



REVIEW ARTICLE

PHARMACOLOGY

PHARMACOVIGILANCE

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Karnataka, India.**ABSTRACT*****Introduction***

India has more than half a million qualified doctors and 15,000 hospitals having bed strength of 6,24,000 . Many new drugs are being introduced in our country. The development of a better system of reporting ADRs has been recommended as a top priority action to prevent ADRs and ADEs. According to WHO Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects and any other drug related problem.

Nature of Work

The ADR monitoring centre will prepare a plan and educate the pharmacovigilance staff with regard to data collection and verification, interpreting and coding of adverse reaction description, coding of drugs, case causality assessment, signal detection and risk management. The pharmacovigilance centre will conduct the seminars and workshops to educate and train all the healthcare professionals, who are the source of information in pharmacovigilance,

Conclusion

Greater integration of pharmacovigilance into clinical practice is still needed. Hence, active participation of all the healthcare professionals is very important to make pharmacovigilance, a successful national programme.



KEYWORDS

Pharmacovigilance; Central drugs standard control organization; WHO aims; Adverse drug reaction monitoring; National pharmacovigilance policy

INTRODUCTION

India has more than half a million qualified doctors and 15,000 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. The certainty of safety in phase 3 clinical trials is uncertain. Because clinical trials generally enroll a selected, limited number of patients¹ and drug use in special situations (such as children, the elderly or pregnant women) or drug interactions may not be studied¹. Therefore, there is a need for a vibrant pharmacovigilance system in the country to protect the population from the potential harm that may be caused by some of these new drugs. Communicating the potential harm of drug use to patients is a matter of high priority and should be carried out by every prescriber². Hence, the development of a better system of reporting ADRs has been recommended as a top priority action to prevent ADRs and ADEs in hospitals³.

Clearly aware of the enormity of task, the Central Drugs Standard Control Organization (CDSCO) has initiated a well structured and highly participative National Pharmacovigilance Programme. It is largely based on the recommendations made in the WHO document titled "Safety Monitoring of Medicinal Products – Guidelines for Setting up and Running a Pharmacovigilance Centre".

Definition: Pharmacovigilance is defined by WHO as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects and any other drug related problem^{4,5}. It plays a vital role in ensuring that doctors together with the patient, have

enough information to make an educated decision when it comes to choosing a drug for treatment⁶. It is the process of: Monitoring medicines as used in everyday practice to identify previously unrecognized adverse effects or changes in the patterns of their adverse effects

- Assessing the risks and benefits of medicines in order to determine what action if any, is necessary to improve their safe use
- Providing information to users to optimize safe and effective use of medicines
- Monitoring the impact of any action taken

Objectives and Aims of the Pharmacovigilance⁷:

1. Contributing to the regulatory assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost effective) use.
2. Improving patient care and safety in relation to use of medicines and all medical and paramedical interventions.
3. Improving public health and safety in relation to use of medicines.
4. Promoting understanding, education and clinical training in pharmacovigilance and its effective communication to the public.
5. Detecting the frequency of (known) adverse reactions.

NATURE OF WORK

The above __objective and __aims to foster the culture of ADEs (adverse drugs events) notification in its first year of operation and



subsequently aims to generate broad based ADR data on the population and share the information with global health-care community through WHO⁸.

The globally reported percentage of hospitalized patients experiencing ADRs ranges from 1.5-35%¹⁰. In India, 0.7 % ADRs are responsible for admission in hospital and 3.7% of the hospitalized patients experience ADRs with 1.8% ADRs being fatal^{9,10}. In order to minimize the patients' sufferings due to ADRs, it is essential to detect the ADRs and implement measures to treat and prevent ADRs.

The Peripheral center (Department of Pharmacology, KIMS, Hubli) will record the Adverse Events (AE) and send to the Regional Centers. They in turn collate and scrutinize the data received from the Peripheral Centers and submit to the Zonal Centers. The Zonal Centers will analyze the data and submit consolidated information to the National Pharmacovigilance Centre. The Zonal Centre will also provide training, general support and coordinate the functioning of the Regional Centers.

