International Journal of Future Innovative Science and Engineering Resea
Volume-1, Issue-I ISSN (Online): 2454- 1966

Research Manuscript Title

An E-Portal for Indian Pharmacovigilance using Data Mining Techniques

Website: www.istpublications.com

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MARCH - 2015

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Abstract

Pharmacovigilance is the process of monitoring and evaluating drug related problems. ADRs lead to considerable morbidity and mortality. It is anticipated that only 6-10% of all ADRs are reported. Some ADRs are visible in clinical trials, but many ADRs are only identified in post marketing Surveillance. Post marketing drug Surveillance primarily relies on Spontaneous Reporting. The information about ADRs can be collected from consumer's experience and view which serves as a good tool. Reporting has several advantages like qualitative details; increase in ADRs reported, newer ADRs being reported, early detection of ADRs and also as a strategy to prevent medication errors. Developing countries also are in favour of consumer reporting of ADRs. Major city hospitals in India have ADR monitoring centers and the presence of large tertiary care facilities, despite of this pharmacovigilance is still in its infancy. Spontaneous ADR reporting form is a major tool for pharmacovigilance system in any country. If a computer based online reporting system is implemented there could be a significant change in the reporting level. Therefore, an e-portal has been developed to improve ADR reporting in order to decrease the physical and economic burden of ADR submission. Designing an e portal with functionalities like ADR monitoring, detecting risks in ADR, rare Drug-Drug Interactions will be an added advantage for pharmaceutical industry in providing drug safety.

Keywords— **Adverse Drug Reactions, Pharmacovigilance, ADR reporting, Safety update report,**

1. INTRODUCTION

Pharmacovigilance (PhV) is the process of monitoring and evaluating drug related problems. The ultimate goal of PhV is to promote safe use of drugs [1,2].The main aim of PhV is to identify hazards associated with drugs and to prevent patients from Adverse Drug Reaction (ADRs)[3]. Drugs introduced in the new era have changed the way in which diseases are managed and controlled. Despite of all the benefits, evidences show that ADR causes illness disability and even death. The top 10 leading causes of death in some countries is due to ADRs [4]. Authors also investigated about drugs creating multiple reactions. ADRs have a major impact on public health by imposing a considerable economic burden to the society [5,6]. The contribution of health professionals, to ADR databases is enormously significant and has encouraged benefit-risk ratio of some drugs [7,8]. A major impact on public health is due to ADR which decline the healthy life style and in turn increasing mortality and morbidity. Only few ADRs are predictable in clinical trials and most of the ADRs are identified through post marketing surveillance.

Post marketing drug Surveillance primarily relies on Spontaneous Reporting System (SRS). Many countries are maintaining different SRS. Spontaneous reporting has contributed significantly to successful PhV. There are several limitations with spontaneous reporting databases. Underreporting remains a major drawback in spontaneous reporting [9,10].The data is difficult to interpret because of variable underreporting. In many countries pharmacist plays an important role in reporting suspected ADRs. However, under reporting and lack of knowledge about the reporting system are clearly evident. Creating awareness about ADR reporting and devising means to make it easy and convenient may aid in improving spontaneous reporting [11].Therefore, a need for summarising the identified risk of drugs, and its potential impacts are essential for monitoring drug safety . Limitations in the sample size consider for clinical trials are less to detect rare ADRs [12].

1.1 Survey about ADR

There are many reasons why the number of ADR is so high. They include:1)the arrival of new drugs in the market;2) the number of drugs prescribed are high;3)the lack of formal system for monitoring Adverse Drug Reactions [13]. Several studies have shown that most ADRs are preventable, provided that the drugs are used rationally. But unfortunately, the most common system failure has been to disseminate the knowledge of PhV to the individuals actually involved in prescribing, i.e., the physicians [14]. Principles and practice of PhV are often discussed in academic manner, rather than pragmatic or applied science. Such discussion are held among pharmacists who are not directly involved in patient care and physicians who treat cases and use drugs generally keep themselves uninvolved. Prevention is better than cure, as in medicine and the application of same principle has given a new dimension to PhV [15].

