Starting a pharmacovigilance center: Actions for implementation

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ABSTRACT

With burgeoning reports of adverse drug reactions due to pharmacotherapy, pharmacovigilance (PV) is the buzz word in health care circles. While there are experts in this rapidly expanding field, there are many health care professionals who do not fully appreciate the import of PV in the context of modern therapeutics. In view of the national directive to institutionalize a PV center in every medical college of India, there is an urgent need to inform, educate, and enlighten the readers about the constitution and dynamics of a PV center, which this article attempts to fulfill.

Key words: Pharmacovigilance, adverse drug reactions, drug safety, pharmacovigilance

INTRODUCTION

Complete drug safety remains subjective with no unanimity in the level of safety, comparison standard, and method of measurement. Following up the safety of marketed medicines put to clinical use in large populations becomes essential and the science pertaining to this is known as pharmacovigilance (PV). World Health Organization (WHO) defines it broadly as "science and activities relating to detection, evaluation, understanding, and prevention of adverse drug reactions or any other drug related problems."[1] The scope of the definition has been broadened to include ethnopharmacological products and complementary blood products, biological, medical devices and vaccines.[2]

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Pharmacovigilance in India was conceived way back in 1986 when 12 regional centers were proposed. Activities went on an insignificant note for about a decade. India then joined the WHO-Adverse Drug Reaction (ADR) monitoring program, based in Uppsala, Sweden. Three centers were assigned the task of ADR monitoring of marketed medicines - All India Institute of Medical Sciences (AIIMS) New Delhi, King Edward Memorial (KEM) Hospital Mumbai, JLN Hospital Aligarh Muslim University. These centers were to report to Drug Regulatory Authority of India. This too did not yield much. Finally in 2005, the WHO sponsored and World Bank funded National Pharmacovigilance Program (NPP) was launched, which is overseen by National Pharmacovigilance Advisory Committee. There are 24 PV centers at present under this program.[3] While the system has elaborated much in the western world, India has woken up a bit late to its importance and is lagging in the implementation of the necessary systems and manpower to get it rolling.[4] To address this concern, Central Drug Standard Control Organization (CDSCO) launched the National Pharmacovigilance Program (NPP) which is in function since January 2005. To give it a further impetus and fortify the drug regulatory framework in the country, the Drug Controller General of India (DCGI) has

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announced the CDSCO's "VISION 2020" which proposes to create a PV center in every medical college in the country which is an ambitious task keeping in view the fact that it is still at low ebb in many government medical colleges and the condition is the same or may be worse in the private institutes. Therefore, it is likely that the proposal may have to negotiate many bottlenecks to pay some dividends. In this backdrop, the article discusses the essentials of setting up a PV center and getting it operational [Figure 1].

THE NEED

The human safety data extrapolated from animal studies are often deviant in many aspects and not conclusively predictive. Although surface clinical trials reveal a fair percentage of ADRs, but they may not always give the fuller picture due to relatively fewer number of patients from a specified geographic location on trial, limited duration of trial, differences in the conditions of use from clinical practice. Gross variations in the effects of medicines exist among populations of different countries and also various regions of the same country which may be attributed to the differences in prescribing practices and diseases, genetics, food habits, and pharmaceutical manufacturing protocols. This issue needs more attention in India as herbal remedies are widely used which may pose problems when used singly or in combination. India, now being a signatory to the World Trade Organization (WTO) and a hub of clinical trials, is fast becoming a market for new molecules whose safety data are not available from other countries. Therefore, it needs to exercise earnest efforts to remedy its lapses in this vital sector of healthcare and generate its own dependable data from long term use of medicines.[5] In addition to these, clinical trials may not always pick up rare adverse reactions. Also with the prevailing heterogeneity in clinical practices in India - allopathy, ayurvedic, homeopathy, unani, siddha and in view of the complex interplay among these various systems of medicine, the need for an efficient monitoring system is further underscored.