The National Pharmacovigilance Advisory Committee (NPAC) oversees the performance of various Zonal, Regional and Peripheral Pharmacovigilance centers as well as recommends possible regulatory measures based on the data received from various centers. It also oversees data collection and assessment, interpretation of data as well as publication of ADR monitoring data. The Committee also periodically evaluates their protocol compliance levels to ensure that the data received is homogenous and can be scientifically pooled for informed regulatory decisions. Wherever necessary, NPAC also seeks the opinion of experts in various specializations.

The ADR monitoring centre will prepare a plan and educate the pharmacovigilance staff with

regard to data collection and verification, interpreting and coding of adverse reaction description, coding of drugs, case causality assessment, signal detection and risk management. Spontaneous reporting of adverse drug reactions is an important method of postmarketing surveillance^{11,12}. Spontaneous reporting systems are created and these have become the primary method of collecting postmarketing information on the safety of drugs. The main function of SRS is the early detection of signals of new, rare and serious ADRs. A SRS enables physicians and, increasingly more often, pharmacists and patients to report suspected ADRs to a pharmacovigilance centre^{13,14,15}. However, spontaneous ADR reporting is underused by physicians in primary health care centers and in hospitals^{16,17} and there is a need to promote pharmacovigilance activities. The success or failure of any spontaneous reporting systems depends on the active participation of the reporters. Although limited schemes for reporting by patients have been initiated recently, healthcare professionals have been the major providers of such reports of suspected ADRs throughout the history of pharmacovigilance. Several interventions to solve the problem of under reporting of ADRs have been proposed¹⁸. Originally, physicians were the only professionals invited to report by judging whether the disease or the medicine causes a certain symptom by exercising the skill of differential diagnosis. It was agreed that accepting ADR reports from physicians only would ensure high quality information and minimize the reporting of unrelated, random associations. Studies have shown however, that different categories of health professionals will observe different kinds of drug related problems^{19,20}.

Some studies have evaluated the effectiveness of educational interventions aimed at increasing reporting among physicians⁽²¹⁻²⁶⁾. The pharmacovigilance centre will conduct the



seminars and workshops to educate and train all the healthcare professionals, who are the source of information in pharmacovigilance, like, clinicians, medical specialists, nurses, medical students (both undergraduate and postgraduate) to emphasise their responsibility to participate in the national pharmacovigilance programme. The pharmacovigilance centre will train the healthcare professionals to create awareness on pharmacovigilance and to enable them to report ADRs. The healthcare professionals will be made aware of pharmacovigilance, the need for it and importance of reporting ADRs and the reporting procedure.

National Pharmacovigilance Policy

Since there are considerable social and economic consequences of adverse drug reactions and the positive benefit/cost ratio of implementing appropriate risk management – there is a need to engage health-care professionals and the public at large, in a well structured programme to build synergies for monitoring adverse drug reactions.

The purpose of the programme is to collate data, analyze it and use the inferences to recommend informed regulatory interventions, besides communicating risks to healthcare professionals and the public.

The National Pharmacovigilance Programme will have the following milestones:

1. **Short-term objectives:** To foster a culture of notification
2. **Medium-term objectives:** To engage several healthcare professionals and NGOs in the drug monitoring and information dissemination processes.
3. **Long-term objectives:** To achieve such operational efficiencies that would make Indian National Pharmacovigilance Programme a benchmark for global drug monitoring endeavors.

National Pharmacovigilance Programme

Before a product is marketed, experience of its safety and efficacy is limited to its use in clinical trials, which are not reflective of practice conditions, as they are limited by the patient numbers and duration of trial as well as by the highly controlled conditions in which Clinical Trials are conducted.

The conditions under which patients are studied during the pre-marketing phase do not necessarily reflect the way the medicine will be used in the hospital or in general practice once it is marketed. Information about rare but serious adverse drug reactions, chronic toxicity, use in special groups (e.g. pregnant women, children, elderly) and drug interactions are often incomplete or not available. Certain adverse drug reactions may not be detected until a very large number of people have received the medicine. Pharmacovigilance is therefore one of the important post-marketing tools in ensuring the safety of pharmaceutical and related health products.

Framework for Pharmacovigilance In India²⁷:

The Central Drugs Standard Control Organization (CDSCO) has initiated a country-wide Pharmacovigilance programme under the aegis of DGHS, Ministry of Health & Family Welfare, Government of India.

