, psychotropics, antibiotics) or when a patient is on multiple drugs.
6. Consider an adverse effect from a drug even if that adverse effect is not in the package insert or standard references.
7. Teach the patient and family the signs and symptoms that should be reported immediately versus those that can wait until the next visit unless bothersome to the patients.
8. When administering a drug be careful to avoid errors that could result from misinterpretation of what is prescribed.
9. Report suspected adverse effects of drug (and medical devices) to respective regulatory authority. For example, in Nepal, the Department of Drug Administration (DDA) at Kathmandu.
10. Contribute to the improvement of patient safety and care by monitoring practice of self and/ or others for adverse effects of drugs.²⁰

Pharmacist's role: The pharmacist is often the last member of the health care team to see the patient before he takes the drug without direct medical supervision. The pharmacist's role is to promote the development, maintenance and ongoing evaluation of a program to reduce the risks of ADRs by detecting, reporting and assessing any suspected ADRs. A pharmacist can perform following strategies to minimize the occurrence of ADRs:

1. Educate the staff (physician, nurses, etc.) and encourage compliance with the ADR reporting program. Include the importance of ADR

reporting, identified trends, common signs and detection tips.

2. Develop prospective review systems for reducing ADRs. For example, target drug projects, residents on high risk medications (warfarin, NSAIDs, etc), residents on >5 medications, and routine monitoring of abnormal laboratory and high- risk patients.
3. Provide in-service programs based on identified trends in reporting and appropriate changes in treatment.
4. Pharmacists should strive to enhance their knowledge in geriatric pharmacotherapy.¹⁹

Role of the physicians: The role of physician in ADR minimizing strategies are immense. Some of them are enumerated below.

1. Supplying information on suspected adverse reactions is as much a moral duty for the physician as are other aspects of patient care.
2. Physicians in practice must recognize that all the effects of new drugs have not been elucidated at the time of marketing. Much of the development of knowledge about adverse effects depends on the ability of individual physicians to detect these effects and to make preliminary attributions to the drug when appropriate.
3. Physicians are urged to keep blank copies of the report form that is mailed to them by the FDA.
4. Physicians need to be assured that their reports are important and that they are used.²¹

Role of hospital Drug and Therapeutics Committee (DTC):^{22,23} The main objective of the Drugs and therapeutics committee in the hospital is to ensure safe and efficacious use of drugs. The committee should develop strategies to implement the ADR monitoring program. It should also define the criteria to include new drugs in the hospital. The committee should meet periodically and discuss the safety issues of drugs in the hospital. If any particular drug/brand is known to cause ADR frequently, then immediate steps should be taken to stop the use of that particular drug. The committee should also closely monitor the newer drugs for any possible side effects. It should ensure proper drug information for the healthcare professionals through development and revision of Hospital formulary. The formulary should mention on the dosage regimen of the drugs, especially in case of renal failure, liver failure etc. It should also emphasize on the teratogenic potential of drugs and the drug use pattern in specialized patient population. This approach can minimize the occurrence of ADRs in the hospital.

In general all the healthcare workers should perform close monitoring on high risk patients (these include, but are not limited to pediatric patients, geriatric patients, patients with hepatic/renal failure and patients receiving multiple drug therapy), high risk drugs (these include drugs with narrow therapeutic index) and target drugs (these are drugs that are indicated to investigate potential adverse drug reactions).

What is the status of ADR monitoring in developed countries?

Today worldwide many regulatory authorities are involved in the safety monitoring of medicines. The WHO program was established in 1968 as a pilot project with the participation of ten countries initially and later strengthened by many. The other authorities includes the United Kingdoms Medicine Control Agency (MCA) and the committee on safety of medicine (CSM) set up in 1964, Vaccines Adverse Event Reporting System (VAERS), set up in 1990 and co-administered by the Department of Health and Human Services (DHHS), the FDA, and the Centers of Disease Control (CDC), the Adverse Drug Reactions Advisory Committee (ADRAC) of Australia, Med watch program of the USFDA, Canadian Adverse Drug Reaction Monitoring program etc.²⁴

Why Nepal needs an ADR monitoring program?