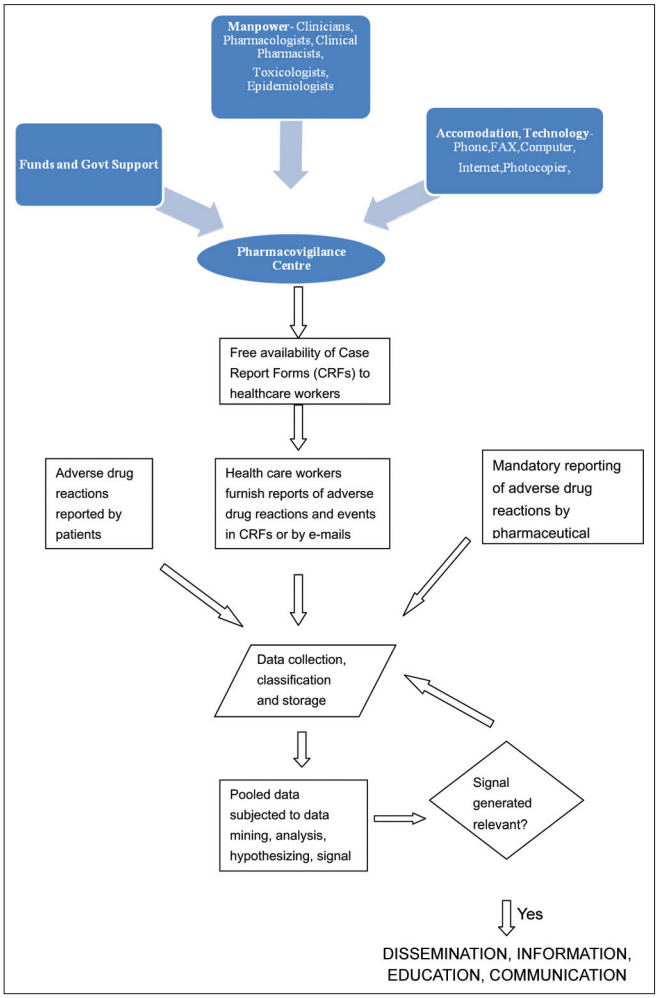

Figure 1: Pharmacovigilance system: Constitution and functioning

GETTING STARTED

Pharmacovigilance is all about drug regulation and rests on sound collaborative ties, coordination, communications, and public relations. The most suitable location for setting up a PV center is dictated by the political governance and its healthcare priorities, including willingness to do, law enactment, its enforcement, funding, organization, staffing, training, and development. For national coordination of PV, governmental support and sustained monitoring is a must. A center can be started in a hospital or at any department, preferably in pharmacology, medicine, clinical pharmacy or clinical toxicology. Initially it may be started in one hospital locally and then extended to other hospitals to cover the entire region which could communicate closely with a zonal center. All zonal centers in turn can report to the national nodal center which would collate the data gathered from the entire country and channel it to the Uppsala Monitoring Center (UMC), Sweden, within specified time line, for global referencing and use. If a center is handling data of an entire country right from the beginning, foolproof channels of effective communication should be ensured with clinicians. The center should have at least one clinical pharmacologist, clinical pharmacist or a physician to start working.[1]

PLANNING THE BASICS

A blueprint should be drawn up to establish and get a PV system to work. Care needs to be taken to establish the following:[1,5]

Communication process

Getting in conversation with health authorities and local, regional, national bodies and groups engaged in clinical medicine, pharmacology, toxicology, epidemiology, briefing them about the importance of the project and its applicability in modern therapeutics

Data acquisition
Designing a template for ADR reporting and making available ADR reporting forms at all times, to hospital departments and general practitioners, on which they can furnish relevant information to the data bank of the center

Dissemination
Producing printed handouts as well as conducting meetings or workshops in hospitals and academia to acquaint health care professionals about the definitions, goals, scope, and methodology of the PV system to create awareness about its relevance in present times

Establishment
Hiring the right qualified and interested staff, getting suitable place for accommodating them as well as the center, making arrangements for telephones, computers, printers, word processors, database management, bibliography support services, and internet

Internal education
Ensuring proper education and frequent updating of the staff belonging to the PV centers by training them in data collection, filtration, mining, verification, interpretation and coding of ADRs, medicines coding, causality assessment, signal detection, risk management, and action in case of serious/fatal adverse drug events (ADE). Data mining is a relatively nascent interdisciplinary area which involves finding correlations and patterns among many fields in large databases with the aim of categorizing the data and summarizing identified relationships[6]

Database
Creating a safely stored, classified database which is retrievable and guarded by required degrees of confidentiality