The programme is coordinated by the National Pharmacovigilance Centre at CDSCO. The National Centre is operating under the supervision of the National Pharmacovigilance

The National Pharmacovigilance Centre at CDSCO

Advisory Committee to recommend procedures and guidelines for regulatory interventions.

The National Pharmacovigilance Centre is based at CDSCO and shall:



1. Monitor the adverse drug reactions of medicines in order to identify previously unexpected adverse drug reactions or indicate that certain reactions occur more commonly than previously believed. This will include the collation, review and evaluation of all spontaneous ADR reports received by the unit on a nation-wide basis. This information will then be keyed into the ADR database for use in aggregate analysis. These reports shall also be submitted to the WHO International Drug Monitoring Programme for international collaboration on drug safety.
2. Review Periodic Safety Update Reports (PSURs) submitted by pharmaceutical companies. Pharmaceutical companies are required to submit the PSURs of all new chemicals drugs. PSURs shall be expected to be submitted every 6 months for the first 2 years of marketing in India, and annually for the subsequent 2 years.
3. Maintain contacts with international regulatory bodies working in pharmacovigilance and exchange information on drug safety.
4. Assess the regulatory information relating to safety in order to determine what action, if necessary, needs to be taken to improve safe use. Based on the available data, the Advisory Committee shall make recommendations on product label amendments, product withdrawals and suspension.
5. Provide information to end-users through adverse drug reaction news, bulletins, drug alerts and seminars.

CONCLUSION

Greater integration of pharmacovigilance into clinical practice is still needed. Drug safety should feature in the medical and pharmacy

curricula. Access to updated, unbiased and clinically relevant drug information is currently inadequate. Research and postgraduate training in the field remains neglected by many institutions of health sciences. The growing alliance between the industry and academia and drug regulatory authorities has implications for pharmacovigilance. The success or failure of any spontaneous reporting system depends on the active participation of reporters. Although limited schemes for reporting by patients have been initiated recently, health professionals have been the major providers of case reports of suspected ADRs throughout the history of pharmacovigilance. However, since only 5% of doctors are estimated to participate in any pharmacovigilance system, this process is not efficient in ensuring that the patient's concerns are being recorded. Hence, active participation of all the healthcare professionals is very important to make pharmacovigilance, a successful national programme. Moreover, there are studies which indicate that systems for recording patient concerns might identify new drug safety signals earlier than the professional reporting systems alone. Safety monitoring during clinical trials is now recognized as one of the major concerns for new drug development with three main topics : 1) the collection of adverse experience information 2) assessment/monitoring of clinical data 3) reporting/communication of clinical data. Educating and training the healthcare professions will make them aware of their responsibility to report ADRs.

Glossary of terms:

National Pharmacovigilance Programme (NPP)

The nationwide programme, sponsored and coordinated by the country's central drug regulatory agency – Central Drugs Standard Control Organization (CDSCO) – to establish and manage a database of Adverse Drug Reactions (ADR) for making informed regulatory



decisions regarding marketing authorization of drugs in India for ensuring safety of drugs.

Peripheral Pharmacovigilance Centers (PPC)

Primary pharmacovigilance centers are relatively smaller medical institutions including individual medical practitioners' clinics, private hospitals, nursing homes, pharmacies etc. They would be identified and coordinated by RPCs / ZPCs in consultation with CDSCO.

Regional Pharmacovigilance Centers (RPC)

Secondary pharmacovigilance centers are relatively larger healthcare facilities attached with medical colleges. They would act as second level centers in the administrative structure of the NPPI. They will function as first contact ADE data collection units also. They would be identified and coordinated by ZPCs in consultation with the CDSCO.

Zonal Pharmacovigilance Centre (ZPCs)

This is a Tertiary pharmacovigilance center. -- Large healthcare facilities attached with medical colleges in metro cities identified by the CDSCO for the purpose. They would act as third level centers in the administrative structure of the NPPI. They will function as First contact ADE data collection units also.

Coordinator

Designated in-charge of a particular participating PVig centre

Investigator

A healthcare professional involved in investigation of drug related adverse events.

Notifier

Any person who suspects to have experienced / observed an ADE and informs any participating Pharmacovigilance centre about it.

Reporter

A healthcare professional who reports ADR on the ADR form.

Monitoring

The process of overseeing drug related adverse events at the PVigC participating in the PVig Programme.