In order to make the drug consumption safer ADR monitoring is required. The formal evaluation of drug by clinical trials and drug issues related to the safety are inadequately studied. In controlled environment, with the highly selected and limited number of patients the formal therapeutic trials are conducted. The exact safety profile of the rug in the real life situations is not known. Moreover, prior to its release, a drug is studied in just 4,000 cases. Therefore, adverse reactions having frequency less than 0.5 to 1% are missed [16]. Children, pregnant women, and elderly are not included in clinical trials for ethical reasons. Therefore, the safety of the drug in these cases remains unknown until its release [15]. Another important drawback of clinical trials is that they can only report adverse reactions that appear within the finite duration of trial. Delayed reactions would be missed. Reporting of adverse drug reactions is done by mainly two methods: spontaneous and intensive. They often serve as a useful source of data or provide early warning signals for the drug related regulatory actions.

Analysis of adverse event reports is one way to monitors the safety of therapeutic goods used. There is the potential for an adverse event to occur with the use of any medicine or vaccine – whether it is supplied on prescription or over-the-counter or as a complementary medicine. When a medicine or vaccine is first registered and made available, information about its safety and efficacy is usually available only from clinical trials. Postmarket monitoring of the safety of drugs and vaccines contributes to a better understanding of their possible adverse effects when they are used outside the controlled conditions of clinical trials [20].

The ADRs produced by certain drugs are often recognised by randomised controlled trials in phase three. Most of the ADRs are identified when the drugs are exposed to large population. There are number of important factors to be considered while reporting an ADR such as identifying the individual to whom the ADR is most likely to occur, age, sex etc [17].

1.2 Survey about SRS

The principal method used for monitoring the safety of marked drugs is SRS. The ADR monitoring programs in use are based on SRS in many countries like UK, USA, India and Australia. In these systems, clinicians encourage reporting any or all reactions associated with drug usage, attention made on arrival of new drugs and serious ADRs. The rational for SRS is to generate signals of potential drug problems, to identify rare ADRs and theoretically to monitor continuously all drug used in a variety of real conditions from the time they are first marketed [18]. The identified ADR undergoes the causality assessment and the harmful reports are documented by the PhV cell of each country to generate alert message to the public.

1.3 Indian scenario

Therefore monitoring of ADR for each country is essential. While considering Indian scenario monitoring of ADRs were started two decades ago (1982)[36]. Five centers were established with the idea of starting a monitoring program nationwide under the chairmanship of Drug Controller of India. ADR monitoring centers are established in 24 states. There are four Regional Centers for Training and Technical Support under National Coordinating Centre (NCC) in Mumbai. Kolkata, Mysore, Ghaziabad. Physicians play an important role in entire monitoring process. In order to have access to patient data and at times in interpretation of reports of suspected adverse drug reactions the co-operation of clinicians is essential. Physicians and pharmacologists are involved in the interpretation of collected data or hypothesis testing on the basis of the reports. These works may involve a panel of physicians reviewing all the collected report. Though the pattern of adverse reactions differs slightly from country to country, adverse reactions to analgesics

(mainly, non-steroidal anti-inflammatory drugs) and antibiotics constitute about half of all such reports in India [19]. In other countries, pharmacists or nurses usually carry out these processes under supervision. To assess the process of PhV cell, an e-portal enclosing all the functionalities are required.

The primary purpose of patient reporting system is to learn from experience. A reporting system must produce a visible, useful response to justify the resource expanded and to stimulate reporting. The important function of reporting is to use the result for data analysis and investigating a serious event that can be disseminated. There are several ways in which reporting can lead to learning and improve safety. It can generate alerts or warning signals regarding new hazards example complication of new drug or serious ADR reported. Lessons learned by health-care organizations by investigating a serious event. Analysing many and multiple reports can lead to insights into underlying system failures.

1.4 Components of a reporting system

The components of the e-portal include the following menu options like warnings and alerts, drug safety update and health professional information, conferences and awareness. The form has been designed as per the norms of CDSCO. An user interface representing all the functionalities in the paper is provided in figure 1.