Nepal is a developing country having a multidimensional variation in several aspects. Among the total of 75 districts about two third are located in hilly regions and the remaining in plains. The effect of drugs may vary from place to place. The climatic condition also varies from season to season and from place to place. This may predispose the occurrence of ADRs. Moreover, there are several races of people having different cultural and social beliefs. The use of complementary medicines which may interact with allopathic drugs and predispose to ADRs should also be considered. Majority of drugs used in Nepal are manufactured in foreign countries and the excipients used may vary. The genetic make up of Nepalese population may vary and hence predispose ADRs. There are no clinical trials done on the Nepalese population prior to approval in Nepal. Hence the risk of occurrence of ADRs can be very high and is infact unknown. Due to the hilly terrain in Nepal, the poor socioeconomic status, the high cost of modern medicines and non-availability of doctors in rural areas, difficulties arise in accessing modern healthcare. Drug retail shops frequently serve as the public's first point of contact with the healthcare system. This makes the people to depend on self-medication.²⁵ Self-medication may also contribute to

ADRs either by the drug it self or by causing an interaction with the prescription drug.

How to begin?^{21,26,27}

Many times the need for the ADR monitoring is felt but somehow it becomes difficult to implement. We hereby make an attempt to provide an approach to develop ADR monitoring program for a hospital in Nepal.

Awareness programs: All the healthcare workers should be asked to report any suspected ADRs to through the ADR reporting form. A well developed ADR program should address the following questions:

Reporting: ADR reporting forms should be placed in all the wards, Out Patient Departments (OPDs) and pharmacy department. Any healthcare workers who come across any ADR can fill this form and send it to the ADR monitoring center of the hospital. The data from these forms can be used to assess the reaction in detail. There are several ADR reporting forms available. Few of them like the yellow card system, blue card system and the one by Med watch. For local use one can modify the forms and prepare one which satisfies the local needs.

Drug information: The ADR and related information of the particular drug(s) should be provided to the reporter.

Causality assessment: The assessment and categorization of the likelihood of a causal relationship between a suspected drug and an ADR is an essential element in ADR monitoring. Based on the causality assessment, an ADR can be classified as one of the following categories; certain, probable, possible, unlikely, conditional/un classified, Unassesable/Un classifiable. There are several causality assessment scales like WHO causality assessment scale, Naranjos scale, Karch and Lasagnas scale, European ABO system, Bayesian neutral network etc. Any one of the scales can be used to carryout the causality assessment.