Promotion
To inculcate and promote the habit of reporting ADRs to the higher center, medical journals, health bulletins and other professional healthcare publications

Networking
To encourage healthcare professionals to contact institutions working on a global scale in PV e.g. Uppsala Monitoring Centre (UMC) WHO department of Essential Medicines and Medicines Policy, Geneva, and net groups like International Network for the Rational Use of Drugs (INRUD), E-drug, and Network for Rational Use of Medicines (NetRUM)

THE MANPOWER AND THE MACHINERY

To begin with, a PV center can kick start with a part time expert who can be a physician or clinical pharmacist with some secretarial support. Gradually, as the data traffic increases, a full time professional should be appointed to maintain the center and secretarial support expanded. The increase in the quantum of work, staff resource requirements are calculated by flatly assuming the time of assessment of a single case as one hour.[1] For the smooth functioning of a PV center, professionals with expertise in pharmacology, clinical medicine, epidemiology, toxicology prove to be fruitful.

Additionally, the center requires a permanent secretariat to handle phone calls, database, and documentation of literature and coordination of activities like interfacing with related departments to maintain secretarial continuity for successful functioning of the center.

An advisory committee serves to get funding and support for the center, monitoring, and evaluation, keeping a tab in the quality of the procedures relating to data collection and mining, data interpretation and publication information. The advisory committee may be represented by the disciplines of clinical medicine, pharmacology, toxicology, epidemiology, phytotherapy, pathology, drug regulation and quality assurance.[1,5,7]

There are a few basic technological requirements for a PV center – uninterrupted electric supply, intercom, multi connection telephone, computer, printer, FAX, internet, photocopier, which should be made available and care should be taken that these remain working at all times. Adequate back up facilities should be present so that work is not paralyzed in case of sudden breakdowns.

DATA ACQUISITION

Pharmacovigilance at present thrives heavily on a regional/country wide reporting of suspected ADRs through spontaneous reporting system from motivated reporters. It usually picks up signals of rare, serious, unprecedented ADRs.[4]

Reports of suspected ADRs are taken in case report forms (CRF) which in PV is defined as a notification relating to a patient with an ADE (or laboratory test abnormality) suspected to be induced by a medicine. The CRF should be distributed to health care professionals across the area covered by a particular PV center regularly, and a suitable system has to be developed to ensure that the filled forms are either collected or could be posted free, or sent by e mail/ FAX to the center, so that there is an uninterrupted and free flow of data.

A CRF should contain minimum following information:[1]

- Patient: Age, gender, medical history in brief, ethnic origin (in some countries)

- ADE monitoring: Detailed description (nature, localization, severity, characteristics), reports of investigations and tests, date of appearance, course, outcome
- Suspected medicines: Name (brand, formulation, ingredient, concentration, manufacturer), dose, route of administration, date of initiation of therapy/date of withdrawal of therapy, indications for use, and rechallenge in case of non serious ADEs
- Other medicines: All other medicines used by the patient (including self medication) including their name, dose, route, date of initiation and withdrawal
- Risk factors: e.g. impaired renal function, past exposure to suspected medicines, history of allergy, and social drug use
- Reporter: Name and address of the reporter (confidential and to be used for data completion, verification, and follow up)

Health care professionals e.g. practicing physicians, pharmacists, nurses, dentists, and midwives are reliable sources of information. Pharmacists and nurses can illuminate on concomitant medication and history of medicine usage. It is imperative for pharmaceutical companies to report any ADRs of their products to regulatory authorities. In the event of patients directly reporting ADRs, it is always better to communicate with their physicians for better understanding and verification of data.

The reporting can be done from peripheral to the regional PV centers, which sweep a particular region, which in turn pool into the zonal database, the analysis of which reflects a gross national overview. The entire national data should be reported to UMC.[1]

BRINGING A REPORTING CULTURE

Reporting of ADR[1,5] is a continuous process and important to cultivate and sustain the attention and interest of healthcare workers so that it gets incorporated as a routine procedure in healthcare. The following measures may be adopted to give a fillip to reporting:

- Easy and free availability of prepaid reporting forms and other modes of reporting
- Duly acknowledging the receipt of ADR reports telephonically or through personal communication
- Providing journal articles, ADR bulletins, newsletters to reporters
- Actively involving the PV center staff in scientific meetings, undergraduate and postgraduate education
- Collaborating with other PV committees
- Collaborating with professional associations
- Utilizing PV data for development of clinical pharmacy and clinical pharmacology

TASKS OF PHARMACOVIGILANCE[1]

Information service

One of the primary responsibilities of a center is to make high quality credible and latest medicine information available to health care professionals. For this, the center should have access to up-to-date and comprehensive literature database. The national centers should preferably have an online access to UMC database and be on the mailing list of ADR bulletins of WHO.