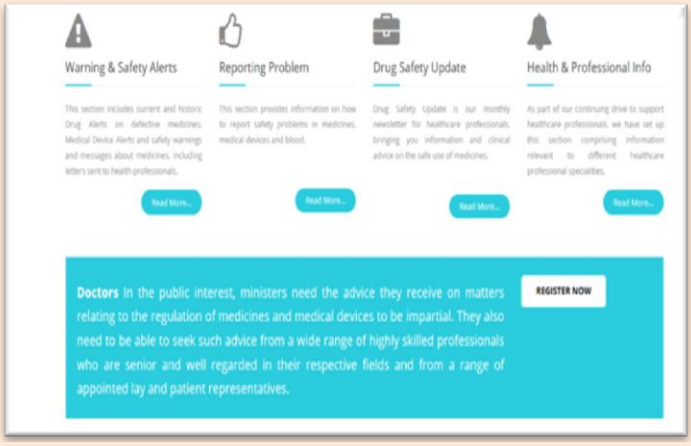

Figure 1: User interface with functionalities.

1.5 Warnings and safety alerts

It provides information for consumers and health professionals on new drug warnings and other safety information, drug label changes, and shortages of medically necessary drug products [32].

Some drug alerts statements provided by FDA are:

1. Alerts Health Care Professionals about Sterile Products
2. Warns healthcare professionals not to use injectable vitamin products distributed by Medical Supply Liquidators.
3. Safety alert on certain Baczol Antigripal and Baczol Expectorante marketed as treatment for respiratory infections.
4. Alerts Health Care Professionals of Infection Risk from Repackaged Avastin Intravitreal Injections.
5. Public Health Alert: Healthcare Professionals Warned Not To Use Certain Intravenous Metronidazole, Ondansetron, and Ciprofloxacin Due To Potential Contamination.

1.6 Drug safety updates and recalls

The Adverse Drug Reaction (ADR) monitoring centers in India is less active and a lot of determination is needed in order to collect drug safety data which may be carried throughout active safety surveillance. A Periodic Safety Update Report (PSUR) is a complete safety experience of drug submitted to the drug regulatory authorities at defined period of time. In India, PSURs for all newly arrived drugs must be submitted every six month for first two

years followed by annually for next two years to the Drug Controller General of India [DCG(I)], New Delhi. Test drugs for their efficacy and safety otherwise they will be withdrawn from the market [26]. Over the past few years, lots of drugs were withdrawn worldwide based on the post marketing surveillance data. This underpins the need for such a surveillance system. Due to safety concerns in the past few years, series of drugs has been withdrawn from market including some of blockbuster drugs amongst them like lipid-lowering drug Lipobay (Baycol; cerivastatin), the anti-obesity drugs fenfluramine and dexfenfluramine, and several others.

The latest data from the Indian drug regulatory authority CDSCO website indicates that around 90 drugs or their combinations were withdrawn from the market because of their low safety profile [27]. DCG(I) has made it mandatory for hospitals in India to implement PSUR for newly introduced drugs [28]. In order to address the safety concern of our hospitalised patients it is essential to take steps for monitoring patients who are on newly introduced drugs and generate data for the periodic reporting of PSURs to the DCG(I). All the leading hospitals of India do mandatory drug safety reporting.

These include [29]:

1. Review possible risks of pain medicine use during pregnancy.
2. Reporting mental health drug ziprasidone (Geodon) associated with rare but potentially fatal skin reactions .
3. Warns about case of rare brain infection PML with MS drug Tecfidera (dimethyl fumarate).
4. Label changes for asthma drug Xolair (omalizumab), including describing slightly higher risk of heart and brain adverse events.
5. Reviews long-term antiplatelet therapy as preliminary trial data shows benefits but a higher risk of non-cardiovascular death

1.7 Drug recalls

Recalls are actions taken by a firm to remove a product from the market [30]. The efficacy as well as safety profiles of the drug are tested. In spite of this, some adverse effects of drugs appear only after the drug is used in the general population. These adverse effects are detected though a process of regular monitoring after the drug is released. If the adverse effects are severe or the risks of using the drug outweigh the benefits, or if the drug is ineffective, the country may ban the drug or the Drug Company may itself voluntarily withdraw the drug. Some drugs may cause adverse effects only when combined with particular drugs. In such cases, only the fixed dose combination is banned and not the individual drugs.