Reporting

The process of providing ADR information by filling in the ADR form appropriately and forwarding the same to the appropriate level.

Notification

Process of informing by a notifier to any participating pharmacovigilance centre about the occurrence of a suspected ADR. The process may involve informing over telephone, in person, email, fax or any other means of communication-verbal or written. All notifiers must give their contact details. Appropriate and adequate measures must be taken to keep track of the notifier. Any follow up action will be initiated on a notification only after the due verification of the notifier. If the notifier cannot be traced back, it will be recorded on the notification slip before closing the case.

Notification slip

A pre-designed structured form made available by the NPPI for written communication of a suspected ADR by the notifier duly signed by him/her wherever feasible.

ADR Form

It's the pre-designed structured form issued by NPPI to record ADR.

Archiving

This is to be done at the Regional / Zonal Centers for a period of 5 years

Audit

A systematic and independent examination (conducted by personnel, independent of the



centre) of center's activities and documents to determine whether center's activities were conducted and the data were recorded, analysed and accurately reported according to the protocol

Confidentiality

In a confidential / secretive manner.

Side Effect

Any unintended effect of a pharmaceutical product occurring at doses normally used in man which is related to the pharmacological properties of the drug.

Comment: This is an old term and is broad enough to include both positive and negative effects of a drug apart from its main properties or indications. Some use the term as synonymous with 'adverse reaction', but the proposed definition will improve clarity of use of this term.

Adverse Event / Adverse Experience

Any untoward medical occurrence that may present during treatment with a pharmaceutical product at the same time, does not necessarily have a causal relationship with this treatment.

Comment: This is a more recent term which some use interchangeably with 'adverse reaction', but, as indicated, it is better reserved for clinical phenomena occurring during drug treatment where causality cannot be or is not ascertained.

Signal

Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information.

Comment: This describes the first alert of a problem with a drug. By its nature a signal cannot be regarded as definitive but indicates the need for further enquiry or action. On the other hand it is prudent to avoid a multiplicity of signals

based on single case reports since follow up of all such would be impractical and time consuming. The definition allows for some flexibility in approach to a signal based on the characteristics of individual problems. Some would like a 'signal' to include new information on positive drug effects, but this is outside the scope of a drug safety Programme.

Adverse Reaction

WHO Technical Report No 498 (1972); 'A response to a drug 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 physiological function.

Comment: This basic definition includes all doses prescribed clinically, but is intended to exclude accidental or deliberate overdose. The sub classification of 'unexpected' was included to facilitate understanding of the type of adverse reaction which is most important in reporting to drug monitoring agencies.

Unexpected Adverse Reaction

An adverse reaction, the nature or severity of which is not consistent with domestic labeling or market authorization, or expected from characteristics of the drug.

Serious Adverse Event or Reaction

A serious adverse event or reaction is any untoward medical occurrence that at any dose:

- Results in death.
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity.
- Is life-threatening.

To avoid any confusion or misunderstanding of the difference between the terms 'serious' and 'severe', the following note of clarification is provided: The term 'severe' is not synonymous with serious. 'Severe' is used to describe the



intensity (severity) of a specific event (as in mild, moderate or severe); the event itself, however, may be of relatively minor medical significance (such as severe headache). Seriousness (not

severity) which is based on patient/event outcome or action criteria serves as guide for defining regulatory reporting obligations