Reaching out

Newsletters, medicine bulletins, columns from reputed medical or pharmaceutical journals may be chosen as routes of effective propagation of latest developments in medicine research and therapy to the healthcare professionals.

Appraisal

The ADR case reports obtained are evaluated by the center staff, employing the collective know-how of clinical medicine, pharmacology, toxicology, and epidemiology.

Secondary prevention of ADRs

Secondary prevention of ADRs can be attempted by distribution of "patient alert cards" which are pocket size cards and could be carried around by patients. They provide relevant information about the medicines including ADRs and go a long way in preventing ADRs.

Data processing

Data is best managed electronically by computer, wherein, data is entered in a hierarchical format according to product name, medicine name or therapeutic category. This facilitates recording detailed case information and easy retrieval. Internationally accepted terminologies regarding classification of medicines (Anatomical Therapeutic Chemical [ATC], International Nonproprietary Names [INN]) and ADRs e.g. WHO Adverse Reaction Terminology (WHO ART), Medical Dictionary for Regulatory Activity (MedDRA) should be used, so that the data can be globally shared.

Hypothesizing

This is one of the chief goals of PV center. Based on the case reports, the center should be able to generate hypothesis or detect a signal with regard to probable ADRs.

Medicine regulation

It is PV center's duty to keep a close eye on the new medicines launched in the market and follow them up to look for newer ADEs, issue warnings, unmask newer indications or changes or to advocate withdrawal of medicines in extreme cases. A center should actively take up activities towards furthering the role of PV with periodic safety update reports (PSURs), registries, risk management-minimization plans, and improved communication with changes in label of medicines.

FUNDING

Money is required to fuel the PV center and it should have an officially approved guaranteed source, which is immune to political governance and economic fluctuations, to direct a steady flow of funds so that the progress of work is not hindered. The requisite financial support required for a particular PV center is estimated based on how big a population the center is schemed to cater and the anticipated rate at which it is going to generate reports. Additional monetary support may be sought from health insurance companies, academia, philanthropic organizations, and government departments with an interest in medicine safety.

It is good to start a program in high spirits, but what is more important is to continue with the tempo to sustain it. The sustainability of PV program in India can be well recognized by the fact that during one calendar year, not even a single ADR report was sent to UMC from a country of 1 billion, and India rates below 1% in PV as compared to the overall world average of 5%.[8] It could be remedied by training our technical manpower in the latest developments in PV, identifying, and supporting centers of excellence across the country which can impart quality training in PV to the health care professionals. Efficient communication both in sharing our own findings with the global database and reaching feedbacks and analyzed reports to the prescribers well in advance should be ensured.[9]

CONCLUSIONS

With piling reports of clinical and economic toll taken by ADRs on the healthcare system, efforts have to be accelerated to contain the damage before it looms large on the country. There is a pressing demand to better define the relationship between the pharmaceutical industry, health care professionals, and medicine regulatory authorities so that deleterious effects of medicines in their routine use could be avoided and if at all this occurs, it should be effectively tackled.[10] PV is the central idea that will enable the country to examine medicine safety data and arrive at tailor made regulatory decisions for its population. For any medicine intervention to succeed, it is desired by the users that the same should be absolutely safe and sans any risk. PV envisions this at its core and scrutinizes the medicines for their ADRs, sets a mechanism for noting ADEs, and communicating these to UMC for global concern, always upholding the safety of people uppermost.

Establishing a robust PV system is an uphill task, but nevertheless, with meticulous planning, proactive approach, continuing zeal and motivation of the concerned staff, if there is will, it can be achieved. PV ensures that future generations will not condemn the present one for its apathy, indifference, and callousness to the gravity of the situation or else modern medicine will be continued to be called as allopathy – the science of other suffering!

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