A number of single drugs as well as fixed dose combinations have been banned for manufacture, marketing and distribution in India. Some drugs banned in India are mentioned below [31]:

1. Fenfluramine and dexfenfluramine
2. Rimonabant was particularly effective in causing weight loss, Sibutramine is a weight loss pill
3. Astemizole and terfinadine
4. Rofecoxib and valdecoxib are popular painkillers
5. Gatifloxacin
6. Rosiglitazone used for type II diabetes.
7. Nimesulide is a painkiller
8. Quinodochlor
9. Phenolphthalein

2.0 Role of health professionals

As a health professional, they play an important role in the ongoing safety of drugs and vaccines in India by reporting adverse events. When they submit a report they contribute to the ongoing collection of information that enables to ensure the safety, effectiveness and quality of drugs and vaccines [20].

In the ongoing evaluation of ADR programs such as development and maintenance pharmacists should make use of their leadership. They should obtain formal endorsement or approval of such programs through appropriate committees (e.g., a pharmacy and therapeutics committee and the executive committee of the medical staff) and the

organization's administration. In settings where applicable, input into the design of the program should be obtained from the medical staff, nursing staff, quality improvement staff, medical records department, and risk managers [21],[22-24]
The pharmacist should facilitate [25]

1. Analyzing each ADR reported

2. Identifying drugs and patients at high risk of being involved in ADRs,

3. Developing policies and procedures for the ADR-monitoring and reporting program,

4. Providing a description about interactions of pharmacists, physicians, nurses, risk managers, and other health professionals in the ADR program and their role and responsibilities

5. Use of the ADR program for educational purposes,

6. Developing, maintaining and evaluating ADR records within the organization,

7. The organizational dissemination and use of information obtained through the ADR program,

8. Reporting serious ADRs to the FDA or the manufacturer (or both), and

9. Publication and presentation of important ADRs to the medical community.

Direct patient care roles for pharmacists should include patient counseling on ADRs, identification and documentation in the patient's medical record of high-risk patients, monitoring to ensure that serum drug concentrations remain within acceptable therapeutic ranges, and adjusting doses in appropriate patients (e.g., patients with impaired renal or hepatic function).Health professionals who become aware of an adverse event in connection with patient's treatment or hospital stay are required to report the event. Health care professionals report to the national database through ADR reporting form. Reports are automatically forwarded to WHO for investigation.

3.0 ADR reporting form

Reporting systems need to be clear on who reports, the scope of what is reported and how reports are made. Reporting of incidents is of little value unless the data collected are analysed and recommendations are disseminated. Experts who understand statistical methods the practice concerns, clinical significance, system issues and potential preventive measures are essential to analyse reported incidents.

Each report must include reporter's contact details, a patient identifier (e.g. initials, but not the full name of the patient or doctor), an explanation about the adverse event and details of the medicine(s) or vaccine(s) suspected of causing the adverse event. Report suspected adverse events to any medicine or vaccine available, including prescription medicines, over-the-counter medicines and complementary medicines.

1. suspected adverse events involving new drugs
2. suspected drug interactions
3. unexpected adverse events (i.e. reactions that are not described in the Product Information)
4. serious adverse events, such as those suspected of causing:
   - inability to work
   - admission to hospital
   - prolongation of hospitalization
   - increased investigation or treatment costs
   - danger to life
   - birth defects
   - death

Even if you are unsure whether to report, you should report serious adverse events. Each adverse event report that is entered into a database is continually analyzed by health professionals to identify potential emerging problems for detailed investigation. If any safety concern relating to a medicine or vaccine, is identified they take regulatory actions [20]. This can include:

1. disseminating information for consumers and health professionals regarding the problem
2. updating the Product Information with new adverse effects, precautions or warnings
3. requiring postmarketing studies
4. imposing limits on their use
5. investigating manufacturing sites
6. recalling products from the market
7. Suspending or cancelling products.

Reports become available on the publicly accessible Database of Adverse Event Notifications. The causality assessment is based on WHO criteria to ensure that the drug has caused the suspected reaction. There should be a temporal association between drug use and the appearance of an adverse reaction. It should disappear (maybe partially), once the drug is stopped (de-challenge). It should reappear when the drug is reintroduced (rechallenge). However, performing this de-challenge and rechallenge is not always possible in real clinical situations. In these cases, one should use the best judgement about the adverse effect profiles of the drug, underlying disease, concomitant medications etc.