REFERENCES

1. Safety of medicines: A guide to detecting and reporting adverse drug reactions. Geneva; World Health Organization:(2002).
2. Karch FE, Lasagna L. Adverse drug reactions: A critical review. *JAMA*. 234: 1236-41. (1975).
3. Ramesh M, Pandit J, Parthasarathi G. Adverse drug reactions in a south Indian hospital, their severity and cost involved. *Pharmacoepidemiol Drug Saf*:12:687-92.(2003).
4. World Health Organisation Collaborating Centre for International Drug Monitoring (2007). The importance of pharmacovigilance. Available at <http://www.who-umc.org>. Cited 18 Dec (2007)
5. The Importance of Pharmacovigilance, World Health Organization (2002).
6. L.Hallmark.A.C, Van Grootheest. Pharmacovigilance: methods, recent developments and future perspectives: *Eur J Clin pharmacol*.64:743-752.(2008).
7. Rajesh Hunashal., Kudagi B.L., Kamadod M.A, Biradar S.S. Drug Information Centre. *The Pharma Review*, 163-168. (2008)
8. Egberts P G., Smulderes M, De Konig H P., Can adverse drug reactions be detected earlier?: a comparison of reports by patients and professionals. *British Medical Journal* ; 313: 530 – 31.(1996).
9. Hepner DL, Castells MC. Anaphylaxis during the perioperative period. *Anesth analg.* ; 97: 1381-95.(2003).
10. Ebo DG, Fisher MM, Hagendorens MM, Bridts CH, Stevens WJ. Anaphylaxis during anaesthesia: diagnostic approach. *Allergy* ; 62: 471-487.(2007).
11. Wysowski DK, Swartz L: Adverse drug event surveillance and drug withdrawals in the United States, 1969-2002: the importance of reporting suspected reactions. *Arch Intern Med* ,165:1363-1369. (2005).
12. Lexchin J: Is there still a role for spontaneous reporting of adverse drug reactions? *CMAJ* , 174:191-192. (2006).
13. van Grootheest K, Olsson S, Couper M et al. Pharmacists' role in reporting adverse drug reactions in an international perspective. *Pharmacoepidemiol Drug Saf* 13:457-464. (2004).
14. van Grootheest K, de Jong-van den Berg : Patients' role in reporting adverse drug reactions. *Expert Opin Drug Saf* 3:363-368. (2004).(*Eur J Clin Pharmacol* (2008) 64:743-752 751)
15. van Grootheest AC, Passier JL, van Puijenbroek EP .Direct reporting of side effects by the patient: favourable experience in the first year. *Ned Tijdschr Geneesk* 149:529-533. (2005).
16. Hazell L, Shakir SA: Under-reporting of adverse drug reactions: a systematic review. *Drug Saf* 29:385-396. (2006).
17. van der Hoft CS, Sturkenboom MC, van Grootheest K, Kingma HJ, Stricker BH:



- Adverse drug reaction-related hospitalisations: a nationwide study in The Netherlands. *Drug Saf* , 29:161-168. (2006).
18. Vallano A, Cereza G, Pedrós C, Agustí A, Danés I, Aguilera C, Arnau JM: Obstacles and solutions for spontaneous reporting of adverse drug reactions in the hospital. *Br J Clin Pharmacol* , 60:653-658. (2005).
 19. Hall M, McCormack P, Arthur N, Feely J. The spontaneous reporting of ADRs by nurses. *British Journal of Clinical Pharmacology* ; 40: 173 – 175. (1995).
 20. Hornbuckle K, Wu H-H, Fung MC. Evaluation of spontaneous adverse event reports by primary reporter - a 15-year review (1983 to 1997). *Drug Information Journal* ; 33: 1117 – 1124. (1999).
 21. Fincham J: A statewide program to stimulate reporting of adverse drug reactions. *J Pharm Pract* , 2:239-244. (1989).
 22. Scott HD, Thacher-Renshaw A, Rosenbaum SE, Waters WJ Jr, Green M, Andrews LG, Faich GA: Physician reporting of adverse drug reactions. Results of the Rhode Island Adverse Drug Reaction Reporting Project. *JAMA* , 263:1785-1788. (1990)
 23. Nazario M, Feliu JF, Rivera GC: Adverse drug reactions: the San Juan Department of Veterans Affairs Medical Center experience. *Hosp Pharm* 29:244-250. (1994).
 24. McGettigan P, Golden J, Conroy RM, Arthur N, Feely J: Reporting of adverse drug reactions by hospital doctors and the response to intervention. *Br J Clin Pharmacol* , 44:98-100. (1997)
 25. Figueiras A, Herdeiro MT, Polónia J, Gestal-Otero JJ: An educational intervention to improve physician reporting of adverse drug reactions: a cluster-randomized controlled trial. *JAMA* , 296:1086-1093. (2006)
 26. Pedrós C, Vallano A, Cereza G, Mendoza-Arán G, Agustí A, Aguilera C, Danés I, Vidal X, Arnau JM: An intervention to improve spontaneous adverse drug reaction reporting by hospital physicians. A time series analysis in Spain. *Drug Saf* , 32:77-83. (2009).
 27. Angell M. The pharmaceutical industry – to whom is it accountable? *New England Journal of Medicine* ; 342 (25):1902-4. (2000).