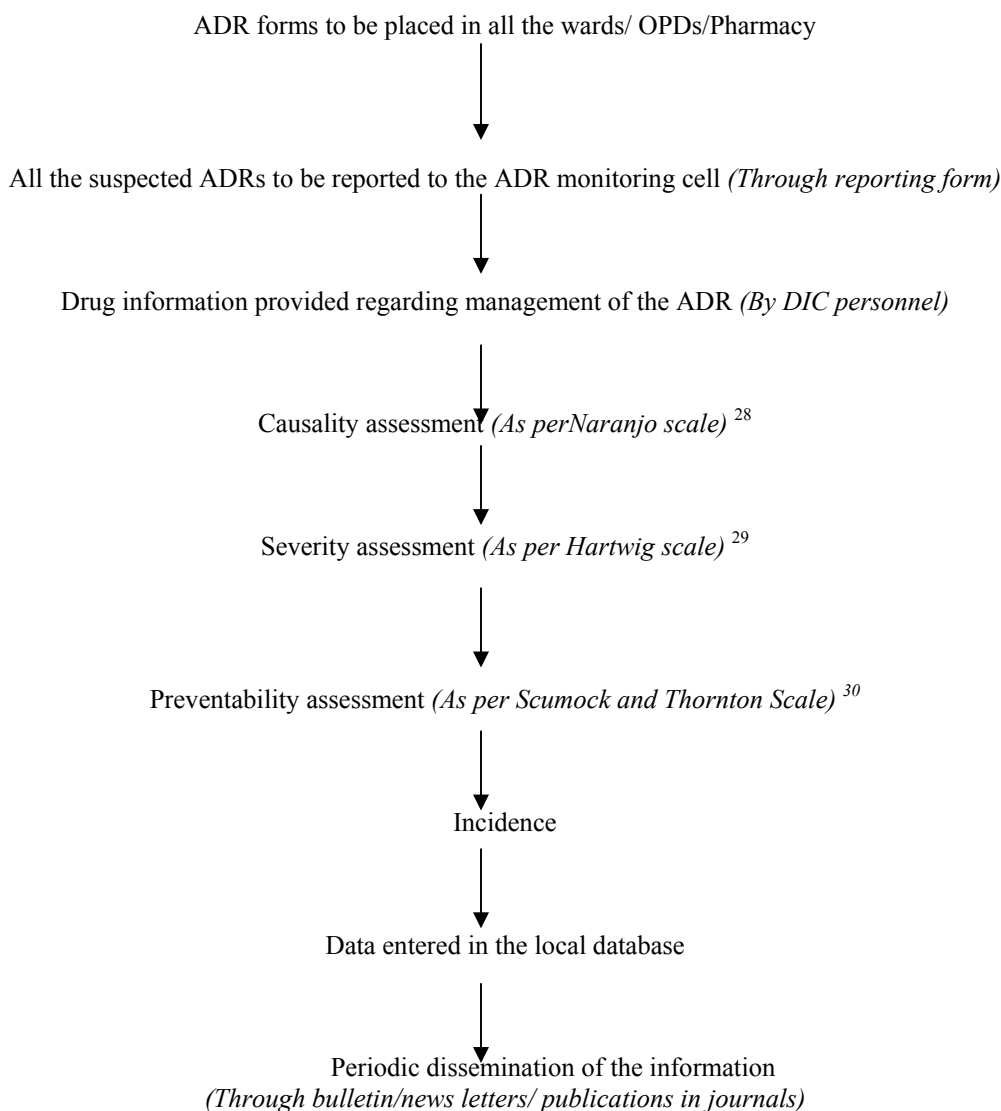
Preventability: The preventability and predictability of the ADRs can be assessed by using the specified scales. For example, Schumock and Thornton Scale can be used.

Incidence: The incidence of Particular ADR should be found out by getting the total number of drugs used in the hospital during the particular period.

Database development: All the data obtained by the program should be entered in a database developed for the program. The data so obtained will be the local data of ADR in the given population.

Dissemination of information: The relevant data regarding ADRs should be periodically disseminated through ADR bulletins, journals and news letters. Interesting case reports can be published in local journals.

A simple approach to develop ADR monitoring program for a 100 bedded hospital



What is the current position of ADR monitoring in Nepal?

The concept of ADR monitoring and Pharmacovigilance is new to Nepal. However, the Department of Drug Administration (DDA),

Kathmandu, the national drug controlling authority of Nepal has taken steps to establish an ADR monitoring program in Nepal. Recently, Nepal has been given an associate member status by the Uppsala Monitoring Center, Sweden, the WHO

collaborating Center for International Drug Monitoring. The ministry of health and population has designated DDA as the national center for ADR monitoring.³¹

ADR monitoring program in Manipal Teaching Hospital

Manipal Teaching Hospital, Pokhara has taken the initiative and started Spontaneous reporting program at the hospital level since September 2004. The ADR reporting forms are placed in the wards, OPDs, Drug Information Center (DIC) of the hospital. The doctors/ Nurses and pharmacists report the ADRs, if any to the Pharmacovigilance cell, a unit of DIC of the hospital. Based on the report, the DIC personnel provide relevant information to the reporter as needed. Since its inception, the DIC has received a total of 80 ADR reports from various quarter of the hospital. The center has plans to upgrade the existing spontaneous reporting program to a full fledged Pharmacovigilance program in the near future.

Conclusion

Of late, it has become the responsibility of all the healthcare workers to develop strategies to report, monitor and prevent ADRs. The drug regulatory authority of Nepal should take necessary steps to promote safe use of drugs in the country. The initial step can begin from a single hospital and later can be expanded to the entire country. Public education should be given to countrymen. Post marketing surveillance studies must be made mandatory before marketing any new drug in the country. The education to students regarding ADR should be given at the primary school level. A formal training program for the healthcare professionals is mandatory before starting the program. A well developed ADR monitoring system can pay a lot to the healthcare system if nurtured well with dedicated, expertise people in the team. If properly developed, a Pharmacovigilance program will be of great value for the hospital, the region and for Nepal.

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