4.0 Detecting rare drug-drug interaction

Discovering unknown Drug-Drug interaction (DDI) as early as possible is highly advantageous. Substantial effort has been taken by Food and Drug Adverse Event Reporting System (FAERS) to identify unknown Drug- Drug interaction. Interactions can direct to safety measures in prescribing, absolute contraindications for combination use, or even drug withdrawal. In particular, understanding drug interactions between commonly prescribed drugs is of great clinical importance. Traditional signal detection algorithm are capable of revealing frequent drugs which are insufficient since people consuming multiple drugs are common nowadays. The authors have developed a novel algorithm for identifying known and unknown DDIs from adverse event reports in SRS. The proposed Prior-Weighted algorithm can be utilized by PhV cell pharmaceutical industry and the physicians to gain knowledge about rare drug interactions [37].

4.1 Steps taken to decrease ADRs

Most of the ADRs are preventable; prescribing minimum dosages of drugs is the simplest way to prevent adverse drug reactions [33]. Dosages should be individualised to the patients and drugs should be tailored to patient's need and not the vice versa [16]. Health professional should be encouraged to report adverse reactions and educated periodically. For postgraduate students in the Department of Pharmacology ADR monitoring should be a compulsory part of training. On the importance of PhV and ADR reporting lectures should be given to undergraduate level. Renal and hepatic status of the patient should be known before drug use and history of drug allergy should be elicited. This is because failure to adjust drug dosages results in adverse drug reactions in cases with renal/hepatic impairment [34].

Recently, the US FDA has developed a Med Watch Program (1993) specifically designed for the reporting of adverse events relating to medical products, equipment, and medication. Both, health professionals and consumers, are encouraged to use Med Watch. The purpose of reporting is to facilitate monitoring and investigation. The aim of an investigation is to avoid the occurrence of further adverse reactions, some of which result in hospital admissions, permanent disabilities, birth defects and/or increased medical or surgical care to prevent permanent impairment or damage [35]. We in India need to start a similar programme for online submission of drug reports. Many physicians imagine that reporting may carry some legal obligation with it. It should be remembered that occurrence of adverse reactions are natural accompaniments of drug treatment due to their inherent properties. They can be prevented through diligent and rational use of drugs [36].In any terms, a physician cannot be held responsible for occurrence of such

reactions and drug usage is not in any way linked to negligence. Therefore, no clinician should refrain from reporting. If this strategy is adopted by all hospitals in India it would be a useful stepping stone in generating a genuine ADR database for our population. All marketed drugs could be monitored simultaneously.

5.0 CONCLUSION AND FUTURE WORK

PhV is still in its infancy in India, this is likely to expand in times. The need for pharmacovigilance grows more than ever before because many new drugs hit the market day by day. Monitoring ADRs is an ongoing and continuing process. Reporting adverse effects of newer particularly of serious nature is compulsory. Even though there are many methods through which ADR reporting can be improved, it is the duty of health professionals to feel the responsibility and understand its importance. Physicians should report death due to drugs, life threatening complications, hospitalisation (initial or prolonged), disability if significant, persistent, or permanent, congenital anomalies, a reaction which requires medical intervention to prevent damage. However it may result in permanent damage and it is important to note that many adverse reactions would subside once the offending agent is discontinued or dosage reduced. Spread awareness about using minimal doses of drugs at least in the beginning of the treatment. To make aware of the methodologies and other technical aspects of the drug monitoring and reporting process medical education programmes for physicians and other health professionals should be conducted regularly. Basically a different approach has been proposed by taking into account multi–item combinations. The proposed data mining methodology demonstrate that multi-item drug combination that causes rare events could be extracted using our methodology. Hence the developed e-portal is an added advance for health professionals and PhV cell to report about ADR. This aims to ensure that new safety information is quickly communicated to the other health professionals, thus reducing further incidents.

Different countries use different ADR reporting form which leads to lot of discrepancy in data capturing. Non –uniformity among the forms lead the WHO database as incomplete [38]. To capture complete adverse event-related information, there is a need to harmonise all countries ADR reporting forms. Since patients are important stakeholders, to overcome underreporting problem it is necessary to encourage patient reporting.

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